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Study Title: A multicenter, randomized, open-label, 2-arm, Phase II study with a safety lead-in phase evaluating the combination of encorafenib and cetuximab versus irinotecan/cetuximab or infusional 5-fluorouracil (5-FU)/folinic acid (FA)/irinotecan (FOLFIRI)/cetuximab in Chinese patients with BRAF V600E mutant metastatic colorectal cancer.

Protocol Reference Number: W00090GE202

NCT Number: NCT05004350

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Clinical Study Protocol Title Page

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A multicenter, randomized, open-label, 2-arm, Phase II study with a safety lead-in phase evaluating the combination of encorafenib and cetuximab versus irinotecan/cetuximab or infusional 5-fluorouracil (5-FU)/folinic acid (FA)/irinotecan (FOLFIRI)/cetuximab in Chinese patients with *BRAF* V600E mutant metastatic colorectal cancer.

Protocol Study Code:	**W00090GE202**
Protocol Version:	**6.0–16MAY2024**
Amendment Number:	**PA04**
Type:	Non Substantial
Compound:	**Encorafenib in combination with Cetuximab**
Study Phase:	**II**
Short Title:	**The NAUTICAL CRC study**
Sponsor Name:	**Pierre Fabre Médicament**
Legal Registered Address:	**Les Cauquillous – 81500 Lavaur – France**

Regulatory Agency Identifier Number(s): 2021LP00253

CCI [redacted]

W00090GE202

AGREEMENT PAGE

Sponsor Medically Qualified Representative Signatory:

PPD

Date

Sponsor Statistician Qualified Representative Signatory:

PPD

Date

Study Coordinating Investigator Signatory:

PPD

Date

Clinical study manager, clinical development physician and all sponsor personnel names with contact information will be provided in Appendix 10.14.

W00090GE202

INVESTIGATOR SIGNATURE FORM

Protocol Version 6.0 dated 16 May 2024

By my signature below, I, ……..……. hereby confirm that I agree:

To conduct the study described in the protocol referenced above, in compliance with GCP, with applicable regulatory requirements and with the protocol agreed upon by the sponsor and given approval / favorable opinion by the Independent Ethic Committee (IEC).

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 -study 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 study.

I have been informed that certain regulatory authorities require the sponsor to obtain and supply details about the investigator's ownership interest in the sponsor or the study intervention 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.

Investigator	**Date**

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1. Protocol Summary

1.1. Synopsis

Protocol Title:	A multice**N**ter, randomized, open-label, 2-**A**rm, Phase II st**U**dy with a safety lead-in phase evaluating the combina**T**ion of encorafen**I**b and cetuximab versus irinotecan/cetuximab or infusional 5-fluorouracil (5-FU)/folinic acid (FA)/irinotecan (FOLFIRI)/cetuximab in **C**hinese patients with *BRAF* V600E mutant metastatic **C**oLo**R**ectal **C**ancer.
Short Title	The NAUTICAL CRC Study
Rationale:	B-RAF proto-oncogene, serine/threonine kinase (BRAF) mutations, which lead to constitutive activation of BRAF kinase and sustained mitogen-activated protein kinase (MAPK) (also known as rat sarcoma viral oncogene homologue [RAS]/proto-oncogene serine/threonine protein kinase [RAF]/mitogen-activated protein kinase [MEK]/extracellular signal-related kinase [ERK]) pathway signalling resulting in increased cell proliferation and survival. The V600E mutation, the most frequent BRAF mutation in colorectal cancer (CRC), provides peculiar clinical and pathological characteristics and is negatively associated with prognosis in patients with metastatic colorectal cancer (mCRC), distinguishing them as a subgroup that obtains modest benefit from standard treatments. Failure to achieve good survival outcomes through standard doublet chemotherapy agents in this population has emphasized the need to develop novel therapeutic approaches. The pivotal Phase III multi-region study (ARRAY 818-302, the "BEACON" study [NCT02928224]), was conducted to evaluate the combination of the BRAF inhibitor encorafenib and epidermal growth factor receptor (EGFR) inhibitor cetuximab (referred to as the "doublet" in this protocol) with or without the MEK inhibitor binimetinib versus the investigator's choice of control treatment (either irinotecan and cetuximab or FOLFIRI and cetuximab), in participants with B-RAF proto oncogene, serine/threonine kinase V600E mutant (*BRAF* V600E) mCRC whose disease had progressed after one or two prior regimens in the metastatic setting. A total of 665 patients were randomized 1:1:1 to receive: · Intervention arm: Encorafenib (300mg QD), binimetinib (450mg BID) and cetuximab · Intervention arm: Encorafenib (300mg QD) and cetuximab (Doublet) · Control arm: irinotecan and cetuximab or FOLFIRI and cetuximab Overall, the combination of encorafenib and cetuximab with or without binimetinib appeared to be two effective regimens in second and third lines mCRC, demonstrating a substantial improvement in overall survival (OS), progression free survival (PFS) and overall response rate (ORR) compared to standard regimens. The more favorable safety and tolerability profile of the doublet over the combination of encorafenib and cetuximab with binimetinib makes it the preferred therapy. Based on these results from the ARRAY 818-302 study, the doublet was approved in the United States (US) in April 2020 and in Europe in June 2020 in *BRAF* V600E mCRC following failure of prior systemic therapy. Pierre Fabre Medicament now wishes to submit an application for the doublet in *BRAF* V600E mCRC in China However, the ARRAY 818-302 study did not include

	patients from mainland China. It is anticipated that the conclusions coming from the global population in the ARRAY 818-302 study can be extended to the Chinese population. The proposed NAUTICAL study has therefore been designed to demonstrate consistency in treatment effect of the doublet at the same doses as in the ARRAY 818-302 study in *BRAF* V600E mCRC Chinese homeland participants to provide bridging data.

Objectives and Endpoints/Estimands:

Objectives	Endpoints
SLI Phase	
Primary	
To assess the safety and tolerability of the doublet.	Incidence of DLTs.
Secondary	
To assess the overall safety and tolerability profile of the doublet	Type and severity of adverse events and SAEs, changes in physical examinations, vital signs, ECGs, clinical safety laboratory assessment values, graded according to NCI CTCAE Version 4.03; dermatological examinations and performance status using the ECOG performance status scale. Incidence of dose interruptions, dose modifications and discontinuations due to adverse events
To provide preliminary PK data of the doublet.	Plasma concentrations of encorafenib and serum concentrations of cetuximab on Day 1 of Cycles 1 and 2 and derived PK parameters (e.g.AUC, C_{min}, C_{max}).
To provide preliminary antitumor activity data of the doublet as measured by ORR and DOR.	ORR, defined as the proportion of participants with a best overall best response of either CR or PR as determined by BICR and investigator assessment per RECIST Version 1.1. DOR, defined as the time from first documented response (CR or PR) to the earliest date of disease progression as determined by BICR and investigator assessment per RECIST Version 1.1, or death due to underlying disease.
Exploratory	
CCI [redacted]	CCI [redacted]
Randomized (Phase II) Phase	

Primary	
To compare the efficacy of the doublet versus irinotecan and cetuximab or FOLFIRI and cetuximab (control) as measured by PFS assessed by BICR.	PFS, defined as the time from the date of randomization to the earliest documented date of disease progression as determined by BICR assessment per RECIST Version 1.1, or death due to any cause.
Secondary	
To compare the efficacy of the doublet versus the control respect to: • PFS by investigator assessment • Overall response rate (ORR) • Duration of response (DOR) • Disease control rate (DCR) • Time To Response (TTR) Overall Survival (OS)	PFS as defined as the interval of time between the date of randomization to the earliest date of disease progression, as determined by investigator assessment per RECIST v1.1, or death due to any cause. ORR (for confirmed and unconfirmed responses) defined as the proportion of participants with a confirmed (resp. unconfirmed) best overall response of either CR or PR, as determined by BICR and investigator assessment per RECIST v1.1. DOR, defined as the time from the date of the first documented response (CR or PR) to the earliest date of disease progression, as determined by BICR and investigator assessment per RECIST v1.1, or death due to any cause DCR, defined as the proportion of participants with a best overall response of either CR, PR or SD, as determined by BICR and investigator assessment per RECIST v1.1 TTR (for confirmed and unconfirmed responses) is defined as the time between date of randomization until first documented response of CR or PR. OS is defined as time from randomization until date of death due to any cause.
To characterize the safety and tolerability of the doublet.	Type and severity of adverse events and SAEs, changes in physical examinations, vital signs, ECGs, clinical safety laboratory assessment values, graded according to NCI CTCAE Version 4.03; dermatological examinations and performance status using the ECOG performance status scale.
To assess the effect of the doublet on QoL.	Change from baseline in the EORTC QLQ-C30, EQ-5D-5L, FACT-C and PGIC questionnaire scores.
To characterize the PK of the doublet in this population.	Plasma concentrations encorafenib and serum concentrations of cetuximab on Day 1 of Cycles 1 and 2 and derived PK parameters (e.g. AUC, C_{min}, C_{max}; 15 participants with serial sampling only) in Chinese participants. Population PK analysis using the ARRAY-818-302 study PK data.
Exploratory	
• CCI [redacted]	CCI [redacted]

• To assess the predictive significance of the MSI status. To investigate the concordance of *BRAF* V600E mutation detection in archived or fresh tumor sample used for participant selection with the presence of this mutation as detected by a candidate companion diagnostic.	CCI [redacted]

Abbreviations: AUC = area under the curve; BICR = blinded (to treatment received) independent central review; BRAF V600E = B-RAF proto-oncogene, serine/threonine kinase V600E-mutant; CCI [redacted] *; C_{max} = maximum concentration; C_{min} = minimum concentration; CR = complete response; DLT = dose limiting toxicity; DCR = disease control rate; DOR = duration of response; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer Patients; EQ-5D-5L = EuroQol-5D-5L; FACT-C = Functional Assessment of Cancer Therapy-Colon Cancer; FFPE = formalin-fixed paraffin-embedded; FOLFIRI =5-fluorouracil/folinic acid+irinotecan;* CCI [redacted] *NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; ORR = overall response rate; OS = overall survival; PCR=polymerase chain reaction; PFS = progression-free survival; PGIC = Patient Global Impression of Change; PK = pharmacokinetic(s); PR = partial response; QoL = quality of life; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; SD = stable disease; SLI = safety lead-in; TTR = time to response.*

Doublet = encorafenib and cetuximab.

Estimands

The primary estimand in the SLI is the DLT rate estimated based on data from DLT-evaluable participants during the DLT-evaluation period, which is the first 28 days after the first dose of study intervention in the SLI. The number and proportion of participants experiencing DLTs during the DLT-evaluation period (from Day 1 to 28) will be summarized for Doublet cohort.

The primary estimand in the randomised phase of the study is the treatment effect in PFS by BICR, as measured by the hazard ratio. PFS is defined as the time from the date of randomization to the earliest documented disease progression per RECIST v1.1, or death due to any cause. The hypothetical strategy will be applied for the new anticancer therapy and for more than two missing assessments. Treatment policy will be applied for tolerability and duration of study treatment using a 1-sided stratified log-rank test.

Details of the estimands attributes are described in section 3.

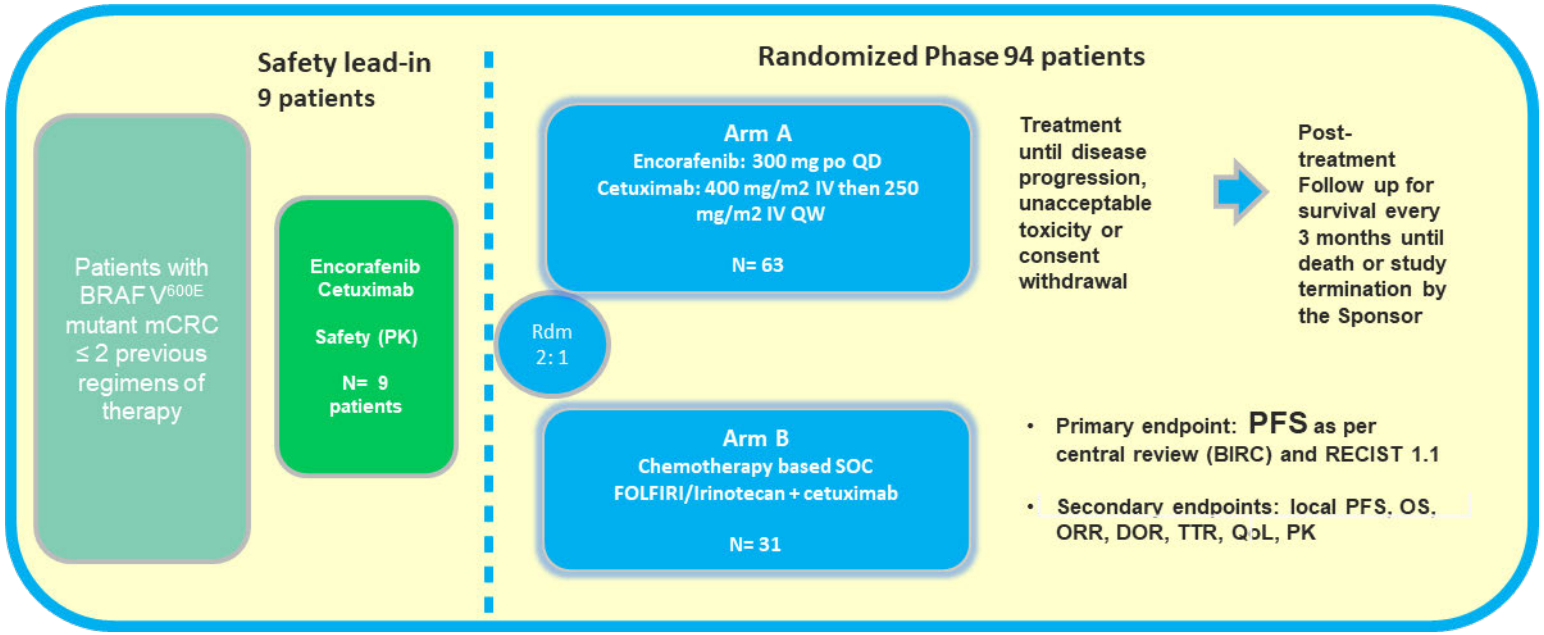
Overall design	This is a Phase II, multicenter, randomized, open-label, parallel group, two-arm bridging study with a safety lead-in (SLI phase) to evaluate the doublet versus irinotecan and cetuximab or FOLFIRI and cetuximab in Chinese participants with *BRAF* V600E mCRC whose disease has progressed after one or two prior regimens in the metastatic setting. Participants will be eligible for the study based on identification of a *BRAF* V600E mutation in the tumor as determined by a local assay result obtained any time before screening and centrally confirmed no later than 30 days from first dose of study intervention or by the central laboratory as part of molecular prescreening.

	Prior to the randomised Phase II, the SLI portion will be conducted at a limited number of sites to assess the safety and tolerability of the doublet in Chinese homeland participants. Dose-limiting toxicities (DLTs) will be evaluated across the first cycle of therapy and the tolerability of the doublet will be assessed. An independent Data Monitoring Committee (DMC) will review both the DLTs and cumulative toxicity at the time the last patient of the SLI has completed the first cycle. The randomized Phase II portion of the study will start as soon as the last participant recruited has completed at least one full cycle (28 days) of treatment and following DLTs and tolerability assessments by an independent DMC (see section 9.6). Eligible participants will be randomized in a 2:1 ratio, respectively to the doublet arm (encorafenib in combination with cetuximab) or the control arm (either irinotecan and cetuximab or FOLFIRI and cetuximab at the investigator's discretion) Randomization will be stratified by baseline ECOG performance status (0 versus 1) and prior use of irinotecan (yes versus no). The primary objective in the Phase II portion of the study is to compare the efficacy, as measured by the primary endpoint of PFS by BICR, of the Doublet vs the Control Arm. Tumor response will be determined by local assessment by the investigator using RECIST Version 1.1. The PFS, overall response rate (ORR), duration of response (DOR) and time to response (TTR) will be assessed according to Section 9.4
Study Coordinating Investigator:	Professor Lin Shen, Beijing Cancer Hospital & Peking University
Study Sites	The study will be conducted at approximately 35 study sites in mainland China.
Number of Participants:	Approximately 147 participants will be screened to achieve 103 participants receiving study intervention (nine in the SLI phase and 94 in the randomized phase). The determination of sample sizes is detailed in Section 9.2
Intervention Groups and Duration	Participants in the SLI will receive 28-day cycles of the doublet (encorafenib 300 mg per oral (PO) once daily (QD**) +** cetuximab 400 mg/m2 by intravenous (IV) infusion for the first dose followed by 250 mg/m2 IV weekly. Based on the results of the SLI, participants randomized to the Phase 2 will receive either– - the doublet (encorafenib (300 mg QD) + cetuximab 400 mg/m2 by IV infusion for the first dose followed by 250 mg/m2 IV weekly) in 28-day cycles or the control arm (either irinotecan and cetuximab or FOLFIRI and cetuximab at the investigator's discretion) in 28-day cycles. Participants will receive study intervention until disease progression, withdrawal of consent/assent, lost to follow-up, or unacceptable toxicity. After discontinuation of study intervention, participants will be followed for survival, until withdrawal of consent, the participant is lost to follow-up, death or final analysis cut-off date.
Data Monitoring Committee:	An independent DMC will evaluate the safety data to confirm the tolerability of the Doublet at the end of the SLI phase. This independent DMC will then review the available safety information after the first 15 participants in the randomized phase treated with doublet have completed at least one cycle of treatment to confirm tolerability and will then be responsible for reviewing safety data at regular intervals (every 6 months).

End of study definition	The end of the study is defined as the timepoint when the last participant has reached the 30-day safety follow-up visit and when the cut-off date for the final analysis has been reached (whichever occurs last). Final analysis cut-off date is the timepoint when all participants have been followed for at least 1 year after the start of study intervention of the last participant randomized and when 70% of the expected deaths in the randomized phase are recorded (whichever occurs last)..

1.2. Schema

The study schema is shown in Figure 1Figure 1: Study Schema for W00090GE202 Safety Lead-in Phase and Randomized Phase



Abbreviations: BICR = blinded (to treatment received) independent central review; *BRAF* V600E = B-RAF proto-oncogene, serine/threonine kinase V600E mutant; DOR = duration of response; FOLFIRI = 5-fluorouracil/folinic acid+irinotecan; IV = intravenous; mCRC = metastatic colorectal cancer; ORR = overall response rate; OS = overall survival; PFS= progression-free survival; PK= pharmacokinetics; PO = per oral; QD = once daily; QoL = quality of life; RECIST = Response Evaluation Criteria in Solid Tumors; TTR = time to response.

1.3. Schedule of Activities

Activities shown in Table 1 are for molecular pre-screening and screening for all participants.

Activities shown in Table 2 are for the SLI phase and the doublet arm of the randomized phase until cut-off date of the final analysis.

Activities shown in Table 3 are for the control arm of the randomized phase until cut-off date of the final analysis.

Activities shown in Table 4 are for post cut-off date of the final analysis period (*).
(*) Participants in Doublet arm that would not have discontinued study intervention at the time of cut-off date for final analysis (see section 4.4) will be followed according to the Schedule of Assessment (SoA) provided in Table 4, ensuring mitigation of risks associated to study intervention (see section 2.3.2).

Table 1: Schedule of Events for Molecular Prescreening and Screening

Procedure/Assessment	Molecular Prescreening[a]	Screening	Randomization
	Any time before screening	Day –28 to–1	
Epoch	**PRESCREENING**	**SCREENING**	
Molecular prescreening informed consent	X		
Molecular prescreening inclusion/exclusion criteria	X		
Tumor sample (archival or fresh) for *BRAF* V600E, *RAS* wt status and MSI testing to be submitted for central laboratory testing	X	X	
Register in IRT system	X	X	
Screening informed consent		X	
Screening inclusion/exclusion criteria		X	
Demographics	X	X	
Height		X	
Medical and disease history		X	
Prior medications/therapies/procedures		X	
Complete physical examination [b]		X	
Weight		X	
Vital signs		X	
ECOG performance status		X	
EORTC QLQ-C30, EQ-5D-5L, FACT-C [h]		X	
ECG		X	
FSH (LH and/or estradiol)[c]		X	
HBV deoxyribonucleic acid (DNA), hepatitis B surface antigen (hBsAg), Hepatitis B core antibody, serum HCV ribonucleic acid (RNA), hepatitis C antibody (HCV Ab) and HIV testing		X	
Pregnancy test[c]		X	

Procedure/Assessment	Molecular Prescreening[a] Any time before screening	Screening Day –28 to–1	Randomization
Epoch	**PRESCREENING**	**SCREENING**	
Hematology[d]		X	
Clinical chemistry[e]		X	
Coagulation[f]		X	
Urinalysis[g]		X	
Tumor evaluation (CT scan, MRI)		X	
Blood sample for CRP		X	
CCI			
Concomitant medications/therapies		X	
Adverse events	X	X	X
Randomize participant using IRT			X[h]
Determination of comparator treatment in the control arm			X[i]

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; *BRAF* V600E = B-raf murine sarcoma viral oncogene homolog B1 V600E mutant; CCI CRP = C-reactive protein; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-5L = EuroQol-5D-5L; FACT C = Functional Assessment of Cancer Therapy-Colon Cancer; FOLFIRI = 5-fluorouracil/folinic acid+irinotecan; FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; INR = international normalized ratio; IRT = interactive response technology; LDH = lactate dehydrogenase; LH = luteinizing hormone; MRI = magnetic resonance imaging; MSI = microsatellite instability; pH = hydrogen ion concentration; PT = prothrombin time; *RAS* wt = rat sarcoma viral oncogene homolog wild type; RBC = red blood cell; SLI = safety lead-in; WBC = white blood cell.

[a] If local BRAF V600E mutation test positive, proceed to screening phase.

[b] Includes cardiovascular, respiratory, gastrointestinal, dermatological, ophthalmological and neurological systems (at a minimum). Ophthalmic examination will include visual acuity (Standard Logarithmic Visual Acuity Chart), tonometry (intraocular pressure), slit lamp examination, and fundoscopy. Physical examinations should be targeted as clinically indicated at subsequent visits.

[c] Serum test for women of childbearing potential only (FSH [LH and/or estradiol] measurements, if applicable).

[d] Erythrocytes (RBC), hematocrit, hemoglobin, platelets; leukocytes (WBC) count with differential: basophils, eosinophils, lymphocytes, monocytes, neutrophils/ANC.

[e] ALT, albumin, alkaline phosphatase, AST, lipase, amylase, bilirubin (total and indirect), blood urea nitrogen/urea, calcium, chloride, creatine kinase, creatinine, glucose, LDH, magnesium, potassium, sodium, total protein, troponin I or T, uric acid.

[f] aPTT, INR or PT.

[g] Blood, glucose, ketones, leukocytes, pH, protein.

[h] Does not apply to participants in the SLI phase. Only for participants in the randomized phase.

[i] For participants in the control arm of the randomized phase, the investigator will determine the best treatment option for the participant (either irinotecan and cetuximab or FOLFIRI and cetuximab). The treatment decision will be recorded in the IRT system.

Table 2: Schedule of Events for Safety Lead-in Phase and Doublet Arm of the Randomized (Phase II) Phase until cut-off date of the final analysis

Procedure/Assessment (± 3-day window for procedures/assessments)	Treatment Phase									Follow-up Phase	
	Cycle 1				Subsequent Cycles[a]				End of Treatment[b]	30-day Safety Follow-up[c]	Survival Follow-up
	Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22			
Epoch	TREATMENT									FOLLOW-UP	LONGTERM FOLLOW-UP
Baseline/eligibility assessments:											
Verify inclusion/exclusion criteria	X[d]										
Medical history from screening to Cycle 1 Day 1	X										
Dosing:											
BSA	X[e]				X						
Encorafenib	X				X						
Issue new encorafenib dosing diary	X				X						
Review encorafenib dosing diary from previous cycle and assess compliance					X				X		
Cetuximab IV infusion	X	X	X	X	X	X	X	X			
Efficacy/PK/biomarker assessments:											
Tumor evaluation (CT scan, MRI)	Every 6 weeks (±7 days) from first dose for the first 24 weeks, then every 12 weeks[f] (±7 days)										
EORTC QLQ-C30, EQ-5D-5L, FACT-C, PGIC[g]	X				X				X	X	
PK blood samples	X[h]				X[h]						
CCI											
Blood sample for MSI testing	X										
Safety assessments:											
Targeted physical examination	X[e]				X				X	X	
Weight	X[e]				X				X	X	
Dermatological examination	X				X[i]				X	X	

Procedure/Assessment (± 3-day window for procedures/assessments)	Treatment Phase									Follow-up Phase	
	Cycle 1				Subsequent Cycles[a]				End of Treatment[b]	30-day Safety Follow-up[c]	Survival Follow-up
	Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22			
Epoch	TREATMENT									FOLLOW-UP	LONGTERM FOLLOW-UP
Vital signs	X	X	X	X	X	X	X	X	X	X	
ECG[j]	X		X		X				X	X	
ECOG performance status	X[e]				X				X	X	
Pregnancy test[k]	X[e]				X				X	X	
Hematology[l]	X[e]		X	X	X				X	X	
Clinical chemistry[m]	X[e]		X		X				X	X	
Coagulation[n]	X[e]				X				X	X	
Urinalysis[o]	X[e]				X				X	X	
Adverse events	Assess continuously[p]										
Concomitant medications/therapies	Assess continuously										
Follow-up assessments:											
Survival status										X	Every 3 months[q]
Documentation of subsequent anticancer therapy										X	Every 3 months[q]
Documentation of disease progression after subsequent anticancer therapy											Every 3 months[q]

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BSA = body surface area[CCI redacted]; CT = computed tomography;ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for cancer patients; EQ-5D-5L = EuroQol-5D-5L; FACT-C = Functional Assessment of Cancer Therapy-Colon Cancer; INR = international normalized ratio; IV = intravenous(ly); LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; MSI = microsatellite instability; PGIC = Patient Global Impression of Change; pH = hydrogen ion concentration; PK = pharmacokinetic(s); PT = prothrombin time; RBC = red blood cell; SLI = safety lead-in; WBC = white blood cell; WOCBP = women of childbearing potential.

[a] If a cycle initiation (CnD1 visit) is postponed due to toxicity, corresponding safety assessments must be recorded as unscheduled visit(s) in the eCRF. Whatever the reason, the CnD1 will be the day of the treatment initiation of cycle "n". If a visit is missed within the cycle (CnD8, CnD15, CnD22), following visits should be performed according to the original schedule..

[b] To be performed at the time of study intervention discontinuation (as soon as possible and ≤14 days after the last dose of study intervention).

Procedure/Assessment (± 3-day window for procedures/assessments)	Treatment Phase									Follow-up Phase	
	Cycle 1				Subsequent Cycles[a]				End of Treatment[b]	30-day Safety Follow-up[c]	Survival Follow-up
	Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22			
Epoch	TREATMENT									FOLLOW-UP	LONGTERM FOLLOW-UP

[c] To be performed approximately 30 days after the last dose of study intervention or before the initiation of subsequent anticancer therapy, whichever occurs first. Following the 30-day safety follow-up, when clinically appropriate, it is recommended participants be monitored with 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.

[d] Inclusion/exclusion criteria are to be verified before the first dose of study intervention.

[e] Procedures do not have to be repeated if performed within 72 hours before Cycle 1 Day 1 (i.e. first day of dosing).

[f] Tumor evaluations are to be performed every 6 weeks (±7 days) from first dose for the first 24 weeks, then every 12 weeks (±7 days) until disease progression or death, withdrawal of consent, initiation of subsequent anticancer therapy, participant is lost to follow-up or the cut-off date for final analysis is reached (whichever occurs first). If a participant discontinues study intervention for reasons other than disease progression, then tumor assessments must continue to be performed according to this schedule.

[g] The questionnaires should be completed only by the participants in randomized phase at the beginning of the study visit before receiving any study intervention, before any other study assessment or consultation with the investigator and before being informed of their current disease status. Note: PGIC is not completed on Cycle 1 Day 1.

[h] Samples for encorafenib and cetuximab PK will be collected during Cycle 1 and Cycle 2 only. Serial PK sampling (predose and at 1, 2, 4 and 6 hours postdose) on Day 1 of both cycles will be performed in 24 participants treated at the recommended dose: all nine participants in the SLI phase and the first 15 participants in the randomised phase at selected sites. Sparse sampling (at 2 and 6 hours postdose on Cycle 1 Day 1 and predose and 2 hours postdose on Cycle 2 Day 1) will be collected in the remaining participants.

[i] Dermatological examinations are to be performed every 8 weeks from Cycle 1 Day 1 (i.e. on Day 1 of Cycles 3, 5, 7…).

[j] Electrocardiograms are to be performed in triplicate predose on Cycle 1 Day 1 (conducted within approximately 5 to 10 minutes total time), followed by a single ECG at remaining timepoints. On Cycle 1 Day 1 and Cycle 2 Day 1, ECGs are to be performed predose and at 2 (± 0.5) hours after administration of encorafenib and before the start of the cetuximab infusion. Electrocardiograms are performed predose at remaining timepoints. Electrocardiograms should be performed before PK and biomarker blood collection at equivalent nominal timepoints.

[k] Local urine test for WOCBP only.

[l] Erythrocytes (RBC), hematocrit, hemoglobin, platelets; leukocytes (WBC) count with differential: basophils, eosinophils, lymphocytes, monocytes, neutrophils/ANC.

[m] ALT, albumin, alkaline phosphatase, AST, lipase, amylase, bilirubin (total and indirect), blood urea nitrogen/urea, calcium, chloride, creatine kinase, creatinine, glucose, LDH, magnesium, potassium, sodium, total protein, troponin I or T, uric acid.

[n] aPTT, INR or PT.

[o] Blood, glucose, ketones, leukocytes, pH, protein.

[p] All adverse events are collected from when the participant first provides informed consent until the 30-day safety follow-up visit.

[q] For participants who discontinue study intervention due to disease progression, the survival follow-up phase will start after the 30-day safety follow-up. For participants who discontinue study intervention for reasons other than disease progression, the survival follow-up phase will start upon disease progression or the start of another anticancer therapy. Participants will be contacted by telephone approximately every 3 months for collection of information during the survival follow-up period. This may be conducted at routine visits as well, and more frequently as needed. Participants will be followed for at least 1 year after the start of study intervention of the last participant randomized. For participants that were lost to follow-up or withdrawal of consent, attempts to determine survival status will be made via access to public records as permitted by local laws.

Table 3: Schedule of Events for Control Arm of the Randomized (Phase II) Phase until cut-off date of the final analysis

Procedure/Assessment (± 3-day window for procedures/assessments)	Treatment Phase									Follow-up Phase	
	Cycle 1				Subsequent Cycles[a]				End of Treatment[b]	30-Day Follow-up[c]	Survival Follow-up
	Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22			
Epoch	TREATMENT									FOLLOW-UP	LONGTERM FOLLOW-UP
Baseline/eligibility assessments:											
Verify inclusion/exclusion criteria	X[d]										
Medical history from screening to Cycle 1 Day 1	X										
Dosing:											
BSA	X[e]				X						
Irinotecan IV infusion (all participants)	X		X		X		X				
5-FU[f] and FA IV infusion (FOLFIRI/cetuximab only)	X		X		X		X				
Cetuximab IV infusion	X	X	X	X	X	X	X	X			
Efficacy/ biomarker assessments:											
Tumor evaluation (CT scan, MRI)	Every 6 weeks (±7 days) from first dose for the first 24 weeks, then every 12 weeks[g](±7 days)										
EORTC QLQ-C30, EQ-5D-5L, FACT-C, PGIC[h]	X				X				X	X	
CCI											
CCI											
Safety assessments:											
Targeted physical examination	X[e]				X				X	X	
Weight	X[e]				X				X	X	
Vital signs	X	X	X	X	X	X	X	X	X	X	
ECG[i]	X		X		X				X	X	
ECOG performance status	X[e]				X				X	X	
Pregnancy test[j]	X[e]				X				X	X	
Hematology[k]	X[e]		X	X	X		X[l]		X	X	

Procedure/Assessment (± 3-day window for procedures/assessments)	Treatment Phase									Follow-up Phase	
	Cycle 1				Subsequent Cycles[a]				End of Treatment[b]	30-Day Follow-up[c]	Survival Follow-up
	Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22			
Epoch	TREATMENT									FOLLOW-UP	LONGTERM FOLLOW-UP
Clinical chemistry[m]	X[e]		X		X				X	X	
Coagulation[n]	X[e]				X				X	X	
Urinalysis[o]	X[e]				X				X	X	
Adverse events	Assess continuously[p]										
Concomitant medications/therapies	Assess continuously										
Follow-up assessments:											
Survival status										X	Every 3 months[q]
Documentation of subsequent anticancer therapy										X	Every 3 months[q]
Documentation of disease progression after subsequent anticancer therapy											Every 3 months[q]

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BSA = body surface area; CA19-9 = carbohydrate antigen 19-9; CEA = carcinoembryonic antigen; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for cancer patients; EQ-5D-5L = EuroQol-5D-5L; FA = folinic aid; FACT-C = Functional Assessment of Cancer Therapy-Colon Cancer; FOLFIRI = 5-fluorouracil/folinic acid+irinotecan; 5-FU = 5-fluorouracil; INR = international normalized ratio; IV = intravenous(ly); LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; MSI = microsatellite instability; PGIC = Patient Global Impression of Change; pH = hydrogen ion concentration; PK = pharmacokinetic(s); PT = prothrombin time; RBC = red blood cell; WBC = white blood cell; WOCBP = women of childbearing potential.

[a] If a cycle initiation (CnD1 visit) is postponed due to toxicity, corresponding safety assessments must be recorded as unscheduled visit(s) in the eCRF. Whatever the reason, the CnD1 will be the day of the treatment initiation of cycle "n". If a visit is missed within the cycle (CnD8, CnD15, CnD22), following visits should be performed according to the original schedule.

[b] To be performed at the time of study intervention discontinuation (as soon as possible and ≤14 days after the last dose of study intervention).

[c] To be performed approximately 30 days after the last dose of study intervention or before the initiation of subsequent anticancer therapy, whichever occurs first.

[d] Inclusion/exclusion criteria are to be verified before the first dose of study intervention.

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

[f] The initial 5-FU dose is given as a bolus (not to exceed 15 minutes) on Days 1 and 15, followed by continuous IV infusion over 46 to 48 hours (2 days) or according to study site standards.

[g]Tumor evaluations are to be performed every 6 weeks (±7 days) from first dose for the first 24 weeks, then every 12 weeks (±7 days) until disease progression or death, withdrawal of consent, initiation of subsequent anticancer therapy, participant is lost to follow-up or the cut-off date for final analysis is reached (whichever occurs first). If a participant discontinues study intervention for reasons other than disease progression, then tumor assessments must continue to be performed according to this schedule.

[h]The questionnaires should be completed by the participants at the beginning of the study visit before receiving any study intervention, before any other study assessment or consultation with the investigator and before being informed of their current disease status. Note: PGIC is not completed on Cycle 1 Day 1.

Procedure/Assessment (± 3-day window for procedures/assessments)	Treatment Phase									Follow-up Phase	
	Cycle 1				Subsequent Cycles[a]				End of Treatment[b]	30-Day Follow-up[c]	Survival Follow-up
	Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22			
Epoch	TREATMENT									FOLLOW-UP	LONGTERM FOLLOW-UP

[i] Electrocardiograms are to be performed in triplicate predose on Cycle 1 Day 1 (conducted within approximately 5 to 10 minutes total time), followed by a single ECG predose at remaining timepoints. Electrocardiograms should be performed before PK and biomarker blood collection at equivalent nominal timepoints.
[j] Local urine test for WOCBP only.
[k]Erythrocytes (RBC), hematocrit, hemoglobin, platelets; leukocytes (WBC) count with differential: basophils, eosinophils, lymphocytes, monocytes, neutrophils/ANC.
[l] A blood sample for hematology is to be collected on Day 15 during Cycle 2 onwards only while participants continue to receive irinotecan.
[m] ALT, albumin, alkaline phosphatase, AST, lipase, amylase, bilirubin (total and indirect), blood urea nitrogen/urea, calcium, chloride, creatine kinase, creatinine, glucose, LDH, magnesium, potassium, sodium, total protein, troponin I or T, uric acid.
[n]aPTT, INR or PT.
[o]Blood, glucose, ketones, leukocytes, pH, protein.
[p]All adverse events are collected from when the participant first provides informed consent until the 30-day safety follow-up visit.
[q]For participants who discontinue study intervention due to disease progression, the survival follow-up phase will start after the 30-day safety follow-up. For participants who discontinue study intervention for reasons other than disease progression, the survival follow-up phase will start upon disease progression or the start of another anticancer therapy. Participants will be contacted by telephone approximately every 3 months for collection of information during the survival follow-up period. This may be conducted at routine visit as well and more frequently as needed. Participants will be followed for at least 1 year after the start of study intervention of the last participantrandomized. For participants that were lost to follow-up or withdrawal of consent, attempts to determine survival status will be made via access to public records as permitted by local laws.

Table 4 : Schedule of Events post cut-off date of the final analysis

Procedure/Assessment (± 3-day window for procedures/assessments	Post cut-off date of the final analysis period					Follow-up Phase
	Cycles[a]				End of Treatment[b]	30-day Safety Follow-up[c]
	Day 1	Day 8	Day 15	Day 22		
Epoch	TREATMENT					FOLLOW-UP
Verify eligibility to continue study[d]:						
Informed consent	X					
Dosing:						
Encorafenib	X					
Cetuximab IV infusion	X	X	X	X		
Tumor evaluation (CT scan, MRI)	As per standard of care (no central review)					
Safety assessments :	**X**	**If clinically relevant**			**X**	**X**
Targeted physical examination (as clinically indicated)	X				X	X
Weight	X				X	X
Dermatological examination	X[e]				X	X
Vital signs	X				X	X
ECG	X[f]				X	X
Pregnancy test[g]	X				X	X
Hematology[h]	X				X	X
Clinical chemistry[i]	X				X	X
Coagulation[j]	X				X	X
Urinalysis[k]	X				X	X
Adverse events	Assess continuously[l]					

[a] If visit is missed theoretical cycle dates (7 days ±3) are kept constant irrespective of whether the visit is done and/or study intervention is administered. If a participant does not attend for the CnD1 visit, the CnD1 assessments must still be performed and recorded as an unscheduled visit in the eCRF.
[b] To be performed at the time of study intervention discontinuation (as soon as possible and ≤14 days after the last dose of study intervention).
[c] To be performed approximately 30 days after the last dose of study intervention or before the initiation of subsequent anticancer therapy, whichever occurs first.
[d] Inform consent to be signed before dosing.
[e] Dermatological examinations are to be performed every 8 weeks from Cycle 1 Day 1 (i.e. on Day 1 of Cycles 3, 5, 7…).
[f] Electrocardiograms are performed predose
[g] Local urine test for WOCBP only.
[h] Erythrocytes (RBC), hematocrit, hemoglobin, platelets; leukocytes (WBC) count with differential: basophils, eosinophils, lymphocytes, monocytes, neutrophils/ANC.
[i] ALT, albumin, alkaline phosphatase, AST, lipase, amylase, bilirubin (total and indirect), blood urea nitrogen/urea, calcium, chloride, creatine kinase, creatinine, glucose, , magnesium, potassium, sodium, total protein, troponin I or T,.
[j] aPTT, INR or PT.
[k] Blood, glucose, ketones, leukocytes, pH, protein.
[l] Until 30-day safety follow up visit all SAE or/and any adverse events leading to study treatment discontinuation are collected. Beyond 30 days after the last dose of study intervention, only related-SAE (SAE considers to be related to the study intervention), must be promptly notified by the investigator to the sponsor via the SAE notification form.

2. Introduction

Encorafenib is currently being developed (with or without binimetinib), in combination with cetuximab, for the treatment of adult patients with B-RAF proto-oncogene, serine/threonine kinase V600E mutant (*BRAF* V600E) metastatic colorectal cancer (mCRC), who have received prior systemic therapy.

2.1. Background

2.1.1. Colorectal Cancer

Colorectal cancer (CRC) is the third most commonly diagnosed cancer worldwide, with over 1.8 million estimated new cases affecting 1,026,000 men and 823,000 women and the second cause of death worldwide with 880,792 (approximately 484,000 men and 397,000 women) estimated deaths in 2018 according to the GLOBOCAN database [Bray 2018, Globocan 2018]. Approximately 25% of patients present with metastases and 50% eventually develop metastatic disease [Van Cutsem 2014]. The survival of CRC is significantly dependent on the stage of cancer at diagnosis.

Colorectal cancer incidence has been steadily rising worldwide within the last decades, especially in developing countries that are becoming more "westernized", including changes in lifestyle and dietary changes and especially an increasing intake of red and processed meat [Mehta 2017]. In China, the incidence is projected reach 20.7 per 100,000 in 2020 assuming the trend seen in the past decade is maintained. There was an increase in the incidence of CRC from 12.8 in 2003 to 18.0 per 100,000 in 2015 [Zhang 2019]. The mortality rate attributable to CRC increased from 5.9 in 2003 to 8.2 per 100,000 in 2015.

Uncontrolled growth is a necessary step for the development of all cancers [Downwood 2003]. In many cancers this is caused by a defect in the mitogen-activated protein kinase (MAPK) signalling pathway (also known as the rat sarcoma viral oncogene homologue (RAS)/proto-oncogene serine/threonine protein kinase [RAF]/mitogen-activated protein kinase kinase [MEK]/extracellular signal-related kinase [ERK] pathway) triggered by the activation of canonical receptor tyrosine kinases such as epidermal growth factor receptor (EGFR).

Standard therapy [NCCN 2020] in patients with unresectable mCRC includes combination regimens with cytotoxic and targeted agents. In the last decade there have been substantial advances in the treatment of mCRC due to the addition of irinotecan, oxaliplatin, the vascular endothelial growth factor (VEGF) inhibitor (i.e. bevacizumab) and the EGFR inhibitors like cetuximab to the standard treatment with 5-fluorouracil (5-FU)/folinic acid (FA).

Cetuximab is an EGFR inhibitor approved for the treatment of EGFR-expressing, rat sarcoma viral oncogene homologue wild type (*RAS* wt) mCRC in combination with chemotherapeutic agents or as a single agent, in previously untreated patients and in patients who have failed irinotecan-based

and oxaliplatin-based regimens or who are intolerant to irinotecan-based regimens (see the locally applicable cetuximab label).

Irinotecan is a topoisomerase-I inhibitor indicated as a component of first-line therapy or as a single agent following progression on an initial 5-FU-based regimen (see locally approved irinotecan label). Irinotecan combined with 5-FU and FA (FOLFIRI) administered biweekly has been shown to be more effective than when irinotecan is combined with bolus 5-FU [Fuchs 2007]. The regimen is considered one of the standard-of-care regimens in second-line mCRC.

2.1.2. BRAF Mutations

Approximately 10 to 15% of CRC tumors have B-RAF proto-oncogene, serine/threonine kinase (BRAF) mutations and over 95% of these are in BRAF exon 15 at V600E and are essentially mutually exclusive with RAS mutations [Barras 2017, Bylsma 2018, Clarke and Kopetz 2015, Davies 2002, De Roock 2010, Sorbye 2015]. These mutations lead to constitutive activation of BRAF kinase and sustained MAPK pathway signalling, resulting in increased cell proliferation and survival [Corcoran 2012], The V600E mutation provides peculiar clinical and pathological characteristics and is negatively associated with prognosis in mCRC patients, associated with a median overall survival (OS) of approximately 12 to 14 months relative to 21 to 25 months for mCRC patients with B-RAF proto-oncogene, serine/threonine kinase wild type *(BRAF* wt) tumors [Loupakis 2009, Sorbye 2015, Van Cutsem 2011], distinguishing them as a subgroup that obtains modest benefit from standard treatments [Barras 2017, Tran 2011]. A reported *BRAF* V600E mutation rate of 4.2% and an association between *BRAF* V600E mutation and more distant metastases (p=0.025) and a worse OS (3 year OS: 16.7% in the *BRAF* V600E subgroup versus 73.2% in the *BRAF* wt subgroup; p<0.001) has been shown in a retrospective study of 212 Chinese patients [Chen 2014].

Since BRAF and RAS mutations impact treatment and prognosis of mCRC patients, BRAF genetic testing is currently recommended by the National Comprehensive Cancer Network (NCCN), European Society for Medical Oncology (ESMO) and Chinese Society of Clinical Oncology (CSCO) for all patients with CRC tumors [NCCN 2020, Van Cutsem 2016, Yuan 2019].

2.1.3. Treatment Options for *BRAF* V600E Metastatic Colorectal Cancer

Until recently, there were no other approved specific treatments for the molecular subset of patients with *BRAF* V600E mCRC. The combination of encorafenib and cetuximab in *BRAF* V600E mCRC following failure of prior systemic therapy was approved in the United States (US) in April 2020 and in Europe in June 2020 (see Section 2.1.4 and Section 2.2 for further detail) but there are currently no licensed first-line treatment appliances available.

Since BRAF and RAS mutations are essentially mutually exclusive, patients with BRAF-mutant mCRC have to date typically been treated with standard-of-care regimens for *RAS* wt mCRC [Van Cutsem 2011] in the first-line setting but with substantially poorer outcomes than patients without *BRAF* wt tumors [Cremolini 2015].

In China, the treatment decision-making is usually based on the NCCN, ESMO and CSCO guidelines [Zhang 2017]. The recommended first-line regimens are dual chemotherapy (for patients suitable for intensive treatment) or monotherapy/dose-reduced dual chemotherapy (for patients not suitable for intensive treatment), with or without bevacizumab. In the first-line setting, an aggressive strategy involving triplet chemotherapy 5-fluorouracil/leucovorin+irinotecan (FOLFOXIRI) and bevacizumab has improved OS for fit patients [Cremolini 2015] and is recommended by the Pan-Asian adapted ESMO Consensus Guidelines for the treatment of "fit" patients with BRAF-mutant mCRC in the first line setting (level II, B) [Yoshino 2018].

After failure of first-line treatment, subsequent lines of treatment have minimal impact with rapidly progressive disease and shorter OS.

In a retrospective analysis of patients 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 patients with BRAF-mutant tumors was 8 weeks and 26 weeks, respectively, compared with a PFS of 26 weeks and an OS of 54 weeks in patients with BRAF wt tumors De Roock 2010. In a study evaluating 5-FU/FA/irinotecan (FOLFIRI) plus panitumumab in a pure second-line setting, patients with BRAF-mutant mCRC had a median PFS of 2.5 months and an OS of 4.7 months, compared with a PFS and an OS of 6.9 and 18.7 months, respectively, in patients with BRAFwt tumors [Peeters 2014]. Finally, in 71 patients with *BRAF* V600E mCRC treated at 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 patients 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 patients receiving ^{2n}d- or ^{3r}d-line therapy corresponded to the timing of the first restaging scan [Morris 2014] suggesting that more efficacious therapies are urgently needed. Currently, there are no agents specifically indicated for patients with *BRAF* V600E mCRC.

The use of single-agent BRAF inhibitors in *BRAF* V600E mCRC has shown limited clinical activity [Hyman 2015, Kopetz 2015], despite being clinically highly active in *BRAF* V600 melanoma [Chapman 2011, Dummer 2018a, Dummer 2018b, Flaherty 2010, Flaherty 2012, Hyman 2015, Long 2015, Long 2017] and non-small cell lung cancer [Planchard 2016]. Cancer cells with BRAF mutations are highly dependent on MEK/ERK signalling and near-complete inhibition of phospho-ERK is required for tumor responses [Corcoran 2012]. Nonclinical in vitro experiments in *BRAF* V600E CRC tumor cells have shown that BRAF inhibition causes a rapid feedback activation of EGFR, permitting sustained MAPK activation and continued proliferation [Corcoran 2012, Prahallad 2012]. Activation of EGFR can be effectively prevented by the combination of a BRAF inhibitor with an anti-EGFR agent such as cetuximab and results in greater antitumor effects than either agent alone in *BRAF* V600E CRC xenograft models [Corcoran 2012, Prahallad 2012, Yang 2012]. These reports suggest that activation of EGFR may partially explain the limited therapeutic effect of BRAF inhibitor monotherapy in patients with *BRAF* V600E mCRC and that this can be overcome with concomitant EGFR inhibition. Subsequent clinical studies confirmed that addition of an EGFR inhibitor can improve the activity of BRAF inhibitors in *BRAF* V600E CRC [Connolly 2014, Hong 2016, Tabernero 2014, Tabernero 2016, van Geel 2017].

BRAF V600E mCRC remains an aggressive disease with a poor prognosis. In order to expand the therapeutic options for patients, there is a critical need to develop new safe and effective treatment

regimens. The dependence of BRAF-mutant CRC cells on MAPK signaling provides a compelling rationale to further evaluate inhibition of BRAF and EGFR to achieve more robust inhibition of the MAPK (RAS/RAF/MEK/ERK) pathway. This, and the failure to achieve good survival outcomes through standard doublet chemotherapy agents in this population, has ignited efforts to combine multiple targeted therapies [Kopetz 2015, Prahallad 2012].

2.1.4. Encorafenib and Cetuximab Combination Therapy

Encorafenib (Braftovi®) inhibits BRAF kinase, thereby inhibiting *BRAF* V600 positive cell growth. Encorafenib is registered in combination with the MEK inhibitor binimetinib in several jurisdictions for the treatment of patients with unresectable or metastatic melanoma with a *BRAF* V600E or V600K mutation, based on results from the Phase III COLUMBUS study [Dummer 2018a, Dummer 2018b].

Initial evidence of clinical activity of the combination of encorafenib and cetuximab (referred to as the "doublet" in this protocol) in patients with *BRAF* V600 mCRC who received at least one prior treatment regimen was demonstrated by the Phase Ib/II study CLGX818X2103 [van Geel 2017], with a confirmed overall response rate (cORR) of 24%, a progression-free survival (PFS) of 4.2 months and OS of 9.3 months with a tolerable safety profile.

A pivotal Phase III multiregion study (ARRAY-818-302, the "BEACON" study [NCT02928224; Kopetz 2019]) evaluated the combination of encorafenib and cetuximab, with or without the MEK inhibitor binimetinib, versus the investigator's choice of control treatment (either irinotecan and cetuximab or FOLFIRI and cetuximab) in participants with *BRAF* V600E mCRC whose disease had progressed after one or two prior regimens in the metastatic setting. The study was designed with a safety lead-in (SLI) phase to assess the safety and tolerability of the combination of encorafenib, binimetinib and cetuximab (referred to as the "triplet") followed by a randomized (Phase III) phase during which 665 participants were assigned to receive encorafenib and cetuximab, with or without binimetinib (triplet arm; n=259 and doublet arm; n=216) or control arm (n=193). Six Japanese participants were also enrolled in a Japanese SLI phase to evaluate the triplet at the dose assessed to be tolerable in the SLI phase for non-Japanese participants. The efficacy analysis included a comparison of Asian versus non-Asian participants.

A preplanned interim analysis (data cut-off 11 February 2019) demonstrated statistically and clinically significant improvements in OS and cORR for the comparison of the triplet arm versus the control arm, meeting both primary endpoints. Secondary analyses including the key secondary analysis were also positive–- there was substantial evidence for PFS benefit of the triplet arm and OS, cORR and PFS benefit of the doublet arm compared to the control arm.

An estimated 40% reduction in risk of death was observed for the doublet arm (to be evaluated in this study) compared to the control arm. The median OS in the doublet arm was 3.0 months longer than that in the control arm, exceeding the historical standard-of-care. There was a statistically significant increase in cORR in the doublet arm compared with the control arm ($p < 0.0001$) and median PFS was 2.7 months longer.

Efficacy results for OS, cORR and PFS for the comparisons of the triplet and doublet arms versus the control arm are summarized in **Table 5.** The results for both the triplet and doublet arms were further consistent across the majority of subgroup analyses performed (based on baseline stratification factors and relevant baseline characteristics)

A more recent descriptive exploratory analysis (data cut-off 15 August 2019) confirmed clinically meaningful benefits consistent with the initial analysis. Whilst the study was not powered to compare the triplet versus the doublet arms, there was no apparent difference between the two arms across efficacy endpoints especially for OS (9.30 vs 9.26 vs 5.88 months for Doublet, Triplet and Control; HRs of 0.61 [95% CI 0.48, 0.77] for the Doublet and 0.60 [95% CI 0.47, 0.75] for the Triplet) and PFS (4.27 vs 4.47 vs 1.54 months for the Doublet, Triplet, and Control respectively) with HRs of 0.40, [95% CI: 0.31, 0.52] for the Doublet and 0.38, [95% CI: 0.29, 0.49] for the Triplet. [Kopetz 2020].

Patient-reported outcomes (PROs) were consistent with the observation of clinical benefit of the triplet and doublet arms relative to the control arm. A large benefit was observed in quality of life (QoL) by three separate instruments (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer Patients [EORTC QLQ-C30], EuroQol-5D-5L [EQ-5D-5L] and Functional Assessment of Cancer Therapy-Colon Cancer [FACT-C]) for the doublet arm over the control arm [Aaronson 1993, Rabin and de Charro 2001, Ward 1999].

Table 5: Summary of Primary Analysis of Overall Survival, Progression Free Survival and Confirmed Overall Response Rate Data in the ARRAY-818-302 Study

	Triplet Arm (N=111)	**Doublet Arm (N=113)**	**Control Arm (N=107)**
cORR (%)[b]			
% (95% CI)	26.1 (18.2, 35.3)	20.4 (13.4, 29.0)	1.9 (0.2, 6.6)
p-value versus control[c]	p<0.0001	p<0.0001	
	Triplet Arm (N=224)	**Doublet Arm (N=220)**	**Control Arm (N=221)**
OS (months)			
Median (95% CI)	9.0 (8.0-11.4)	8.4 (7.5-11.0)	5.4 (4.8-6.6)
HR (95% CI) & p-value versus control[a]	0.52 (0.39-0.70) p<0.0001	0.60 (0.45-0.79) p=0.0002	
PFS (months)			
Median (95% CI)	4.3 (4.1, 5.2)	4.2 (3.7, 5.4)	1.5 (1.5, 1.7)
HR (95% CI) & p-value versus control[a]	0.38 (0.29-0.49) p<0.0001	0.40 (0.31-0.52) p<0.0001	

Abbreviations: CI = confidence interval; cORR = confirmed overall response rate; FOLFIRI = 5-fluorouracil/folinic acid+irinotecan; HR = hazard ratio; OS = overall survival; PFS = progression free survival.

Triplet arm = encorafenib+binimetinib+cetuximab; doublet arm = encorafenib+cetuximab; control arm = irinotecan/FOLFORI+cetuximab.

Data from preplanned interim analysis (data cut-off 11 February 2019).

[a] One-sided stratified log rank.

[b] First 331 randomized participants with *BRAF* V600E tumors evaluable for efficacy.

[c] Cochran-Mantel-Haenszel test.

Common adverse events were those associated with BRAF, MEK and EGFR inhibitors, including gastrointestinal and skin toxicities. Based on achieved dose intensity and rates of treatment discontinuation, the triplet and doublet regimens were generally well tolerated with a manageable toxicity profile. The safety and tolerability profile of the doublet over the triplet appeared more favorable with less severe gastrointestinal toxicities and lower rates of reduction and interruption of encorafenib.

These results led to the approvals, both in the US and Europe, of the doublet for the treatment of *BRAF* V600E mCRC following failure of prior systemic therapy.

A Phase II clinical study (W00090GE201, the "ANCHOR" study) is also currently being conducted to investigate the triplet regimen as a first-line therapy [Grothey 2020].

Further information is provided in the Investigator's Brochure for encorafenib.

2.2. Study Rationale

Encorafenib is registered in combination with binimetinib for the treatment of adult patients with unresectable or metastatic melanoma with a *BRAF* V600 mutation in Argentina, Australia, the European Union (EU), Japan, in Switzerland and the US.

The doublet is approved in the US and Europe in *BRAF* V600E mCRC following failure of prior systemic therapy. BRAF inhibitors are currently not approved nor recommended (outside of a clinical study) in China in BRAF-mutant mCRC.

Based on the unmet medical need in China and the results from the ARRAY-818-302 study together with data from the ethnic sensitivity analysis, Pierre Fabre Médicament also wishes to submit an application for the doublet in China in patients with *BRAF* V600E mCRC whose disease has progressed after prior regimens in the metastatic setting and who are naïve to prior RAF, MEK and EGFR-inhibitor therapy, with a commitment to perform a local study.

The proposed study has therefore been designed to demonstrate consistency in treatment effect of the combination of the doublet at the same doses as in the ARRAY-818-302 study in *BRAF* V600E mCRC Chinese homeland patients to provide bridging data. The study contains a SLI phase to assess the safety and tolerability of encorafenib and cetuximab in a small number of participants prior enrolling participants in the randomized phase.

It is anticipated that the conclusions coming from the global population in the ARRAY-818-302 study can be extended to the Chinese population of patients. Overall, the doublet appeared to be two effective regimens in second and third line mCRC, demonstrating a substantial improvement in OS, cORR and PFS compared to standard regimens. The more favorable safety and tolerability profile of the doublet over the triplet makes it the preferred therapy for unselected patients with pretreated BRAF-mutant mCRC.

A large amount of data from several encorafenib clinical studies which have included Asian patients has been analyzed across indications, including mCRC. There was consistency in the

pharmacokinetics (PK), safety and efficacy data between Asians and non-Asians, in all indications tested [Internal Data]:

Encorafenib PK data in Asians show no major difference with non-Asians when analyzed within each study or when analyzed as population PK analysis.

There is no apparent ethnic difference in exposure response and dosing regimen between Asians and non-Asians.

There is no difference in safety profiles in Asians for encorafenib as a single agent (n=16 in melanoma) or in combination with cetuximab (n=25 in mCRC) compared to non-Asians.

There were consistent efficacy results comparing Asians to non-Asians.

In addition, there is no difference in the encorafenib dosing regimen between the EU, Japan or US in the approved indication of melanoma.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of encorafenib may be found in the Participant Information Sheet plus the Investigator's Brochure and Development Safety Update Report for encorafenib and the locally approved Product Information for cetuximab, irinotecan, 5-FU and FA.

2.3.1. Benefit Assessment

BRAF V600E-mutant mCRC has emerged as a distinct biologic entity, typically refractory to standard chemotherapy regimens approved for the treatment of mCRC and associated with a very poor prognosis [Ursem 2018]. The V600E mutation is the most common BRAF mutation and the risk of mortality in mCRC patients with this mutation is more than two times higher than for those with *BRAF* wt disease [Ardekani 2012]. The doublet has a proven benefit/risk, demonstrating prolonged PFS and improved ORR and OS compared to a standard regimen combining irinotecan (with or without 5-FU and FA) with an acceptable safety profile. This has led to marketing authorisations in the US and EU (see Section 2.1.4).

It is anticipated that results seen with the doublet in the ARRAY-818-302 study can be translated to Chinese patients with *BRAF* V600E mCRC.

2.3.2. Risk Assessment

The sponsor believes that the overall likelihood of differences in the safety and efficacy profile of doublet due to ethnicity differences is low and race is unlikely to be a factor significantly affecting exposure. In the ARRAY-818-302 study:

In the doublet arm the most commonly reported adverse events (incidence ≥30%) were nausea, diarrhea, dermatitis acneiform, abdominal pain and fatigue for Caucasian participants and decreased appetite, diarrhea and nausea for Asian participants. Adverse events with ≥20% difference in

incidence between Asian and Caucasian participants were myalgia (36.0% versus 13.3%) and asthenia (4.0% versus 26.5%).

In the control arm, the most commonly reported adverse events (incidence ≥30%) were diarrhea, dermatitis acneiform, vomiting, asthenia and nausea for Caucasian participants and diarrhea, dermatitis acneiform, nausea, vomiting and decreased appetite, nausea, stomatitis and neutrophil count decreased for the Asian participants. Adverse events with ≥20% difference in incidence between Asian and Caucasian participants were asthenia (8.3% versus 32.4%) and neutrophil count decreased (36.1% versus 5.4%).

As with all clinical studies, the participants are at risk of exposure to toxicities associated with the study treatments in this Phase II clinical study. Important risks and measures to mitigate these risks are summarized in Table 6. In addition, appropriate measures already used in the ARRAY-818-302 study are proposed to limit toxicities and allow participants to receive the most appropriate combination and dose(s).

Table 6: Important Risks and Mitigation Strategies in W00090GE202

Risk of Clinical Significance	Summary of Data/Rationale for Risk (Evidence linking the risk to the Study Intervention)	Mitigation Strategy
QT prolongation	QT prolongation is a class effect for BRAF inhibitors. For encorafenib, the determined IC_{50} for hERG inhibition indicates an unlikely effect of encorafenib on QT prolongation and no clinical risk is predicted for QT prolongation. Safety pharmacology results suggest encorafenib administration has the potential to result in small increases in QTc interval and mild increases in heart rate at a clinically relevant dose. Small increases in QTc interval and mild increases in heart rate were apparent in the participants receiving 300 mg encorafenib. Due to the theoretical risk of clinical complications (Torsades de Pointes, ventricular arrhythmia) due to sustained QT	Risk for QT prolongation is appropriately described in the Investigator's Brochure for encorafenib. Administration of medicinal products with a known potential to prolong QT/QTc should be avoided, where possible. Participants at high risk of QT prolongation are excluded from the study as outlined in Section 5.2.2. Monitoring and dose adjustments for QT prolongation are outlined in Appendix 10.6.1.

Risk of Clinical Significance	Summary of Data/Rationale for Risk (Evidence linking the risk to the Study Intervention)	Mitigation Strategy
	prolongation, QT prolongation class-effect is considered as potential.	
Secondary skin neoplasms: cutaneous squamous cell carcinoma and new primary melanoma	Secondary skin neoplasms including cutaneous SCC and new primary melanoma represent a known class-effect with the use of BRAF inhibitors. Cutaneous SCC and new primary melanoma have been identified as adverse drug reactions for encorafenib single agent, based on the clinical study data.	Skin neoplasm are appropriately described in the Investigator's Brochure for encorafenib. Dermatological examinations will be performed for participants receiving encorafenib (SLI phase and doublet arm of the randomized phase) to monitor for the possible development of keratoacanthoma and/or SCC and new primary melanoma, as these have been reported to occur with selective BRAF inhibitor treatment (Protocol Section 8.3.3). Early reporting of skin symptoms through careful and ongoing dermatologic monitoring throughout treatment and it is recommended that this monitoring should continue for 6 months after discontinuation of study treatment.
Non-cutaneous malignancies with RAS mutation	As for other BRAF inhibitors and based on its mechanism of action, encorafenib may promote malignancies associated with RAS mutation associated with activation of RAS through mutation or other mechanisms. No cases of non-cutaneous malignancy with RAS mutation possibly related to encorafenib were identified from the pooled safety data of the clinical development program, however due to the seriousness of this class-effect risk, non-cutaneous carcinoma is considered an important potential risk.	Routine cancer detection and treatment as well as preventive measures for different known risk factors of different cancers. Dose modifications are outlined in protocol Appendix 10.6.1.
Over-exposure due to concomitant use with strong and moderate CYP450 3A4 inhibitors	Encorafenib is primarily metabolized by CYP3A4. Based on the PK data, the use of strong CYP3A4 inhibitors was not allowed during clinical studies. Concomitant administration of encorafenib and strong or moderate CYP3A4 inhibitors may lead to increased encorafenib exposure and potential increase in toxicity.	Drug-drug interaction properties of encorafenib are appropriately described in the Investigator's Brochure for encorafenib. 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 before use of moderate CYP3A4 inhibitors (or as close as can be

Risk of Clinical Significance	Summary of Data/Rationale for Risk (Evidence linking the risk to the Study Intervention)	Mitigation Strategy
		achieved without exceeding the target dose) (Section 6.5.1.3).
Over-exposure in participants with moderate to severe hepatic impairment	Results from a dedicated clinical study indicate a 25 % higher total encorafenib exposures in participants with mild hepatic impairment (Child-Pugh Class A) compared with subjects with normal liver function. This translates into a 55% increase of the unbound encorafenib exposure. The PK of encorafenib has not been evaluated clinically in participants with moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment. As encorafenib is primarily metabolized and eliminated via the liver and based on PBPK modelling, participants with moderate to severe hepatic impairment may have greater increases in exposure than patients with mild hepatic impairment. No dosing recommendation can be made in moderate or severe hepatic impairment.	Over-exposure in participants with moderate to severe hepatic impairment is appropriately described in the Investigator's Brochure for encorafenib. Participants with impaired hepatic function, defined as Child-Pugh Class B or C should not be included the study (Protocol Section 5.2.2).
Abbreviations: BRAF = B-raf murine sarcoma viral oncogene homolog B1; CYP450 = cytochrome P450; hERG = human ether-à-go-go-related gene; IC_{50} = half maximal inhibitory concentration; PBPK = physiologically based pharmacokinetic; PK = pharmacokinetics; RAS wt = rat sarcoma viral oncogene homologue wild type; SCC = squamous cell carcinoma; SLI = safety lead-in.		

2.3.3. Overall Benefit: Risk Conclusion

The benefit to study participants in this bridging study is expected to be of the same magnitude as that observed in the ARRAY-818-302 study and no major difference in the safety and tolerability of the doublet are expected. Based on the ethnicity analysis, available data and the limitations inherent to the size of the Asian population, no dose adjustment is recommended/required for participants based on race.

A review of the available safety data from post marketing experience and clinical studies has not changed the benefit/risk profile of encorafenib, which remains favourable when used in its approved indications and in accordance with the prescribing information. A review of individual case safety reports originating from Asian participants has shown that the pattern of adverse events related to study intervention grouped using the Medical Dictionary for Regulatory Activities (MedDRA) is generally consistent with the global population.

Taking into account the measures taken to minimize risk to participants in this study, the potential risks identified in association with the study intervention are justified by the anticipated benefits that may be afforded to participants with *BRAF* V600E mCRC.

3. Objectives and Endpoints

Objectives and endpoints are correlated in Table 7 for the SLI phase. Objectives, endpoints and estimands are provided in Table 8 for the randomized phase.

Table 7: Objectives and Endpoints in the SLI Phase

SLI		
	Estimands	
Objectives	**Endpoints**	**Other attributes**
Primary		
To assess the safety and tolerability of the doublet	Incidence of DLTs during the DLT-evaluation period (which is the first 28 days after the first dose of study intervention in the SLI). DLTs are defined in Section 4.1.3	**Population**: all participants with either a local or a central laboratory confirmed result of BRAF V600E-mutant mCRC, as defined by the screening inclusion/exclusion criteria in Section 5.1.1 and Section 5.1.2 which corresponds to the target population of the SLI part of the study. **Intercurrent events**: hypothetical strategy will be applied for the intercurrent events. The intercurrent event is treatment discontinuation for reasons other than treatment-related toxicity that leads to < 75% of the planned dose of each study intervention during the DLT evaluation period. Participants without DLTs and with the intercurrent event will not be included in the DLT rate calculation. **Population-level summary measure**: DLT rate defined as the number of DLT-evaluable participants with DLTs in the DLT-evaluation period divided by the number of DLT-evaluable participants.
Secondary		
To assess the overall safety and tolerability profile of the doublet	Type and severity of AEs and SAEs according to NCI CTCAE Version 4.03, changes in physical examinations, vital signs, ECGs, clinical safety laboratory assessment values; dermatological examinations and performance status using the ECOG performance status scale. Incidence of dose interruptions, dose modifications and discontinuations due to AEs.	NA

SLI		
	Estimands	
Objectives	**Endpoints**	**Other attributes**
To provide preliminary PK data of the doublet.	Plasma concentrations Encorafenib and serum concentrations of cetuximab on Day 1 of Cycles 1 and 2 and derived PK parameters (e.g. AUC, Cmin, Cmax) in Chinese participants.	NA
To provide preliminary antitumor activity data of the doublet as measured by ORR and DOR	ORR, defined as the proportion of participants with a best overall best response of either CR or PR as determined by BICR and investigator assessment per RECIST Version 1.1. DOR, defined as the time from first documented response (CR or PR) to the earliest date of disease progression as determined by BICR and investigator assessment per RECIST Version 1.1, or death due to underlying disease.	NA
Exploratory		
CCI		

Table 8: Objectives and Endpoints in the Randomized (Phase II)

Randomized Phase 2		
	Estimands	
Objectives	**Endpoints**	**Other attributes**
Primary		
To compare the doublet versus the control as measured by PFS assessed by BICR.	PFS by BICR, defined as the time from the date of randomization to the earliest documented disease progression as determined by BICR assessment per RECIST v1.1, or death due to any cause.	**Population**: all participants with either a local or a central laboratory confirmed result of BRAF V600E-mutant mCRC, as defined by the screening inclusion/exclusion criteria in Section 5.1.1 and Section 5.1.2 which corresponds to the target population of the Phase 2 part of the study. **Intercurrent events**: hypothetical strategy will be applied for the new anticancer therapy and for more than two missing assessments. Treatment policy will be applied for tolerability and duration of study treatment. Details of the intercurrent events and censoring rules for the primary analysis are summarized in section 9 **Population-level summary measure**: hazard ratio for PFS and corresponding 2-sided CI based on Cox proportional hazard model stratified by at baseline and. PFS will be compared between the two treatment arms using a 1-sided stratified log-rank test.
Secondary		
To compare the efficacy of the doublet versus the control respect to: • PFS by investigator assessment • Overall response rate (ORR) • Duration of response (DOR) • Disease control rate (DCR)	• PFS as defined as the interval of time between the date of randomization to the earliest date of disease progression, as determined by investigator assessment per RECIST v1.1, or death due to any cause. • ORR (for confirmed and unconfirmed responses) defined as the proportion of participants with a confirmed (resp. unconfirmed) best overall response of either CR or PR, as	NA

Randomized Phase 2		
	Estimands	
Objectives	**Endpoints**	**Other attributes**
• Time to Response (TTR) • Overall Survival (OS)	determined by BICR and investigator assessment per RECIST v1.1. • DOR, defined as the time from the date of the first documented response (CR or PR) to the earliest date of disease progression, as determined by BICR and investigator assessment per RECIST v1.1, or death due to any cause • DCR, defined as the proportion of participants with a best overall response of either CR, PR or SD, as determined by BICR and investigator assessment per RECIST v1.1 • TTR (for confirmed and unconfirmed responses) is defined as the time between date of randomization until first documented response of CR or PR. • OS is defined as time from randomization until date of death due to any cause	
To characterize the safety and tolerability of the doublet	Type and severity of adverse events and SAEs according to NCI CTCAE Version 4.03, changes in physical examinations, vital signs, ECGs, clinical safety laboratory assessment values, dermatological examinations and performance status using the ECOG performance status scale.	NA

Randomized Phase 2		
	Estimands	
Objectives	**Endpoints**	**Other attributes**
To assess the effect of the doublet on QoL.	Change from baseline in the EORTC QLQ-C30, EQ-5D-5L, FACT-C and PGIC questionnaire scores.	NA
To characterize the PK of the doublet in this population.	Plasma concentrations encorafenib and serum concentrations of cetuximab on Day 1 of Cycles 1 and 2 and derived PK parameters (e.g. AUC, Cmin, Cmax; 15 participants with serial sampling only) in Chinese participants. Population PK analysis using the ARRAY-818-302 study PK data.	NA
Exploratory		
CCI		

Randomized Phase 2		
	Estimands	
Objectives	Endpoints	Other attributes
CCI [redacted]		

The study population is defined in Section 5. Intercurrent events are detailed in Section 6.5.2 (prohibited medications), Section 7.1 (study intervention discontinuation) and Section 7.2 (study discontinuation). Estimands are described in more detail in Section 9.4.1.

4. Study Design

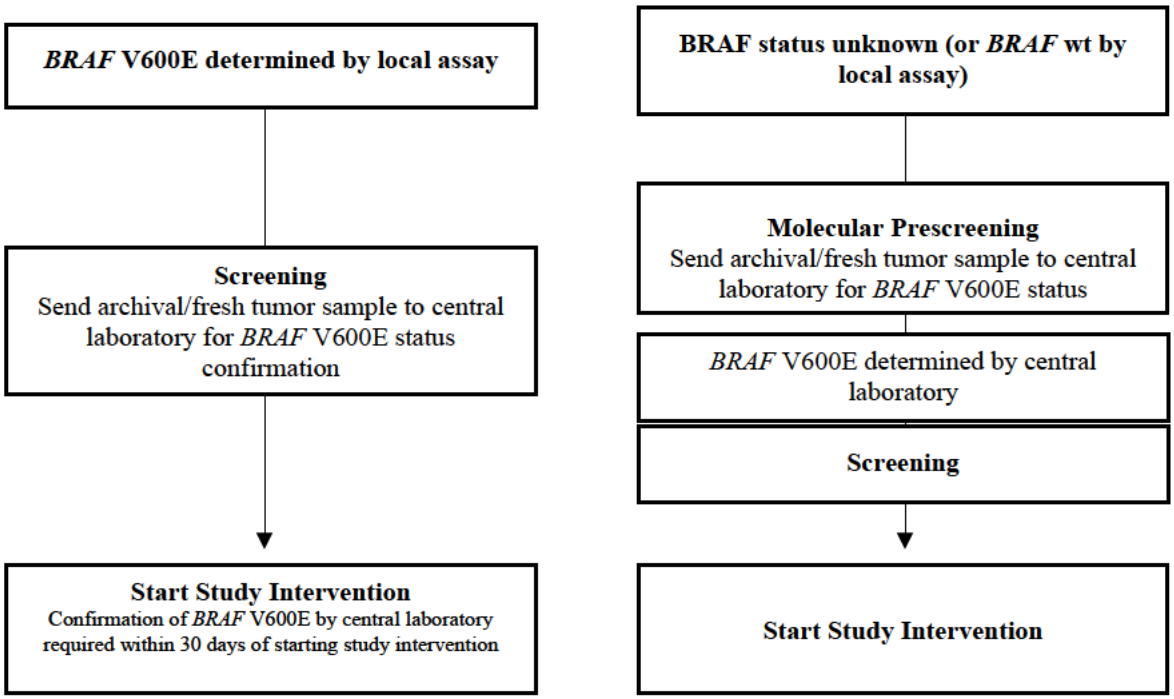
4.1. Overall Design

4.1.1. Study Design Overview

This is a Phase II, multicenter, randomized, open-label, parallel group, two-arm bridging study with a SLI phase to evaluate the doublet versus irinotecan and cetuximab or FOLFIRI and cetuximab in Chinese participants with *BRAF* V600E mCRC whose disease has progressed after one or two prior regimens in the metastatic setting.

Participants will be eligible for the study based on identification of a *BRAF* V600E mutation in the tumor as determined by a local assay result obtained any time before screening or by the central laboratory as part of molecular prescreening. If the participant is enrolled based on local assay results, the BRAF V600E status must be confirmed by the central laboratory no later than 30 days from first dose of study intervention (see Figure 2). Full details are provided in Section 8.1.1.

Figure 2: Identification of *BRAF* V600E Mutation



Abbreviations: *BRAF* V600E = B-RAF proto-oncogene serine/threonine kinase V600E mutant; *BRAF* wt =BRAF wild type.

The study scheme is shown in Figure 1. The study contains a SLI phase to assess the safety and tolerability of the doublet prior enrolling participants in the randomized (Phase II) phase:

SLI phase: The SLI phase will be conducted at a limited number of study sites. A total of nine evaluable participants will be assigned to treatment on a rolling basis in a single cohort. All nine participants will receive 28-day cycles of encorafenib once daily (QD) and cetuximab once weekly, see Section 6.1.

Dose-limiting toxicities (DLTs) will be evaluated across the first cycle of therapy and the tolerability of the doublet will be assessed by the sponsor or sponsor representative and the investigator by regular communication.

An independent Data Monitoring Committee (DMC) will review both the DLTs and cumulative toxicity at two timepoint:

- At the time the first three patients of the SLI have completed the first cycle.
- at the time the last patient of the SLI has completed the first cycle.

The randomized phase of the study will start as soon as the last participant recruited has completed at least one full cycle (28 days) of treatment and following a tolerability assessment by an independent Data Monitoring Committee (DMC) (see Section 9.6).

Due to early recruitment faster than expected, the screening/enrolment have been put on hold while the first 3 patients were under treatment in the SLI phase and an ad-hoc independent DMC was performed to ensure the safety and the tolerability of patients.

Further details are provided in Section 4.1.3.

Randomized (Phase II) phase: Eligible participants will be randomized in a 2:1 ratio to the doublet arm or control arm, respectively:

Doublet arm: 63 participants will receive encorafenib QD and cetuximab once weekly in 28-day cycles (see Section 6.1).

Control arm: 31 participants will receive either irinotecan and cetuximab or FOLFIRI and cetuximab (at the investigator's discretion) in 28-day cycles. Irinotecan or FOLFIRI will be given every 2 weeks and cetuximab once weekly (see Section 6.1). The choice of irinotecan or FOLFIRI must be declared before randomization.

Randomization will be stratified by baseline Eastern Cooperative Oncology Group (ECOG) performance status (0 versus 1) and prior use of irinotecan (yes versus no).

The independent DMC will review the available safety information after the first 15 participants in the randomized phase of the study treated with the doublet have completed at least one cycle of treatment to confirm tolerability and then will be responsible for reviewing safety data at regular intervals (every 6 months).

4.1.2. Study Procedures and Assessments

Participants without a locally available *BRAF* V600E result may undergo molecular tumor prescreening with the central laboratory BRAF mutation assay at any time before screening as long as they meet all the molecular prescreening inclusion/exclusion criteria (see Section 5.1.1 and Section 5.2.1). For patients with a locally available BRAF V600E result, a representative tumor specimen (primary or metastatic, archival or newly obtained) will be provided for central BRAF testing.

Participants will be screened for eligibility in the 28 days before the start of study intervention.

Eligible participants will enter the treatment phase made up of weekly clinic visits. Study intervention will be administered until death, disease progression[1] or one of the other predefined criteria for study intervention discontinuation is met (see Section 7.1).

An end of treatment visit will be completed at the time of study intervention discontinuation (as soon as possible and ≤14 days after the last dose of study intervention).

There will be a follow-up period after the end of treatment. A safety follow-up visit will be performed approximately 30 days after the last dose of study intervention or before the initiation of subsequent anticancer therapy, whichever occurs first. Participants will then enter survival follow-up and will be followed for subsequent anticancer therapies, disease progression following the initiation of subsequent therapies and survival status every 3 months (or more frequently as needed) until death, one of the other criteria for participant discontinuation from the study (see Section 7.2), the participant is lost to follow-up (see Section 7.3) or the cut-off date for final analysis is reached (see Section 4.4).

For participants who definitely discontinue study intervention due to disease progression, survival follow-up will start after the 30-day safety follow-up.

For participants who definitely discontinue study intervention for reasons other than disease progression, survival follow-up will start upon disease progression or the start of another anticancer therapy.

Tumor assessments by radiological imaging (e.g. computed tomography [CT], magnetic resonance imaging [MRI], X-ray, different methods of whole-body bone scans) will be performed at baseline (within 28 days of the first dose in the SLI phase or within 28 days of randomization for the randomized phase), every 6 weeks (±7 days) for the first 24 weeks, then every 12 weeks (±7 days) thereafter until disease progression[1] or death, withdrawal of consent, initiation of subsequent anticancer therapy, participant is lost to follow-up or the cut-off date for final analysis is reached (whichever occurs first). After cut-off date for final analysis, tumor assessment will be done in accordance with local clinical practice. Tumor response will be determined locally by the investigator and by blinded (to treatment received) independent central review (BICR) using Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1.

[1] In special circumstances, continuation of treatment beyond disease progression may be allowed (see Section 6.1).

Patient-reported outcomes will be assessed using the EORTC QLQ-C30, EQ-5D-5L and FACT-C questionnaires and Patient Global Impression of Change (PGIC) until the cut-off date for final analysis is reached.

Safety assessments include recording of adverse events and concomitant medications, physical examinations, dermatological assessments, clinical safety laboratory assessments (including pregnancy testing for women of childbearing potential [WOCBP]), vital signs, electrocardiograms (ECGs), cardiac function tests (where required) and ECOG performance status.

After Final analysis cut-off date, safety assessments include recording of all serious AE until 30 days after study intervention discontinuation and any AE leading to study intervention discontinuation, physical examinations (where required), dermatological assessments, clinical safety laboratory assessments (including pregnancy testing for women of childbearing potential [WOCBP]), vital signs, electrocardiograms (ECGs), cardiac function tests (where required).

Blood samples for characterization of the PK of encorafenib and cetuximab will be collected on the first day of treatment (Cycle 1 Day 1) and at steady state after 1 month treatment (Cycle 2 Day 1) Serial blood samples will be collected from a subset of 24 participants treated at the recommended dose at selected sites (all nine participants in the SLI phase and the first 15 participants at the selected sites in the doublet arm of the randomized phase). Sparse sampling will be performed in all remaining participants in the doublet arm. CCI [redacted] The *BRAF* V600E, *RAS* wt status and deoxyribonucleic acid (DNA) mismatch repair (dMMR) system/MSI-High status of all participant's tumors will be confirmed centrally.

The schedule of activities for molecular prescreening and screening for all participants is shown in Table 1. The schedule of activities for the treatment and follow-up phases is shown in Table 2 for the SLI phase and the doublet arm of the randomized phase until cut-off date of the final analysis, in Table 3 for the control arm of the randomized phase until cut-off date of the final analysis and in Table 4 for the doublet arm of the randomized phase post cut-off date of the final analysis.

4.1.3. Assessment of Tolerability in Safety Lead-in Phase

Participants in the SLI phase will be assessed for DLTs during the first cycle of treatment with the doublet. A DLT is defined as any adverse event or abnormal laboratory value assessed as unrelated to disease, disease progression, intercurrent illness or concomitant medications/therapies resulting in the inability to tolerate at least 75% relative dose intensity [(administered dose in mg/planned dose in mg) x 100] of encorafenib or cetuximab occurring within the first 28 days of study intervention (Cycle 1) that satisfies at least one of the criteria listed in Table 9.

Table 9:Criteria for Defining Dose Limiting Toxicities

Cardiac disorders • Supraventricular tachycardia–- includes, but not limited to, extrasystoles and sinus tachycardia Grade ≥3.
General disorders and administration site conditions • Fatigue Grade 3 for >14 consecutive days.
Respiratory disorders • Interstitial lung disease/pneumonitis Grade ≥2.
Skin and subcutaneous tissue disorders • Rash, HFSR or photosensitivity Grade 3 for >14 consecutive days despite maximal skin toxicity treatment (according to local practice). • Rash, HFSR or photosensitivity Grade 4.
Gastrointestinal disorders • Diarrhea Grade 3 for ≥48 hours despite optimal use of antidiarrheal therapy. • Diarrhea Grade 4. • Nausea/vomiting Grade 3 for ≥48 hours despite optimal use of antiemetic therapy. • Nausea/vomiting Grade 4.
Investigations • Total bilirubin increase Grade ≥3. • AST or ALT increase Grade ≥3 in conjunction with total bilirubin increase Grade ≥2 of any duration. • AST or ALT increase Grade 3 for >7 consecutive days. • AST or ALT increase Grade 4. • Serum creatinine increase Grade ≥3. • ANC decrease Grade 4 for >7 consecutive days. • Platelet count decrease Grade 3 with signs of clinically significant bleeding. • Platelet count decrease Grade 4. • ECG QTcF prolonged ≥Grade 3.
Eye disorders **Uveitis** Grade 3 for >21 consecutive days confirmed by ophthalmologic examination. Grade 4 confirmed by ophthalmologic examination
Eye disorders –Visual disturbances without ocular (retinal) changes • Blurred vision, flashing lights, floaters: Grade ≥3.
Eye disorders – (other specify) • Grade 3 for >21 consecutive days. • Grade 4 confirmed by ophthalmic examination.
Other hematologic and non-hematologic toxicities0 Any other Grade ≥3 adverse event except lymphocyte count decreased (lymphopenia) Grade ≥3 unless clinically significant.

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; DLT = dose-limiting toxicities; ECG = electrocardiogram; HFSR = hand-foot skin reaction; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; QTcF = QT interval corrected for heart rate using Fridericia's formula.

Grades according to NCI CTCAE grading system.

QTcF must be prolonged on two separate ECGs.

Isolated laboratory changes (e.g. alkaline phosphatase, cholesterol, lipase, serum amylase) or those due to sampling or laboratory errors without associated clinical signs or symptoms may be determined to not be DLTs upon review and agreement by the investigator and sponsor's medical monitor.

A total of nine participants will be assigned to treatment in the SLI phase on a rolling basis in a single cohort. To be evaluable for tolerability assessment by the independent DMC prior to the randomized phase of the study, participants must:

Experienced an event meeting the DLT criteria or

Received ≥75% relative dose intensity [(administered dose in mg/planned dose in mg) x 100] of each of the two drugs (encorafenib and cetuximab) during Cycle 1.

Non-evaluable participants will be replaced in order to achieve nine evaluable participants in the SLI phase.

Enrollment will be put on hold if at least three participants experience DLTs until a discussion with the independent DMC can occur.

If DLTs are observed in less than three of nine evaluable participants, the independent DMC will review data after the ninth participant has been followed for at least one 28-day cycle (Cycle 1). All data available at the time of review will be included (as these participants will be enrolled over time, the independent DMC will have cumulative data available beyond the first 28 days on some participants). If the independent DMC determines the doses to be tolerable in the first nine evaluable participants based on observing DLTs in <33% participants and evaluation of the overall toxicity profile, the study will proceed to the randomized phase. The independent DMC will make a recommendation if the doses are not deemed tolerable.

4.2. Scientific Rationale for Study Design

This is a bridging study to evaluate the doublet in Chinese participants with *BRAF* V600E mCRC whose disease has progressed after one or two prior regimens in the metastatic setting.

The study has been designed to confirm that the conclusions from the doublet arm of the randomized (Phase III) phase of the ARRAY-818-302 study remain applicable in a Chinese population. The eligibility criteria described in this study protocol are designed to identify participants for whom study intervention is considered appropriate and to provide a comparable population to the ARRAY-818-302 study. Disease epidemiology in the Chinese population is similar to that in other Asian populations assessed in prior studies (see Section 2.2). Based on available data with encorafenib, no pertinent difference has been observed with respect to PK, safety and efficacy in Asian patients compared to Caucasian patients.

Several lines of evidence suggest that *BRAF* V600E mCRC is a distinct histological subtype associated with a unique clinical phenotype. The predominant BRAF mutations in CRC affect V600E and result in a constitutively active BRAF protein. BRAF and RAS mutation status will be assessed at baseline according to current recommendations for genotyping (NCCN 2020), Van Cutsem 2016, Yuan 2019] on formalin-fixed and paraffin embedded (FFPE) tissue. As time to treatment initiation is critical for untreated *BRAF* V600E mCRC patients, participants may be assigned to treatment using local laboratory assessment of *BRAF* V600E status. Lack of *BRAF* V600E confirmation by the central laboratory may be due to discordance between the local assay and central laboratory results (potential false positive local assay results) or due to inadequate or poor sample condition for central testing (indeterminate results). If at any time there is lack of *BRAF* V600E confirmation by the central laboratory in a total of 10 participants (10% of the total planned) or discordance between the local assay and the central laboratory in five participants (5% of the total planned), all subsequent participants will only be assigned to treatment using central laboratory results to minimize the number of participants without *BRAF* V600E mCRC who would be exposed to study intervention.

Since the safety of the combination of encorafenib and cetuximab has not been previously tested in Chinese participants, the study includes a SLI phase to evaluate the tolerability of the doublet in a small group of nine participants first. The SLI phase will be conducted at a limited number of sites where safety will be assessed carefully through regular visits and assessments. Dose limiting toxicities will be evaluated and an independent DMC will assess the tolerability prior to the randomized (Phase II) phase in a larger number of participants.

The randomized phase of the study has a two-arm, active comparator-controlled design to compare the efficacy and safety of the doublet to a standard regimen combining irinotecan (with or without 5-FU and FA) and cetuximab.

The study will involve a 2:1 ratio randomization of participants, respectively, to the encorafenib and cetuximab doublet combination intervention arm and the control arm with the standard regimen combining irinotecan (with or without 5-FU and FA) and cetuximab. As this is a bridging study, the unequal randomization in a 2:1 manner will allow a more efficient study. The principle behind this approach is that it minimizes the number of control participants who are exposed to the control treatment while both maintaining the benefit/risk as well as ensuring the number of pre-specified events will occur to adequately power this study [Avins 1998].

The choice of whether to treat with FOLFIRI or irinotecan in the control arm will be at the discretion of the investigator. The combination of irinotecan and cetuximab is one of the options recommended by the NCCN for patients who have previously received irinotecan-based or oxaliplatin-based combination regimens and its use in this setting is consistent with current labelling of cetuximab. The use of FOLFIRI is consistent with ESMO guidelines which recommend the use of cytotoxic doublets containing 5-FU with an EGFR inhibitor in patients with *RAS* wt mCRC whose disease has progressed on one prior regimen Van Cutsem 2014]. In addition to the ARRAY-818-302 study, it has been used in the control arm of several other Phase III studies in the pure second-line Peeters 2014, Tabernero 2015, Van Cutsem 2015]. In one of the few head-to-head comparisons of irinotecan and FOLFIRI found in the literature, mCRC patients without specific molecular characterization of their disease, the treatment groups did not differ significantly in overall QoL

changes, response rate or PFS. The authors reported these findings to be consistent with a metanalysis [Clarke 2011].

The randomized phase of the study is open-label due to the study intervention in each arm (two oral and three intravenous [IV] therapies) and the different patterns of adverse events expected. The measures described in Section 6.3 will be implemented to minimize bias.

The investigational and comparator treatments administered in the study (see Section 6.1 for a description of study intervention and Section 4.3 for dose justification) reflect those in the doublet and control arms of the ARRAY-818-302 study. The more favorable safety and tolerability profile of the doublet over the triplet regimen in this study (see Section 2.1.4) makes it the preferred therapy for participants with pretreated BRAF-mutant mCRC.

The schedule of assessments performed, and outcome measures assessed also reflect those in the ARRAY-818-302 study:

Tumor response will be assessed by radiologic imaging using RECIST Version 1.1 to allow a full assessment of the extent of disease at baseline and for subsequent assessment of progression of existing lesions or the appearance of new ones. A central review will be performed to limit the potential for bias in assessing response. Tumor responses will be confirmed by repeat assessment (not earlier than 4 weeks from the one the response is first observed) to avoid overestimating the response rate observed.

The primary efficacy endpoint, PFS as assessed by BICR, is deemed appropriate for a bridging study.

Overall survival is a universally accepted direct measure of benefit that will be easily and precisely measured by documenting the date of death.

The QLQ-C30, FACT-C and EQ-5D-5L are widely used, well-characterized and valid measures in the treatment of cancer patients. These questionnaires will be used to explore PRO measures of health-related QoL, functioning, cancer symptoms and treatment-related side effects. The PGIC is a scale often used to anchor and characterize PRO findings [Aaronson 1993, Coon and Cappelleri 2016, Mesa 2013, Rabin and de Charro 2001].

Pharmacokinetics and exposure will be explored as no comprehensive data are available with the doublet in Chinese participants.

CCI

[redacted]

CCI [redacted]

Dermatological evaluations will be performed to monitor for the possible development of keratoacanthoma and/or squamous cell carcinoma based on experience in prior clinical studies with encorafenib and other selective BRAF inhibitors. Dermatologist examination and/or dermatologic biopsy will also be performed if clinically indicated.

Routine monitoring of adverse events, physical examinations, clinical laboratory safety evaluations, pregnancy tests, vital signs and ECGs will be performed for all participants. The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.03 [NCI CTCAE 2010], a standardized classification of adverse effects of drugs used in cancer therapy, will be used as an assessment of severity, where applicable.

4.3. Justification for Dose

The doses, timing of dosing and route of administration of study intervention are the same as in the ARRAY-818-302 study to generate bridging data. The observed safety profile of the doublet in this study was generally consistent with prior reported experience and with known effects of BRAF and EGFR inhibitors.

The dose of encorafenib is 300 mg per oral (PO) QD, corresponding to its single agent recommended Phase II dose (RP2D). This dose has also been shown in clinical studies to result in tumor regression and clinical responses as a single agent [Dummer 2013, Gomez-Roca 2014].

In combination with cetuximab dosed as per its approved label (400 mg/m^2 followed by 250 mg/m^2 IV QW) encorafenib 300 mg QD has demonstrated its effectiveness and an acceptable safety profile with manageable toxicities in the pivotal Phase III Study ARRAY-818-302. [Kopetz 2020]. Pharmacokinetic data from Asian patients who have been exposed to encorafenib do not suggest any ethnic differences across different population and indicate that specific dose adjustments for individual ethnic populations are not required. Data from the 818-302 study did not reveal any ethnic differences that impacted on the safety and efficacy of the doublet.

Cetuximab, irinotecan, FA and 5-FU are administered according to the Chinese-approved Product Information.

Permitted dose modifications are detailed in Section 6.6.

4.4. End of Study Definition

The end of the study is defined as the timepoint when the last participant has reached the 30-day safety follow-up visit and when the cut-off date for the final analysis has been reached (whichever occurs last).

Final analysis cut-off date is the timepoint when all participants have been followed for at least 1 year after the start of study intervention of the last participant randomized and when 70% of the expected deaths in the randomized phase are recorded (whichever occurs last).

5. Study Population

It is planned to treat a total of 103 Chinese homeland participants with *BRAF* V600E mCRC whose disease has progressed after one or two prior regimens in the metastatic setting. The sample size rationale is provided in Section 9.2.

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

Each participant fulfilling all inclusion criteria and none of the exclusion criteria will be eligible. Molecular prescreening will be performed at any time before screening in participants whose *BRAF* V600E status is unknown (or is *BRAF* wt by local assay). Molecular prescreening is not required in participants whose *BRAF* V600E status is known or is identified by local assessment at any time before screening.

5.1. Inclusion Criteria

5.1.1. Inclusion Criteria for Molecular Prescreening

All the following inclusion criteria must be met for a participant to be eligible to undergo molecular tumor prescreening:

1. Provide a signed and dated molecular prescreening informed consent document.

   Note: See Appendix 10.1.4

2. Chinese male or female participant with age ≥18 years at the time of informed consent.
3. Histologically- or cytologically-confirmed CRC that is metastatic.
4. Eligible to receive cetuximab per Chinese-approved label with regard to tumor *RAS* mutation status (i.e. approved for *RAS* wt status).
5. Able to provide a sufficient amount of representative tumor specimen for central prospective laboratory testing of *BRAF* mutation status and also retrospective *RAS* wt status and MSI testing.
   i. *Note: Representative tumor specimen: primary or metastatic, archival or newly obtained.*
   ii. *BRAF mutation status see Section 8.1.1.*

5.1.2. Inclusion Criteria (Treatment Period)

1. All the following inclusion criteria must be met for a participant to be eligible for this study: Provide a signed and dated screening informed consent document.

   Note: See Appendix 10.1.4.

2. Chinese male or female participant with age ≥18 years 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 a *BRAF* V600E mutation in tumor tissue previously determined by a local assay at any time before screening or by the central laboratory.

   Note: See Section 8.1.1.

5. Able to provide a sufficient amount of representative tumor for central prospective confirmatory laboratory testing of *BRA*F mutation status and also retrospective *RAS* wt status and MSI testing, as well as for comparison between central prospective laboratory testing of BRAF V600E mutation and a candidate companion diagnostic.

   Note:

   i. Representative tumor specimen: primary or metastatic, archival or newly obtained.

   ii. BRAF mutation status see Section 8.1.1.

6. Eligible to receive cetuximab per Chinese-approved label with regards to tumor *RAS* mutation status. i.e. approved for *RAS* wt status.
7. Progression of disease after one or two prior regimens in the metastatic setting.

   Note :

   i. For disease relapsed during treatment or within 6 months following adjuvant therapy, the corresponding therapy will be considered metastatic disease.

   ii. Maintenance therapy given in the metastatic setting will not be considered as a separate regimen.

8. Evidence of measurable disease according to RECIST Version 1.1.

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

9. ECOG performance status 0 or 1.
10. Adequate bone marrow function at screening and baseline characterized by the following:

    a. Absolute neutrophil count ≥1.5×10^9/L.

    b. Platelets ≥100×10^9/L.

    c. Hemoglobin ≥9.0 g/dL. Transfusion will be permitted provided the participant has not received more than two units of red blood cells in the prior 4 weeks to achieve this.

11. Adequate renal function at screening and baseline:
    a. Serum creatinine ≤1.5 × upper limit of normal (ULN) or
    b. Calculated creatinine clearance ≥50 mL/min by Cockcroft-Gault formula.
12. Adequate electrolytes at screening and baseline, defined as serum potassium and magnesium levels within institutional normal limits.

    Note: Replacement treatment to achieve adequate electrolytes is allowed.
13. Adequate hepatic function at screening and baseline characterized by the following:
    a. Serum total bilirubin ≤1.5 × ULN and <2 mg/dL.

       Note: Total bilirubin >1.5 × ULN and ≥2 mg/dL *is allowed if indirect bilirubin is ≤1.5 × ULN.*
    b. Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) ≤2.5 × ULN or ≤5 × ULN in the presence of liver metastases.
14. Mean triplicate QT interval corrected for heart rate according to Fridericia's formula (QTcF) value ≤480 msec at screening.
15. Participant able to take oral medications.
16. Willing and able to comply with scheduled visits, treatment plan, laboratory tests and other study procedures.
17. Female participants 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.

    Note: See *Section 5.3.1, Appendix 10.2.1 and Appendix 10.2.2.*
18. Male participants must agree to take appropriate precautions to avoid fathering a child.

    Note: See Section 5.3.1 and Appendix 10.2.2.

5.2. Exclusion Criteria

5.2.1. Exclusion Criteria for Molecular Prescreening

Participants meeting any of the following criteria are not eligible to undergo molecular tumor prescreening:

1. Prior anti-EGFR treatment
2. More than two prior regimens in the metastatic setting.

   Note:

   i. For disease relapsed during treatment or within 6 months following adjuvant therapy, the corresponding therapy will be considered metastatic disease.

ii. Maintenance therapy given in the metastatic setting will not be considered as a separate regimen.

3. Known contraindication to receive cetuximab or irinotecan at the planned dose according to the most recent cetuximab and irinotecan local label.

4. Known history of Gilbert's syndrome or is known to have any of the following genotypes: uridine 5'-diphospho-glucuronosyltransferase (UGT)1A1*6/*6, UGT1A1*28/*28 or UGT1A1*6/*28.

Note: Does not apply to participants enrolled in the SLI phase of the study.

5. Leptomeningeal disease.

6. Known history of acute or chronic pancreatitis within 6 months before the start of the study intervention.

7. History of chronic inflammatory bowel disease or Crohn's disease requiring medical intervention ≤12 months prior to the start of study intervention.

Note: Medical intervention like immunomodulatory or immunosuppressive medications or surgery.

8. Known history of a positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS). Testing for HIV must be performed at sites where mandated locally.

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

5.2.2. Exclusion Criteria (Treatment Period)

1. Prior treatment with any RAF inhibitor, cetuximab, panitumumab or other EGFR inhibitors.

2. Symptomatic brain metastasis.

Note: Participants 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 MRI or CT demonstrating no current evidence of progressive brain metastases at screening).

3. Leptomeningeal disease.

4. Use of any herbal medications/supplements or any medications or foods that are moderate or strong inhibitors or inducers of cytochrome P450 (CYP)3A4/5 ≤1 week before the start of study intervention.

Notes:

i. Of which, herbal medication including use of St. John's Wort (hypericum perforatum) and traditional Chinese medicine known to be a moderate or strong inhibitor or inducer of CYP3A4/5.

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

5. Known history of acute or chronic pancreatitis within 6 months before the start of study intervention.

6. History of chronic inflammatory bowel disease or Crohn's disease requiring medical intervention ≤12 months prior to the start of study intervention.

Note: Medical intervention like immunomodulatory or immunosuppressive medications or surgery.

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

a. History of acute myocardial infarction, acute coronary syndromes (including unstable angina, coronary artery bypass grafting, coronary angioplasty or stenting) ≤6 months prior to the start of study intervention.

b. Symptomatic congestive heart failure (i.e. New York Heart Association Grade 3 or higher).

c. History or current evidence of clinically significant arrhythmia and/or conduction abnormality ≤6 months before start of study intervention, except atrial fibrillation and paroxysmal supraventricular tachycardia.

8. Uncontrolled severe hypertension defined as persistent elevation of systolic blood pressure ≥150 mmHg or diastolic blood pressure ≥100 mmHg despite current therapy.

9. Impaired hepatic function, defined as Child-Pugh Class B or C.

10. Known history of Gilbert's syndrome or is known to have any of the following genotypes: UGT1A1*6/*6, UGT1A1*28/*28 or UGT1A1*6/*28.

Note: Does not apply to participants enrolled in the SLI phase of the study.

11. Impaired gastrointestinal function or disease which may significantly alter the absorption of encorafenib.

Note: e.g. ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection.

12. Previous or concurrent malignancy* within 5 years of study entry or other non-invasive or indolent malignancy without sponsor approval.

Note:

**Except cured basal or squamous cell skin cancer, superficial bladder cancer, prostate intraepithelial neoplasm, carcinoma in-situ of the cervix.*

13. History of thromboembolic* or cerebrovascular events** ≤6 months before starting study intervention.

Note:

**Except venous thrombosis related to indwelling catheter and treated with low grade anticoagulants.*

***Including transient ischemic attacks, cerebrovascular accidents, deep vein thrombosis or pulmonary embolism.*

14. Residual NCI CTCAE ≥Grade 2 toxicity from any prior anticancer therapy, except for Grade 2 alopecia or Grade 2 neuropathy.

15. Known history of a positive test for HIV or known AIDS. Testing for HIV must be performed at sites where mandated locally.

16. Participants with active Hepatitis B virus (HBV) and Hepatitis C virus (HCV) or any other severe viral active infection (e.g. severe acute respiratory syndrome coronavirus [SARS-CoV-2] infection). Active hepatitis is defined as:

- Combination of HBV deoxyribonucleic acid (DNA) >1000 IU/mL or >2500 copies/mL plus positive Hepatitis B surface antigen (hBsAg) plus positive Hepatitis B core antibody.

- Combination of HBV deoxyribonucleic acid (DNA) >1000 IU/mL or >2500 copies/mL plus positive Hepatitis B surface antigen (hBsAg)

- Combination of HBV deoxyribonucleic acid (DNA) >1000 IU/mL or >2500 copies/mL plus positive Hepatitis B core antibody.

- Positive serum HCV ribonucleic acid (RNA) and antibody to HCV (HCV Ab).

Note:

Patients with no prior history of HBV infection who have been vaccinated against HBV and who have a positive antibody against hepatitis B surface antigen as the only evidence of prior exposure may be enrolled.

17. Known contraindication to receive cetuximab or irinotecan at the planned dose, according to the most recent cetuximab and irinotecan local label.

18. Participant's conditions that contra-indicates the use of study intervention and may affect interpretation of results or may render the participant at high risk from complications.

Note:

Conditions are, in the opinion of the investigator, any medical or psychiatric conditions, metabolic dysfunction, physical examination finding or clinical laboratory finding suggesting disease/condition.

19. Participants who have any medical condition that would, in the investigator's judgment, prevent participation in the clinical study due to safety concerns or compliance with study procedures.

20. Treatment with any of the following:

a. Cyclical chemotherapy within a period of time that was shorter than the cycle length used for that treatment (e.g. 6 weeks for nitrosourea, mitomycin-C) before starting study intervention.

c. Biologic therapy (e.g. antibodies) except bevacizumab or aflibercept, continuous or intermittent small molecule therapeutics or any other investigational agents within a period of time that is ≤5 half-lives or ≤28 days (whichever is shorter) before starting study intervention.

d. Bevacizumab or aflibercept therapy ≤3 weeks before starting study intervention.

e. Radiation therapy that included >30% of the bone marrow.

21. Participation in a clinical study with administration of an investigational product within 4 weeks prior to the first dose of study intervention.

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

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

24. Is mentally unable to understand the nature, objectives and possible consequences of the study; or he/she refuses to its constraints.

5.3. Lifestyle Considerations

5.3.1. Contraception

Women of childbearing potential must agree to take appropriate precautions to avoid pregnancy through 30 days after the last dose of encorafenib.

Male participants must agree to take appropriate precautions to avoid fathering a child and prevent exposure of seminal fluid to the partner from screening through 90 days after the last dose of encorafenib.

Participants and investigators should be referred to the approved local labels of the products used in this trial (cetuximab, irinotecan, 5-FU, calcium folinate) for management of contraception.

The methods of contraception outlined in Appendix 10.2.2 are permitted under this protocol for use by the participant and his/her partner. These methods should be communicated to the participants and their understanding confirmed.

Note: Since encorafenib is a strong CYP3A4 inducer, 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

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

5.3.3. Meals and Dietary Restrictions

Participants must refrain from the consumption of grapefruit, pomegranates, star fruits, Seville oranges, aslime, sour orange, citrus depressa or products containing the juice of any of these items from 7 days before the start of study intervention until after the final dose due to potential CYP3A4 interaction with encorafenib. Orange juice is allowed.

There are no restrictions on dosing or PK sampling in relation to the timing of meals.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but who do not meet one or more of the inclusion and exclusion criteria or do not complete the screening process. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to respond to queries from regulatory authorities.

The following will be recorded in the electronic case report form (eCRF) for screen failures:

For participants failing molecular prescreening: results of local BRAF assay and adverse events related to a study procedure during molecular prescreening.

For participants failing screening: date of informed consent, review of inclusion/exclusion criteria, adverse events related to a study procedure during the screening period and any medications used to treat those adverse events.

Screen failures will not be rescreened.

6. Study Intervention

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo or medical device(s) intended to be administered to a study participant according to the study protocol. The interventions in this study are:

Encorafenib: a novel, oral, highly selective adenosine triphosphate (ATP)-competitive small-molecule kinase inhibitor with potent and selective inhibitory activity against mutant BRAF kinase, a member of the MAPK (RAS/RAF/MEK/ERK) pathway, which plays a prominent role in controlling several key cellular functions including growth, proliferation and survival in tumor cells expressing metastatic *BRAF* V600E mutations, including mCRC cell lines.

Cetuximab: a marketed recombinant, human/mouse chimeric immunoglobulin (Ig) G1 monoclonal antibody produced in a mammalian cell line (Sp2/0) by recombinant DNA technology. It 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.

Irinotecan: a marketed topoisomerase-I inhibitor and a member of the camptothecin class, which is activated by hydrolysis in vivo to an active metabolite, SN-38, and inactivated by glucuronidation with UGT1A1. It is given to treat CRC either alone or as a combination treatment, including FOLFIRI.

FOLFIRI: irinotecan combined with infusional 5-FU and FA.

The antineoplastic agent 5-FU is an analogue of uracil, a component of RNA. It interferes with the synthesis of DNA by blocking the conversion of deoxyuridylic acid to thymidylic acid by the cellular enzyme thymidylate synthetase, it may also interfere with RNA synthesis.

FA is frequently used to diminish the toxicity and counteract the action of folate antagonists, such as 5-FU. It stimulates folate antagonist efflux and protects cells from the effects of folate antagonist by repletion of the reduced folate pool.

6.1. Study Intervention(s) Administered

Participants will receive study intervention according to Table 10. The investigational product is encorafenib, which will be administered in combination with cetuximab (SLI phase and doublet arm of the randomized phase). The starting dose in the SLI is the one proven active and well tolerated in the ARRAY 818-302 study. The comparator combination treatment will be the investigator's choice of either irinotecan and cetuximab or FOLFIRI and cetuximab (control arm of the randomized phase).

In addition to the information provided in this protocol, refer to the Pharmacy Manual and the Investigator's Brochure for encorafenib or the Summary of Product Characteristics for cetuximab, irinotecan, 5-FU and FA for the management of participants concerning contraindications, duration of contraception, special warnings and precautions and medications that are contraindicated or that must be used with caution.

Participants with known contraindications to either 5-FU or FA may be included in the study but must be treated with irinotecan and cetuximab if randomized to the control arm.

Table 10: Detail of Study Interventions

Study Interventions	Pharmaceutical Form and Route of Administration	Starting Dose	Frequency
SLI Phase			
Encorafenib	4 × 75 mg oral hard capsule	300 mg	QD
Cetuximab	IV infusion	400 mg/m^2 initial dose (120-minute infusion), then 250 mg/m^2 (60-minute infusion) thereafter.	Once weekly
	Randomized Phase: Doublet Arm (*dose confirmed in SLI phase*)		
Encorafenib	4 × 75 mg oral hard capsule	300 mg	QD
Cetuximab	IV infusion	400 mg/m^2 initial dose (120-minute infusion), then 250 mg/m^2 (60-minute infusion) thereafter.	Once weekly
Randomized Phase: Control Arm			
	Either Irinotecan and cetuximab		
Irinotecan	IV infusion	180 mg/m^2 (90-minute infusion or according to study site standards).	Every 2 weeks
Cetuximab	IV infusion	400 mg/m^2 initial dose (120-minute infusion), then 250 mg/m^2 (60-minute infusion) thereafter.	Once weekly

Or FOLFIRI and cetuximab			
Irinotecan	IV infusion	180 mg/m^2 (90-minute infusion or according to study site standards).	Every 2 weeks
Folinic acid0	IV infusion	400 mg/m^2 (120-minute infusion or according to study site standards) or maximal dose tolerated in a prior regimen.	Every 2 weeks
5-FU0	IV bolus/IV infusion	400 mg/m^2 initial dose bolus (not to exceed 15 minutes), then 1200 mg/m^2/day × 2 days (total 2400 mg/m^2 over 46 to 48 hours) continuous infusion or maximal dose tolerated in a prior regimen.	Every 2 weeks
Cetuximab	IV infusion	400 mg/m^2 initial dose (120-minute infusion), then 250 mg/m^2 (60-minute infusion) thereafter.	Once weekly
	Abbreviations: FA = folinic acid; 5-FU = 5 fluorouracil; FOLFIRI =5-fluorouracil/folinic acid+irinotecan; IV = intravenous(ly); QD = once daily; SLI = safety lead-in. Participants who experienced unacceptable toxicities requiring 5-FU and FA dose reductions in prior regimens may start treatment at the highest doses which were previously tolerated.		

Study intervention will be administered in 28-day cycles until death, disease progression, one of the other criteria for study intervention discontinuation is met (see Section 7.1) or the participant is lost to follow-up (see Section 7.3).

Lifestyle considerations in relation to dosing are detailed in Section 5.3. There are no restrictions on dosing in relation to the timing of meals.

Management of dose modifications (including dose interruptions and retreatment) are detailed in Section 6.6.

Continuing study treatment beyond disease progression for any participant up to EoS is only to be considered under special circumstances when it is believed that the participant may clinically benefit from continued treatment beyond progression. If it is judged by the investigator (in consultation with the sponsor) to be in the best interest of the participant, the participant may remain on study intervention as long he/she continues to benefit, according to the investigator's assessment. Special circumstances can be defined by e.g. mixed responses and appearance of new brain metastases (only) which are treatable with stereotactic radiotherapy or surgery but does not require whole brain radiotherapy.

Treatment beyond progression is not allowed in the following cases:

Participants with clear evidence of radiographic and clinical disease progression at multiple sites or clear evidence of new lesions outside the central nervous system.

Participants with rapid progression of disease at critical anatomical sites (e.g. cord compression) requiring urgent alternative medical intervention.

Participants who have clinically relevant worsening of laboratory values.

Participants who have a clinically significant decline in ECOG performance status at time of progression.

6.1.1. Encorafenib

Encorafenib is manufactured by Pierre Fabre Médicament and supplied by the sponsor as hard capsules for PO administration in dosage strength of 75 mg. The hard capsules are packaged in blister as specified in MA N°EU/1/18/1314. Encorafenib hard capsules consist of encorafenib drug substance and the following excipients: copovidone, poloxamer 188, succinic acid, microcrystalline cellulose, colloid silicon dioxide, crospovidone and magnesium stearate of vegetable origin. The hard capsule shell is commercially available. Each blister will be labelled, at a minimum, with:

a. Name of the sponsor

b. Protocol number

c. Packaging batch number

d. Treatment number

e. Expiry date as year/month (EXP: YYYY/MM)

f. Dosage of the tested product

g. Number and dose formulation of the product

Encorafenib will be provided in packs. Each pack of encorafenib will contain twenty blisters of six 75 mg hard capsules. Each pack will be labelled at a minimum with:

a. Name and address of the sponsor

b. Pharmaceutical dosage form, route of administration, quantity of dosage units, name/identifier and strength/potency

c. Packaging batch number

d. Study reference code allowing identification of the study

e. Study participant identification: treatment number

f. Directions for use (reference may be made to a leaflet or other explanatory document intended for the participant or person administering the product)

g. "FOR CLINICAL TRIAL USE ONLY"

h. Storage conditions

i. Expiry date as year/month (YYYY/MM)

This pack labelling contains a tear-off flap with the following information:

a. Protocol number

b. Packaging batch number

c. Treatment number

Labels will be in the local language and comply with the local legal requirements.

Encorafenib will be sent to a local facility (sponsor designee) for storage before onward distribution to each study site prior to, and during, the study. Full information can be found in the Pharmacy Manual for the study and Investigator's Brochure for encorafenib.

A fixed-flat dose of 300 mg PO encorafenib will be administered QD. Each dose will be taken in the morning with a large glass of water (~250 mL), at approximately the same time each day. The hard capsules should be swallowed whole and not chewed or crushed. Doses of encorafenib that are omitted due to adverse events or any other reason can be taken up to 12 hours before the next dose; if less than 12 hours to the next dose, the regular dosing schedule must continue and participant should be instructed to check with the investigator or designee. It is forbidden to double the next dose. If the participant vomits at any time after dosing, the dose of encorafenib should not be re-administered.

On the days when there are visits to the study site, the encorafenib dose will be taken under the supervision of the investigator or designee. Encorafenib will be administered at least 30 minutes before cetuximab, without regard to when cetuximab premedications are administered (see

Section 6.1.2) and after any predose blood samples have been taken. On all other days, the encorafenib dose will be self-administered at home. The study site personnel will train the participant and/or the participant's caregiver on encorafenib dosing requirements.

Participants will receive a diary to document self-administration of encorafenib to include the dose, date of dosing (and time if applicable), if the participant vomited after dosing, if any doses were missed and the reason for the missed dose. One diary will be provided per cycle. On the days when encorafenib is administered at the study site, these details will be recorded in the eCRF by the study site personnel.

6.1.2. Cetuximab, Irinotecan, 5 Fluorouracil and Folinic Acid

Cetuximab, irinotecan, 5-FU and FA will be supplied locally whenever possible and sent to a local facility (sponsor designee) for storage prior to onward distribution to each study site prior to, and during, the study.

Commercially available vials packaged in commercial boxes will be labelled, at a minimum, with a unique identifier (study intervention number), the lot number, study reference code allowing identification of the study and the name and address of the sponsor designee. Labels will be in the local language and comply with the local legal requirements. The vials will be used according to local regulations. Full information can be found in the Pharmacy Manual for the study and locally-approved Product Information.

Each infusion should be prepared using aseptic technique according to the locally-approved Product Information and study site standards.

Cetuximab, irinotecan, 5-FU and FA will be administered by IV infusion according to study site standards. The doses will be calculated based on body surface area (BSA). The date, dose, infusion start time and duration (including any infusion interruptions) will be recorded in the eCRF. Doses that are omitted for adverse events or any other reason should not be made up.

6.1.2.1. Cetuximab

Cetuximab will be given at the study site once weekly on Days 1, 8, 15 and 22 (±3 days) of every 28-day cycle.

A loading dose of 400 mg/m^2 with a recommended infusion duration of 120 minutes will be given on Cycle 1 Day 1; a maintenance dose of 250 mg/m^2 with a recommended 60-minute IV infusion duration will be given at all other visits.

Premedication for routine cetuximab infusions should be given according to the label and with the national and/or study site standards (see Section 6.5.1.1). This is mandatory for the first infusion. Pre-medication for subsequent infusions is based upon clinical judgment, study site standards and presence/severity of prior infusion reactions. Premedication should be administered no sooner than 1 hour after administration of encorafenib and 30 minutes before cetuximab infusion.

The infusion rate should not exceed 10 mg/minute (the first infusion rate should not exceed 5 mg/minute). The dose should not be administered as an IV push or bolus.

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 participant should be closely monitored and treated in line with study site standards. Medications may be given to prevent or treat infusion reactions (see Section 6.5.1.1). Any rechallenge with cetuximab after an infusion reaction must be discussed with the sponsor.

Cetuximab administration should be completed 1 hour prior to the start of irinotecan or FOLFIRI infusion for participants in the control arm of the randomized phase.

6.1.2.2. Irinotecan

A 180 mg/m^2 dose of irinotecan administered as a 90-minute IV infusion (or according to study site standards) will be given at the study site every 2 weeks on Days 1 and 15 (±3 days) of every 28-day cycle.

6.1.2.3. Folinic Acid and 5 Fluorouracil

Folinic acid and 5-FU will be given at the study site every 2 weeks:

A 400 mg/m^2 dose of FA will be administered as a 120-minute IV infusion (or according to study site standards) on Days 1 and 15 (±3 days) of every 28-day cycle. Folinic acid may be administered concurrently with irinotecan via separate infusion lines.

5-fluorouracil will be administered immediately following completion of the FA infusion. A 400 mg/m^2 bolus (not to exceed 15 minutes) will be administered IV on Days 1 and 15, followed by 1200 mg/m^2/day for 2 days (total 2400 mg/m^2 over 46 to 48 hours) continuous IV infusion (or according to study site standards).

Participants who required 5-FU and FA dose reductions in prior regimens (e.g. as part of FOLFOX or FOLFOXIRI regimens) may start treatment at the highest doses which were previously tolerated.

6.2. Preparation/Handling/Storage/Accountability/Return/Destruction

6.2.1. Accountability on Site and Return/Destruction

Full shipping, storage and handling details will be provided in the Pharmacy Manual and the locally-approved Product Information for cetuximab, irinotecan, 5-FU and FA.

Labelled, packaged study intervention will be shipped to each study site by the sponsor designee and will contain a temperature monitoring device. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention and only authorized study site personnel may supply or administer study intervention. All study intervention must be stored according to Section 6.2.2.

The investigator, institution or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation and record maintenance (dates and quantities of study intervention received, to whom study intervention is dispensed [participant-by-participant accounting] and accounts of returned and destroyed intervention).

To ensure adequate records, all study intervention will be accounted for on an accountability inventory form as instructed by the sponsor.

Drug accountability must be performed by the clinical research associate (CRA) on a regular basis during the study according to the Monitoring Plan. The investigator must retain all unused or expired study intervention supplies until the CRA has confirmed the accountability records. If site policy prohibits holding study intervention supplies for CRA review, then a copy of the standard operating procedure for processing returns must be provided to the sponsor.

At the end of the study, all used and unused study intervention including packaging should be noted and destructed on site or at sponsor's designee facility (central warehouse). Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

6.2.2. Storage

At the time of the delivery to the study site, the following information will be provided together with the accompanying letter:

Details of storage conditions that should be respected.

A letter of release for the Investigational Medicinal Product from the Sponsor's Qualified Person upon request and for the first delivery only.

The CRA will ensure during the initiation visit that study interventions have been received in good condition and the acknowledgment of receipt has been performed in the interactive response technology (IRT) system.

All study intervention must be stored in a secure, environmentally controlled and monitored (manual or automated) area in accordance with the labelled storage conditions and applicable regulatory requirements with access limited to the investigator and authorized study site personnel.

Encorafenib hard capsules should be stored according to the information on the labels (refer to the Pharmacy Manual for further information details). Stability studies to support the encorafenib storage conditions have been conducted by the manufacturer or an affiliate. The manufacturer will continue to monitor the stability of encorafenib and the sponsor will alert the site if a lot is nearing the end of its anticipated shelf life.

Cetuximab, irinotecan, 5-FU and FA should be stored according to the locally-approved Product Information.

6.2.3. Expiry Date

The investigator or designee should ensure that the study intervention expiry date has not been exceeded. If applicable, the investigator will send an Extension Notification Form to the study manager to request additional study intervention with an extended expiry date. If the expiry date has been exceeded, then the affected study intervention supplies must be quarantined to prevent them from being used. Accountability and final disposition will follow the process in Section 6.2.1.

The study manager will complete a "Request for Delivery of Investigational Product Form" and send it to the Investigational Medicinal Product Management Service of the Institut de Recherche Pierre Fabre (IRPF) that in turn, will ensure new study intervention is supplied.

6.2.4. Recall

In case of recall of study intervention (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:

Put all study interventions concerned by the recall in quarantine.

Stop the administration of the concerned study interventions to the participants.

Inform the concerned participants that they must immediately stop taking these study interventions and bring them back.

The study manager/CRA will organize the return of the recalled products to the Investigational Medicinal Product Management Service of IRPF, according to the sponsor's procedures.

6.3. Measures to Minimize Bias: Randomization and Blinding

All participants will be assigned a unique participant code corresponding to the study site number and the participant's number according to chronological order (once having provided written informed consent). Participants will be registered for the study using an IRT system after informed consent is provided if the participant meets all eligibility requirements. The telephone number and call-in directions and/or the log in information instructions for the IRT system will be provided to each study site before initiation.

All participants in the SLI phase will receive the doublet. In the randomized phase, participants will be randomized in a 2:1 ratio respectively to the doublet arm (encorafenib and cetuximab) or to the control arm (irinotecan and cetuximab or FOLFIRI and cetuximab, at the investigator's discretion). Randomization will be stratified according to Section 9.4.1.2.

Potential bias will be reduced by central randomization and BICR evaluation of imaging data.

The investigator will allocate study intervention to each participant on Day 1 of each cycle during the treatment period via the IRT system. Returned encorafenib should not be re-dispensed.

Full information is described in the IRT Manual.

6.4. Study Intervention Compliance

The study will be monitored by a CRA approved by the sponsor (see Appendix 10.1.8.4). During monitoring, all procedures will be assessed for compliance with the protocol, including study intervention preparation, administration and accountability. Source documents (see Appendix 10.1.9) will be reviewed and compared with the data entries in the eCRFs to ensure consistency.

6.4.1. Encorafenib

On cetuximab dosing days, encorafenib will be administered at the study site at least 30 minutes before cetuximab. The encorafenib dosing information will be recorded on the source documents and in the eCRF.

The investigator or designated study site personnel should instruct the participant to take the remaining doses of encorafenib at home according to the protocol. The dose and number of encorafenib tablets prescribed, dispensed to the participant, any dose changes and all missed doses during the study must be recorded in the eCRF. The participant will be reminded to bring back the encorafenib bottle and the participant diary from the previous cycle to the study site on Day 1 of each cycle. Compliance will be assessed by direct questioning, counting returned tablets and reviewing the diary entries and documented in the source documents and eCRF. Study intervention start and stop dates, including dates for intervention delays and/or dose modifications and any non-compliance from the prescribed dosage regimen should be recorded in the eCRF.

6.4.2. Cetuximab, Irinotecan, 5-Fluorouracil and Folinic Acid

Cetuximab, irinotecan, 5-FU and FA (given as calcium folinate) will be administered by IV infusion at the study site by the investigator or designee, under medical supervision. The date, dose, infusion start time and duration (including any infusion interruptions) will be recorded on the source documents and in the eCRF. The dose of study intervention and participant identification will be confirmed at the time of dosing by study site personnel other than the person administering the study intervention.

6.5. Concomitant Medication and Therapeutic/Diagnostic Procedures

Any medication (including vaccines) other than study intervention (including non-prescription or prescription medicines or vitamins) taken in the period from 28 days before the first administration of study intervention up to 30 days after the last dose of study intervention must be recorded, except for anticancer therapy (see section 8.2.2). Any changes in dose of a medication during the study must also be recorded. The following information must be recorded in the eCRF:

The name of the medication.

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, blood or platelet transfusions etc.) not planned by the study protocol must also be recorded. 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 eCRF (adverse events, medical history). The following information must be noted in the eCRF:

The name of the procedure.

The indication.

The duration (start date and end date).

Investigators should use caution when prescribing concomitant medications, as clinical experience with these compounds in participants with cancer is often limited. Investigators should contact the sponsor or designee when they are unsure whether a medication should be prescribed to a participant in the clinical study.

6.5.1. Authorized Medications, Therapeutic and Diagnostic Procedures

In general, the use of any concomitant medications deemed necessary for the care of the participant is permitted, unless otherwise specified. Additional information regarding concomitant medications is provided in the Investigator's Brochure for encorafenib and the locally approved Product Information for cetuximab, irinotecan, 5-FU and FA.

6.5.1.1. Cetuximab Premedication and Treatment of Infusion Reactions

Premedication for routine cetuximab infusions may be used in accordance with the label* and with local regulations and/or study site 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. Premedication for subsequent infusions is based upon clinical judgment and presence/severity of prior infusion reactions. Premedication should be administered no sooner than 1 hour after administration of encorafenib and 30 minutes before 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 participant who has previously experienced an infusion reaction. Dose modifications for cetuximab infusion reactions are provided in Section 6.6 and Table 30.

6.5.1.2. Supportive Care Recommended Guidelines for Management of Toxicities

Clinical judgment and experience of the treating physician should guide the management plan of each participant.

Participants should be treated for cetuximab-induced and/or encorafenib-induced skin toxicity following the supportive care recommended guidelines for the management of these toxicities and prophylaxis measures referred to in Appendix 10.3.1.

Hand-foot skin reactions (HFSR) have been reported for encorafenib, so it is recommended that participants are informed before starting study intervention to avoid activities that can cause friction to the hands and/or feet. Supportive measures for prevention and/or management of HFSR should be initiated. Participants should be treated for encorafenib-induced HFSR following the supportive care recommended guidelines for the management of these toxicities referred to in Appendix 10.3.2.

Participants should be treated for diarrhea according to study site guidelines and/or as indicated in the locally-approved Product Information; prophylactic antiemetics should only be administered if the participant experiences nausea or vomiting and at the discretion of the investigator. It is recommended that participants use drugs that do not cause QT prolongation. Note that some antiemetics have a known risk for Torsade de Pointes (see Section 6.5.1.3.3).

For participants in the control arm, lacrimation, rhinorrhea, miosis, diaphoresis, hot flashes, flushing, abdominal cramping, diarrhea or other symptoms of early cholinergic syndrome may occur during or shortly after receiving irinotecan. Atropine, 0.25 to 1.0 mg IV or subcutaneously, may be used (unless clinically contraindicated to treat these symptoms) at the discretion of the treating physician. Combination anticholinergic medications containing barbiturates or other agents should not be used because these may affect irinotecan metabolism. Anticholinergics should be used in caution in participants with potential contraindications (e.g. obstructive uropathy, glaucoma and tachycardia). Late diarrhea (e.g. developing more than 24 hours after irinotecan) should be managed with loperamide.

Prophylactic antiemetics should be started only once the participants experiences nausea or vomiting and at the discretion of the investigator. It is recommended that participants use drugs that do not cause QT prolongation. Note that some antiemetics have a known risk for Torsade de Pointes (see Section 6.5.1.3.3**)**.

6.5.1.3. Authorized Therapies requiring Caution and/or Action

Participants should be closely monitored for the occurrence of adverse events whilst taking these therapies.

6.5.1.3.1. Cytochrome P450 and Uridine 5'-diphospho-glucuronosyltransferase Substrates and Inhibitors

In vitro, encorafenib is a reversible inhibitor of CYP2B6, CYP2C9, CYP3A4 and UGT1A1. It is also a time-dependent inhibitor of CYP3A4. Permitted medications to be used with caution in this

study include those that are sensitive substrates of CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A4 (see Table 21 and Table 22) and UGT1A1 (see Table 23) or those substrates that have a narrow therapeutic index.

In vivo, encorafenib is a strong CYP3A4 inducer, concomitant use with hormonal contraceptive, may reduce their effectiveness. At least one form of non-hormonal contraception is therefore required during participation in this study (see Section 5.3.1). Caution should also be exercised in participants receiving concomitant treatment with other drugs that are substrates of CYP3A4 as the efficacy of these drugs could be reduced when administered with encorafenib. If the coadministration of narrow therapeutic index CYP3A4 substrates cannot be avoided, adjust the dose of these substrates in accordance with their approved Product Information.

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 (see Section 6.5.2). Concomitant use of moderate CYP3A4 inhibitors (see Table 24) 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 before use of moderate CYP3A4 inhibitors (or as close as can be achieved without exceeding the target dose). The encorafenib dose that was taken before initiating the CYP3A4 inhibitor may be resumed after the inhibitor has been discontinued for three to five elimination half-lives. Strong inhibitors of CYP2C19 should be used with caution when co-administered with encorafenib.

6.5.1.3.2. Transporter Substrate and Inhibitors

In vitro data showed that encorafenib is a substrate of the transporter P-glycoprotein (P-gp) and a breast cancer resistance protein (BCRP) inhibitor. Use of medications that are known to inhibit or induce P-gp or BCRP should be used with caution (see Table 25). Encorafenib is also a potent inhibitor of the renal transporters, organic anionic transporter (OAT)1, 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, OCT2, OATP1B1 and OATP1B3 should be used with caution (see Table 26).

6.5.1.3.3. 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 with concomitant medications with a known, conditional or possible risk to prolong the QT interval and/or induce Torsade de Pointes (see Table 27**)**. Participants 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.

6.5.2. Prohibited Medications and Therapeutic/Diagnostic Procedures

Prohibited medications and therapeutic/diagnostic procedures at screening in relation to participant exclusion (see Section 5.2) must not be prescribed for the duration of the study.

None of the concomitant therapies and therapeutic/diagnostic procedures listed below are allowed during the treatment phase:

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.

Investigational drugs (other than study interventions) and devices.

Radiation therapy (not including palliative radiotherapy at focal sites that covers ≤10% of the bone marrow reserve). Calculation of the percentage of active bone marrow reserve can be performed using information in appendix 10.10 [Hindorf 2010]

Herbal preparations/medications. Participants should stop using herbal medications (including use of St. John's Wort [hypericum perforatum] and traditional Chinese medicine susceptible to be a moderate or strong inhibitor or strong inducer of CYP3A4/5) 7 days before the first dose of study intervention.

Concomitant systemic strong CYP3A4 inhibitors or strong inducers which are likely to significantly increase or decrease encorafenib exposure, respectively (listed in

Table 28).

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

6.6. Dose Modification

Participants will be monitored for adverse events throughout the study. The severity of adverse events will be graded according to NCI CTCAE Version 4.03 [NCI CTCAE 2010].

In case a dose reduction is necessary, an individual participant may have their dose of encorafenib and/or cetuximab reduced to the dose levels specified in Table 11.

Table 11: Dose Levels for Dose Modification

	Encorafenib (mg) QD	Cetuximab (mg/m^2) Once weekly	Irinotecan (mg/m^2) Every 2 weeks)	5-FU (mg/m^2) Every 2 weeks	
				Bolus	Infusion (over 46 to 48 hours)
Starting Dose	300	Initial dose: 400 Thereafter: 250	180	400	2400
Dose level -1	225	200	150	200	2000
Dose level -2	150	150	120	0	1600
Dose level -3	-	-	100	0	1200

Abbreviations: *BRAF* V600E = B-RAF proto-oncogene, serine/threonine kinase V600E-mutant; FA = folinic acid; 5-FU = 5 fluorouracil; FOLFIRI = 5-fluorouracil/folinic acid+irinotecan; mCRC = metastatic colorectal cancer; QD = once daily.

No reduced dose of irinotecan is accepted at study entry

Notes:

Participants must discontinue cetuximab or irinotecan treatment if a toxicity leading to a dose reduction re-occurs with the same or worse severity at the lower dose.

Due to the lack of efficacy of single agent encorafenib or cetuximab in *BRAF* V600E mCRC, participants who cannot tolerate these agents in combination must discontinue both study interventions together.

Due to the lack of efficacy of single-agent cetuximab or 5-FU/FA in *BRAF* V600E mCRC, participants who cannot tolerate irinotecan either alone or as a component of FOLFIRI should discontinue all study interventions together.

If a participant develops toxicity, the dose should be modified as outlined in Table 29, Table 30, Table 31 and Table 32 for encorafenib, cetuximab, FOLFIRI and irinotecan when given without 5-FU and FA, respectively. These tables include criteria for interruption, reduction and discontinuation of study intervention. All dose modifications should be based on the worst preceding toxicity. All dosing interruptions and modifications must be recorded in the eCRF.

Dose reductions due to study intervention-related adverse events or laboratory abnormalities in an individual participant are permitted as follows:

No dose re-escalation of encorafenib is allowed after a dose reduction due to prolonged QTcF ≥501 msec. For other events, encorafenib may be reduced by two dose levels to 150 mg. If the event causing a dose reduction improves to the 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 re-escalation. There is no limit to the number of times the participant can have their dose reduced or re-escalated.

Cetuximab may be reduced by two dose levels to 150 mg/m^2 and irinotecan by three dose levels to 100 mg/m^2. Following a dose reduction due to an adverse event, no subsequent dose re-escalation will be permitted for the duration of the treatment phase. If study intervention is resumed at the same dose after resolution of an adverse event and the same toxicity reoccurs with the same severity, any re-initiation of study intervention must be at the next lower dose level irrespective of duration (with some exceptions for skin toxicity).

For FOLFIRI dose modification, dose modifications of irinotecan, 5-FU bolus or 5-FU infusion, as shown in Table 11, are to be made independently, based on the specific types of toxicity observed. In general, if a dose is reduced because of toxicity, it is not to be re-escalated to the starting level. Participants who require multiple dose reductions during a cycle for a Grade 2 toxicity could, however, begin the following cycle at one dose level higher, at the investigator's discretion.

6.7. Intervention after the End of the Study

Not applicable

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1. Discontinuation of Study Intervention for Individual Participants

Participants may withdraw their consent to participate in the study at any time for any reason without prejudice to their future medical care by the physician or at the study site. However, participants should be asked if they are willing to be contacted by telephone or to be followed up at routine visit for monitoring of survival. If a participant withdraws consent, the date, stated reason for and level of consent withdrawal should be documented. Participant data collected up to the date of consent withdrawal will be included in the analyses. Any blood or tissue samples collected up to the date of withdrawal of consent will be analysed.

Wherever possible, the tests and evaluations listed for the end of treatment visit should be carried out and an effort should be made to continue follow-up. The sponsor should be notified of all study withdrawals through the designated eCRFs in a timely manner.

7.1.1. Temporary Discontinuation and Rechallenge

Adverse event, clinically significant laboratory abnormalities and dosing errors leading to a dose interruption and the conditions for re-starting study intervention are provided in Table 29, Table 30, Table 31 and Table 32.

If a dose interruption of more than 28 days occurs due to COVID-19 restrictions, treatment may be resumed after consultation with the sponsor and provided the patient is still beneficing of the therapy (i.e. still in response or stable disease and not progressing).

7.1.2. Permanent Discontinuation

In addition to participants who die from any cause, during the conduct of the study, participants who meet any of the following criteria must permanently discontinue study intervention:

- Disease progression as defined by RECIST Version 1.1 (continuation of treatment beyond progression is permitted in special circumstances, see Section 6.1).
- Withdrawal of consent for study intervention but providing consent to return for end of treatment assessments and follow-up.
- Unacceptable adverse events or failure to tolerate study intervention (as described in Table 29, Table 30, Table 31, Table 32).
  - Adverse events or clinically significant laboratory abnormalities leading to a dose interruption of >28 consecutive days for encorafenib, >4 missed consecutive doses of cetuximab or two consecutive irinotecan, 5-FU or FA doses; unless judged by the investigator and sponsor medical monitor or designee to be in the best interest of the participant to continue study intervention.
  - Participants must discontinue cetuximab or irinotecan treatment if a toxicity leading to a dose reduction re-occurs with the same or worse severity at the lower dose.
  - Due to the lack of efficacy of single agent encorafenib or cetuximab in *BRAF* V600E mCRC, participants who cannot tolerate these agents in combination must discontinue both study interventions together.
  - Due to the lack of efficacy of single-agent cetuximab or 5-FU/FA in *BRAF* V600E mCRC, participants who cannot tolerate irinotecan either alone or as a component of FOLFIRI should discontinue all study interventions together.
- Changes in the participant's condition or development of an intercurrent illness which renders them unacceptable for further treatment in the investigator's opinion.
- Receipt of non-protocol-specified anticancer therapy for study indication (chemotherapy, biological therapy or radiation therapy that includes >30% of the bone marrow reserve).
- Participant becomes pregnant or begins breastfeeding.
- Significant protocol deviation that, in the opinion of the investigator and/or sponsor, renders the participant unsuitable to receive further study intervention.
- Lost to follow-up (see Section 7.3).

A participant meeting any of the following criteria may be discontinued from study intervention if, during the course of the study:

- Is found not to have met all eligibility criteria if the investigator determines that he/she would not benefit from participation in the study due to the eligibility deviation.
- Is found to have a tumor that is BRAF wt by the central laboratory or the local assessment cannot be confirmed (see Section 8.1.1).
- Is non-compliant with study procedures or study intervention administration in the opinion of the investigator (see Section 6.4).

Participants who discontinue study intervention should be requested to return for end of treatment visit assessments and 30-day safety follow-up visit assessments and then be contacted by telephone or be monitored at routine visit for survival status. If the participant refuses to be contacted, attempts to determine survival status should be made via access to public records where permitted by local laws.

Notes:

Participants in the SLI phase who discontinue study intervention for any reason other than a DLT (see Section 4.1.3) before completing at least 75% relative dose intensity [(administered dose in mg/planned dose in mg) x 100] of the encorafenib or cetuximab doses in Cycle 1 will be not be evaluable for the tolerability assessment and will be replaced in order to achieve nine evaluable participants.

Participants who discontinue study intervention prior to study completion in the randomized phase of the study will not be replaced.

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, compliance or administrative reasons. This is expected to be uncommon.

- The participant will be discontinued from the study for the following reasons: Death.
- Withdrawal of consent for all study assessments and procedures (including follow-up).
- Non-compliance with study assessments and procedures.
- Lost to follow-up.
- Termination of the study site or study by the sponsor/competent authority (described in Appendix 10.1.2 and Appendix 10.1.10**)**.

Where applicable, participants should be requested to return for the assessments scheduled for the end of treatment visit before withdrawal.

7.3. Lost to Follow up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. The following actions must be taken if a participant fails to return to the clinic for a required study visit:

Study site personnel must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.

Before a participant is deemed lost to follow-up, the investigator or designated study site personnel must make every effort to regain contact with the participant (where possible, three telephone calls

and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. Study Assessments and Procedures

Study procedures and their timing are summarized in the schedule of assessments (Table 1 for the molecular prescreening and screening assessments and Table 2 and Table 3 for the treatment phase and follow-up phase assessments until cut-off date for final analysis, and in Table 4 for the assessment post cut-off date of the final analysis). Adherence to the study design requirements, including those specified in the schedule of assessments, is essential and required for study conduct. Additional, unscheduled visits or procedures may be performed at the discretion of the investigator (including samples for safety reasons or because of technical issues with the samples). Details must be recorded in the eCRF.

Immediate safety concerns should be discussed with the sponsor promptly upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. Protocol waivers or exemptions are not allowed. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (e.g. blood count) and obtained before provision of informed consent may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the schedule of assessments.

The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed one standard blood donation.

8.1. Prescreening/Screening Assessments and Procedures

8.1.1. BRAF Testing

Participants will be eligible for the study based on identification of a tumoral *BRAF* V600E mutation determined according to Figure 2.

All participants must provide a primary or metastatic tumor specimen for central laboratory testing of *BRAF* V600E status. This may be an archival sample or newly obtained. A FFPE tumor tissue block or a minimum of 10 slides (optimally up to 15 slides) should be provided.

If a block is provided, it is highly recommended to use the one used for local BRAF testing.

If slides are provided, it is highly recommended to cut them in the block used for local testing.

If tumor block used for local testing is exhausted, a new block can be prepared from same tumor location.

For patients with no sufficient material as described above, investigator should contact sponsor representative.

Note that tumor samples previously determined to be *BRAF* wt by local assessment may also be submitted to the central laboratory. In particular, tumors with clinicopathological features of BRAF mutations such as right colon tumors, poorly differentiated, mucinous or signet-ring carcinomas, or tumors metastasized to the peritoneum [Yokota 2011], may be considered for testing by central laboratory regardless of the results of prior local BRAF mutation testing.

Where possible, the *BRAF* V600E status will be known/determined by local laboratory assessment at any time before screening. Only polymerase chain reaction (PCR) and next generation sequencing (NGS)-based local assay results will be acceptable. Tissue specimens will be collected, handled and analyzed at the local laboratory according to the study site's standard procedures. The confirmation of *BRAF* V600E by the central laboratory must be obtained no later than 30 days after the first dose of study intervention.

Participants whose *BRAF* V600E status is unknown or cannot be determined locally (or previously determined to be *BRAF* wt by local assay) must have the central laboratory confirmation before screening.

The central *BRAF* V600E result will be made available on the central laboratory website and will be entered into the eCRF.

Central testing cannot be repeated to resolve discordances with a local result once the central laboratory delivers a definitive result (either positive or negative). Additional samples may be submitted If the result from the central laboratory is indeterminate or the sample is deemed inadequate for testing.

Lack of *BRAF* V600E confirmation by the central laboratory may be due to discordance between the local assay and central laboratory results (potential false positive local assay results) or due to inadequate or poor sample condition for central testing (indeterminate results). If at any time in the study there is lack of *BRAF* V600E confirmation (unconfirmed and discordant results combined) in a total of 10 participants (10% of the planned total) or discordance between the local assay and the central laboratory in five participants (5% of the planned total), local BRAF testing will no longer be accepted for eligibility and all subsequent participants will be required to have *BRAF* V600E determined by the central laboratory. In that particular case, and in order to save time to obtain central results, participants with local positive *BRAF* V600E mutation results are accepted for central *BRAF* V600E mutation confirmation before screening visit; these participants will follow the molecular prescreening procedures (see section 8.1.2). Information regarding study sites and laboratories associated with discordant results will be maintained and results from laboratories with more than one prior discordant result will not be accepted. Study sites with more than two participants assigned to study treatment having indeterminate or discordant results will be required to assign study treatment to all subsequent participants based only on central laboratory assay results. Under exceptional circumstances, in order to save time to obtain central results before future

participants can be randomized at sites with more than two participants assigned to study treatment having indeterminate or discordant central results, patients with local positive *BRAF* V600E mutation results are accepted for central *BRAF* V600E mutation confirmation before screening visit; these participants will follow the molecular prescreening procedures (see section 8.1.2).

In cases where there is discordance between the local laboratory and central laboratory results in an individual participant 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 intervention, the participant may only continue treatment if there is no clinical indication of deterioration or disease progression and the investigator determines that the participant is deriving benefit. The participant must be informed that the BRAF mutation status is unconfirmed, receive a separate Participant Information Sheet and Informed Consent Form (abbreviated to "ICF") that includes this information and describes alternative treatment options and provide additional informed consent for continued treatment (see Appendix 10.1.4).

Participants without centrally confirmed *BRAF* V600E mutation will be considered non-evaluable for the Efficacy Set (ES) (see Section 9.4.2).

Information regarding tissue specimen collection requirements, sample handling and shipment to the central laboratory will be provided in the Laboratory Manual.

8.1.2. Molecular Prescreening

Molecular prescreening will be performed at any time before screening in participants whose *BRAF* V600E status is unknown (or is *BRAF* wt by local assay). Molecular prescreening is not required in participants whose *BRAF* V600E status is known or is identified by local assessment at any time before screening (except for exceptional circumstances reported in section 8.1.1).

All participants undergoing molecular prescreening must provide a primary or metastatic tumor specimen for central laboratory *BRAF* V600E testing following provision of molecular prescreening informed consent (see Appendix 10.1.4). If an archival tumor sample is not available, a fresh tumor biopsy must be obtained. A tumor block or a minimum of 6 slides for BRAF testing, a minimum of 3 slides for companion diagnostic purpose and the remaining slides for RAS and MSI testing will be provided (among the minimum 10 to optimally 15 slides requested).

Information regarding tissue specimen collection and processing, handling and shipment will be provided in the Laboratory Manual.

Participants will be registered for the study using IRT after informed consent is obtained (see Section 6.3).

Participants undergoing molecular prescreening may be screened once central *BRAF* V600E status is confirmed.

8.1.3. Screening

All participants will undergo screening within the 28 days before the start of study intervention. Participants must provide screening informed consent (covering screening, study intervention and assessments) before any screening procedures to determine eligibility for participation in the study are performed (see Appendix 10.1.4). Participants who have not undergone molecular prescreening will be registered for the study using IRT after informed consent is obtained (see Section 6.3).

All participants whose *BRAF* V600E status is known/identified by local assessment must provide a primary or metastatic tumor specimen for confirmation of *BRAF* V600E status unless already provided at prescreening (see Section 8.1.1 and 8.1.2 for further details). If an archival tumor sample is not available, a fresh tumor biopsy must be obtained. When possible, the same tissue source sent for local assessment should be submitted to the central laboratory in order to minimize the potential for discordance. A tumor block or a minimum of 6 slides for BRAF testing, a minimum of 3 slides for companion diagnostic purpose and the remaining slides for RAS and MSI testing will be provided (among the minimum 10 to optimally 15 slides requested).

The following will be recorded at screening for all participants:

Demographic variables (including age, sex and race) and height.

Disease history including stage, tumor location, organs involved and sites of metastases, baseline tumor mutation status including details of prior antineoplastic treatments including number of prior metastatic regimens.

Other past and present medical history considered by the investigator to be significant (re-checked on Cycle 1 Day 1 to cover the elapsed period since screening).

Prior and concomitant medications/therapies/procedures (to cover the 28 days before the first dose of study intervention).

The following assessments will be performed:

Complete physical examination and weight (see Section 8.3.2) and dermatological examination (see Section 8.3.3).

Vital signs (see Section 8.3.7), ECG (see Section 8.3.8), cardiac function (see Section 8.3.9) tests and ECOG performance status (see Section 8.3.10).

Local clinical laboratory blood tests:

- Safety tests (hematology, clinical chemistry and coagulation) (see Section 8.3.5).
- Viral serology tests for HBsAg (hepatitis B surface antigen), HBcAb, HBV DNA when HBsAg and/or HBcAb positive and hepatitis C antibody, HCV RNA when HCV Ab positive, and HIV. If required, analysis of follicle stimulating hormone (FSH) (see Appendix 10.2.1), luteinizing hormone and/or estradiol to confirm postmenopausal status in females.
- Pregnancy test in WOCBP (see Section 8.3.6).

Samples will be collected, handled and analyzed at the local laboratory according to the study site's standard procedures, unless some parameters can't be analysed locally, then to send for central analysis (see Section 8.3.6).

Urine test: Urinalysis (see Section 8.3.5).

Baseline tumor assessment by CT/MRI (see Section 8.2.1) and QoL (see Section 8.2.3).

Blood and tumor biomarker assessments (see Section 8.9).

Participant eligibility will be verified against the inclusion and exclusion criteria once all screening procedures are completed. The eligibility check will be embedded in the IRT system (see Section 6.3). Eligible participants in the randomized phase will further be randomized to the doublet arm or control arm using IRT before the first dose of study intervention. The treatment decision (irinotecan and cetuximab or FOLFIRI and cetuximab) will also be recorded for participants in the control arm.

8.2. Efficacy Assessments

8.2.1. Tumor Response

Tumor response will be evaluated according to RECIST Version 1.1 (see Appendix 10.7). The PFS, overall response rate (ORR), duration of response (DOR) and time to response (TTR) will be assessed according to Section 9.4.

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.

A brain MRI or CT scan in participants with a history of asymptomatic brain metastases.

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 according to local standard of care (e.g. Tc99m bone scan, fluorodeoxyglucose-positron emission tomography [FDG-PET], sodium fluoride-positron emission tomography or whole-body bone MRI scan).

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.

All post-screening assessments should be performed every 6 weeks (±7 days) from the first dose for the first 24 weeks of treatment then every 12 weeks (±7 days) thereafter until disease progression [2] or death, withdrawal of consent, initiation of subsequent anticancer therapy, participant is lost to follow-up or the cut-off date for final analysis is reached (whichever occurs first).

[2] In special circumstances, continuation of treatment beyond disease progression may be allowed.

If a participant discontinues study intervention for reasons other than disease progression, then tumor assessments must continue to be performed according to this schedule.

From the cut-off date for final analysis and until the end of study (see section **4.4**), tumor evaluations will be performed as per standard of care.

If a participant misses a scheduled tumor evaluation or a technical error prevents the evaluation, the participant may continue treatment until the next scheduled assessment, unless signs of clinical progression are present. If there is suspicion of disease progression based on clinical or laboratory findings before the next scheduled assessment, an unscheduled assessment should be performed.

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

Regardless of whether study intervention is discontinued, the following should be performed at all postbaseline assessments:

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.

All CT scans in the study should be performed with IV contrast. If a participant 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 contraindicated.

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

Any lesions that have been subjected to locoregional 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 according to 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.

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

8.2.1.1. Local Assessment

When possible, each study site should have a single designated investigator responsible for the interpretation of scans and response evaluations for study participants. At a minimum, a single investigator should perform all interpretation of scans and response evaluations for an individual participant.

The investigator will evaluate efficacy outcome measures e.g. radiological disease progression in order to make clinical decisions during the course of the study and to determine the participant's next study visit.

8.2.1.2. Central Assessment

All imaging data acquired for efficacy purposes will be transmitted to an imaging vendor for BICR. Image transmission to the imaging vendor should be accomplished according to the Imaging Vendor Manual.

Full details of the BICR process are included in the Independent Review Charter. The images will be read by personnel who are blinded to treatment assignment, clinical history, participant outcomes and the responses assigned to them during local assessment. BICR of imaging data will be performed retrospectively and will not be provided to investigators for decisions regarding participant treatment.

8.2.2. Overall Survival and Subsequent Therapies

For participants who discontinue study intervention due to disease progression, the survival follow-up phase will start after the 30-day safety follow-up. For participants who discontinue study intervention for reasons other than disease progression, the survival follow-up phase will start upon disease progression or the start of another anticancer therapy.

During survival follow-up, participants will be followed approximately every 3 months, or more frequently as needed, until death, one of the other criteria for participant discontinuation from the study (see Section 7.2), the participant is lost to follow-up (see Section 7.3) or the cut-off date for final analysis is reached. This follow-up may be performed by telephone calls or at routine visits to the hospital.

Subsequent anticancer therapies, disease progression following the initiation of subsequent therapies and survival status will be recorded during follow-up.

To determine OS, the date of death will be recorded in the eCRF. For participants that are lost to follow-up or withdraw of consent, attempts to determine survival status should be made via access to public records, as permitted by local laws.

8.2.3. Quality of Life

Patient reported outcome assessments will be collected only for randomized Phase II patients, using the QoL questionnaires EORTC QLQ-C30, EQ-5D-5L, FACT-C at screening and on Day 1 of each cycle, the end of treatment visit and the 30-day safety follow-up visit. The PGIC will also be assessed on Day 1 of each cycle from Cycle 2 onwards, the end of treatment visit and the 30-day safety follow-up visit:

The EORTC QLQ-C30 incorporates nine multi-item scales: five functional scales (physical, role, cognitive, emotional and social); three symptom scales (fatigue, pain, nausea and vomiting); and a global health and QoL scale. Several single-item symptom measures are also included [Aaronson 1993].

The EQ-5D-5L essentially consists of the EQ-5D descriptive system and the EQ visual analogue scale (VAS). The descriptive system has five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), each is rated according to a five-point verbal rating scale (VRS) (1. no problems, 2. slight problems, 3. moderate problems, 4. severe problems and 5. extreme problems) and translated into a five-digit number that describes the participant's health state. The EQ VAS records the participant's self-rated health on a vertical VAS and used as a quantitative measure of health outcome [Rabin and de Charro 2001].

The FACT-C consists of 36 items, presented on a five-point Likert scale, in four domains of well-being (physical, emotional, social and functional) and the Colorectal Cancer Subscale [Ward 1999].

The PGIC will ask participants to evaluate their CRC symptoms since starting study intervention according to a seven-point VRS (1. very much improved, 2. much improved, 3. minimally improved, 4. no change, 5. minimally worse, 6. much worse, 7. very much worse) [Mesa 2013].

The questionnaires should be administered in the participants' local language at the beginning of the study visit before receiving any study intervention, before any other study assessment or consultation with the investigator and before being informed of their current disease status.

Attempts should be made to collect all questionnaires for all participants, including those who discontinue the study before the 30-day safety follow-up visit. If the participant refuses to complete the questionnaires, this should be documented in study source records. This is not considered a protocol deviation.

Completed questionnaires, including both responses to the questions and any unsolicited comments written by the participant, should be reviewed by the investigator or designated study site personnel to ensure every question has been answered, there is only one response for each question and if any responses indicate potential adverse events. If omissions or double responses occur, they should be brought to the attention of the participant. Investigators must not encourage the participant to change responses reported in questionnaires.

8.3. Safety Assessments

8.3.1. Adverse Events

Requirements for recording and reporting adverse events and serious adverse events (SAEs) are described in Section 8.4.

8.3.2. Physical Examinations

A physical examination will be carried out on each body system at screening and repeated on Cycle 1 Day 1 (if not performed within 72 hours before Cycle 1 Day 1 (i.e. first day of study intervention), on Day 1 of each subsequent cycle, the end of treatment visit and the 30-day safety follow-up visit. Body weight will also be measured as part of the physical examination.

A complete physical examination including assessments of the cardiovascular, respiratory, gastrointestinal, dermatological, ophthalmological and neurological systems (at a minimum) will be performed at screening. Ophthalmic examination will include visual acuity (Standard Logarithmic Visual Acuity Chart, see Appendix 5), tonometry (intraocular pressure), slit lamp examination, and fundoscopy. Physical examinations should be targeted as clinically indicated at subsequent visits.

Measurements of BSA will be made on Cycle 1 Day 1 and Day 1 of each subsequent cycle to calculate the dose for study intervention infusions. All assessments during the treatment phase should be made predose.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

Physical examination will be globally evaluated as “normal/abnormal”. Further target inspection will be undertaken for any abnormal finding and an adverse event recorded if the abnormal finding is clinically significant.

8.3.3. Dermatological Examination

Dermatological examinations will be performed for all patients at screening then for participants receiving encorafenib (SLI phase and doublet arm of the randomized phase) only. This is to monitor for the possible development of keratoacanthoma and/or squamous cell carcinoma and new primary melanoma, as these have been reported to occur with selective BRAF inhibitor treatment. This assessment will be performed at screening and every 8 weeks from Cycle 1 Day 1 (i.e. on Day 1 of Cycles 1, 3, 5, 7…), the end of treatment visit and the 30-day safety follow-up visit. All assessments during the treatment phase should be made predose.

Following the 30-day safety follow-up (when clinically appropriate) it is recommended further dermatological examinations be performed for up to 6 months after the last encorafenib dose or until initiation of another antineoplastic therapy.

In case of occurrence of suspicious skin lesions, participants should undergo complete surgical excision of the skin lesion following study site standards. The evaluation may be done by the dermatologist if clinically indicated.

8.3.4. Other examinations/Chest, abdomen and pelvis CT scanner

Based on its mechanism of action, encorafenib may promote malignancies associated with activation of RAS through mutation or other mechanisms.

Head and neck examination, chest/abdomen computerised tomography (CT) scan, anal and pelvic examinations (for women) and complete blood cell counts prior to initiation, during and at the end of treatment will be performed as clinically appropriate.

8.3.5. Clinical Safety Laboratory Assessments

Laboratory tests performed before the start of study intervention to determine eligibility or baseline status only (i.e. for viral serology and tests to confirm postmenopausal status for females) are detailed in Section 8.1.3. Pregnancy testing is detailed in Section 8.3.6.

Blood samples for hematology, clinical chemistry, coagulation and urine samples for dipstick urinalysis will be taken at screening and repeated on Cycle 1 Day 1 (if not performed within 72 hours before Cycle 1 Day 1 (i.e. first day of study intervention), on Day 1 of each subsequent cycle, the end of treatment visit and the 30-day safety follow-up visit. Additional blood samples will be taken as follows:

- For hematology:

- Cycle 1 Days 15 and 22 for all participants.

- Day 15 of each cycle from Cycle 2 onwards for participants in the control arm of the randomized phase continuing to receive irinotecan only.

- For clinical chemistry: on Cycle 1 Day 15 for all participants.

All assessments during the treatment phase should be made predose. All clinical chemistry assessments should be made after the participant has fasted for at least 8 hours.

The parameters to be assessed at each timepoint are listed in Table 12.

Calculated creatinine clearance (Cockcroft-Gault formula) will be measured at screening and baseline for purposes of determining eligibility to participate in the study (see section 5.1.2):
- Female: CrCl=(140-age) × weight (Kg) × 0.85 /72× serum creatinine (mg/dL);
- Male: CrCl=(140-age) × weight (Kg) × 1.00 /72× serum creatinine (mg/dL.

Unscheduled clinical laboratory tests may be obtained at any time during the study at the investigator's discretion. Laboratory test results required to make decisions regarding potential dose modifications (as specified in Section 6.6) should be reviewed before study intervention administration.

Table 12: Protocol-required Clinical Laboratory Safety Assessments

Hematology	Erythrocytes (RBC), hematocrit, hemoglobin, platelets Leukocytes (WBC) count with differential: basophils, eosinophils, lymphocytes, monocytes, neutrophils/ANC
Chemistry[a]	Albumin, alkaline phosphatase, ALT, AST, lipase, amylase, bilirubin (total and indirect) blood urea nitrogen/urea, calcium, chloride, creatine kinase, creatinine, glucose, LDH*, magnesium, potassium, sodium, total protein, troponin I or T, uric acid* * LDH and uric acid won't be collected after final analyses cut-off date.
Coagulation	aPTT, INR or PT
Urinalysis	Specific gravity Blood, glucose, leukocytes, ketones, pH, protein by dipstick Microscopic examination (if blood or protein abnormal)

Abbreviations: aPPT = activated partial thromboplastin time; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; INR = international normalized ratio; LDH = lactate dehydrogenase; pH = hydrogen ion concentration; PT = prothrombin time; RBC = red blood cell(s); SAE = serious adverse event; ULN = upper limit of normal; WBC = white blood cell.

[a] Details of liver clinical chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Table 29. All events of ALT >3 × ULN and bilirubin >2 × ULN (>35% direct bilirubin) or ALT >3 × ULN and INR >1.5, if INR measured which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE.

Blood samples will be collected, handled and analyzed at the local laboratory according to the study site's standard procedures and the latest updated references. If needed, lipase and amylase will be collected locally and sent to central laboratory for analysis. Ranges from the laboratory will be used to identify abnormal values. Urinalysis will be performed in the clinic or at the local laboratory, according to study site standards.

The investigator must review the laboratory report, document this review and record any clinically relevant changes occurring during the study as an adverse event. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. An abnormal laboratory value that is not associated with an already reported adverse event is to be recorded as an adverse event only if an action on the study intervention is made as a result of the abnormality, if intervention for management of the abnormality is required or at the discretion of the investigator.

All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

If laboratory values from non-protocol specified laboratory assessments performed at the study site's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g. adverse event, SAE or dose modification), then the results must be recorded in the eCRF.

8.3.6. Pregnancy Testing

Pregnancy tests will be performed on females determined to be WOCBP only (see Appendix 10.2.1). All tests must be sensitive to 25 IU/L β-hCG.

A serum test will be performed by the study site's local laboratory at screening. Local urine pregnancy tests will be repeated on Cycle 1 Day 1 (if not performed within 72 hours before Cycle 1 Day 1 (i.e. first day of study intervention), on Day 1 of each subsequent cycle, the 30-day safety follow-up visit and at the end of treatment visit. Further tests may be performed at any time if pregnancy is suspected. All assessments during the treatment phase should be made predose.

The pregnancy tests at screening and predose on Cycle 1 Day 1 must be negative for inclusion. Any positive pregnancy tests during the treatment period will result in immediate discontinuation of study intervention (see Section 7.1). If any urine test cannot be confirmed as negative (e.g. an ambiguous result), a serum pregnancy test is also required.

Pregnancies will be managed as defined in Section 8.4.5.

8.3.7. Vital Signs

Tympanic temperature, pulse rate, respiratory rate, systolic blood pressure and diastolic blood pressure will be measured using study site standard techniques at screening and repeated on each visit during the treatment phase, the end of treatment visit and the 30-day safety follow-up visit.

Limits for abnormal values for blood pressure should be graded according to NCI CTCAE Version 4.03.

Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g. television, cell phones). All assessments during the treatment phase should be made predose and before blood collection for laboratory tests.

Any treatment-emergent abnormal findings should be recorded as adverse events.

8.3.8. Electrocardiograms

12-lead ECGs will be obtained using an internationally recognized 12-lead cardiograph that automatically calculates the heart rate and measures PR, QRS complex, QT and QTcF intervals. All the original print-outs will be maintained with the source documents. Each print-out will include the participant's code, date, time, technician's initials and investigator's signature.

12-lead ECGs should be preceded by at least 5 minutes of rest in supine position for the participant in a quiet setting without distractions (e.g. television, cell phones):

A single ECG measurement will be performed at screening to determine eligibility.

During Cycle 1, ECGs will be performed as follows:

A triplicate ECG predose on Day 1 (conducted within approximately 5 to 10 minutes total time). The mean of the triplicate ECG measurements will serve as the participant's baseline value for all postdose comparisons.

For participants receiving the doublet only (SLI phase and doublet arm of the randomized phase): a single ECG at 2 (±0.5) hours after administration of encorafenib and before the start of the cetuximab infusion on Day 1.

A single ECG predose on Day 15.

During Cycle 2, ECGs will be performed as follows:

A single ECG predose on Day 1.

For participants receiving the doublet only (SLI phase and doublet arm of the randomized phase): a single ECG at 2 (±0.5) hours after administration of encorafenib and before the start of the cetuximab infusion on Day 1.

Further ECGs will be performed on Day 1 predose in all subsequent cycles, the end of treatment visit and the 30-day safety follow-up visit.

12-lead ECGs will be performed before blood collection, where applicable.

Interpretation of the tracing, heart rate, PR, QRS complex and QTcF interval will be made locally by the investigator or designated physician and evaluated as normal or abnormal and recorded in the eCRF. Clinically significant abnormalities present at screening and new or worsened clinically significant findings occurring after screening will be reported in the eCRF. 12-lead ECGs for which treatment-emergent abnormal results are collected will be repeated until the values returned to normal or to a stable status. The frequency with which such checks are made will be defined by the investigator according to the degree of abnormality. If appropriate, the participant will be referred to a local cardiologist.

8.3.9. Cardiac Function

NA.

8.3.10. Eastern Cooperative Oncology Group Performance Status

An assessment of ECOG performance status will be made at screening (see Table 13). All participants must have a score of 0 or 1 for inclusion. Assessments will be repeated on Cycle 1 Day 1 (if not performed within 72 hours before Cycle 1 Day 1 (i.e. first day of study intervention), on Day 1 of each subsequent cycle, the end of treatment visit and the 30-day safety follow-up visit, till the cut-off date of final analysis is reached. ECOG performance status should be obtained on the scheduled day, even if study intervention is being held.

Table 13: Eastern Cooperative Oncology Group 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. Adverse Events and Serious Adverse Events

Adverse events and SAEs are defined in Appendix 10.8. Events meeting these definitions are also specified.

8.4.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All adverse events will be collected from when the participant first provides informed consent[3] until 30 days after study intervention discontinuation. If the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study and he/she considers the event to be related to the study intervention or study participation, the investigator must promptly notify the sponsor.

After cut-off date of final analysis:
•Until 30-day safety follow up visit all SAE or/and any adverse events leading to study treatment discontinuation are collected.
•Beyond 30 days after the last dose of study intervention, only related-SAE (SAE considers to be related to the study intervention), must be promptly notified by the investigator to the sponsor via the SAE notification form

8.4.2. Method of Detecting, Recording and Reporting Adverse Events and Serious Adverse Events

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate or the participant's legally authorized representative). Care will be taken not to introduce bias when detecting adverse events. Open-ended (participant’s spontaneous reporting) and non-leading verbal questioning of the participant are the preferred methods.

The investigator and designated study site personnel are responsible for detecting, documenting and recording events that meet the definition of an adverse event/SAE and remain responsible for

[3]Molecular prescreening or screening, whichever occurs first.

following up events that are serious, considered related to the study treatment or study procedures, or that caused the participant to discontinue the study or study intervention (see Section 7).

The records of adverse events must describe the nature (diagnosis, signs and symptoms), intensity, date/time of onset, date/time of end, outcome and actions taken with study intervention, relationship to study intervention (in the investigator's opinion) and whether the event is serious or not.

The process of recording, evaluating and assessing adverse events/SAEs for intensity and causality is provided in Table 14.

Table 14: Process for Recording, Evaluating and Assessing Adverse Events and Serious Adverse Events

Recording
When an adverse event/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory reports and diagnostics reports) related to the event. For a recurrent adverse event (that resolves and subsequently recurs), each recurrence must be recorded as a separate adverse event. For a continuous adverse event (i.e. unresolved between participant assessments), any change in intensity (improvement or worsening) or seriousness must be recorded with the indication of the start and (if applicable) the end of the change within the same adverse event report. The investigator will then record all relevant adverse event/SAE information in the eCRF. It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the sponsor or designee in lieu of completion of adverse event/SAE. There may be instances when copies of medical records for certain cases are requested by sponsor or designee. In this case, all participant identifiers, except for the participant number, will be redacted on the copies of the medical records before submission. The investigator will attempt to establish a diagnosis of the event based on signs, symptoms and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the adverse event/SAE.
Assessment of Intensity
The investigator will make an assessment of intensity for each adverse event/SAE. Wherever possible this should be performed using the NCI CTCAE Version 4.03 scale [NCI CTCAE 2010]. For any term not specifically listed, intensity should be assigned as Grade 1 through 5 according to the following categories: Grade 1 (mild): asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. Grade 2 (moderate): minimal, local or non-invasive 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 (death related to adverse event). Note: An event is defined as 'serious' when it meets at least one of the predefined seriousness criteria (see Appendix 10.8.2) NOT when it is rated as severe.
Assessment of Causality
The investigator is obligated to assess the relationship between study intervention and each occurrence of each adverse event/SAE. A "reasonable possibility" of a relationship conveys that there are facts, evidence and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

The investigator will use clinical judgment to determine the relationship. Alternative causes, such as underlying disease(s), concomitant therapy and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated. The investigator will also consult the Investigator's Brochure and/or locally approved Product Information, for marketed products, in his/her assessment. For each adverse event/SAE, the investigator **must** document in the medical notes that he/she has reviewed the event and has provided an assessment of causality. There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor's Corporate Vigilances Division. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor's Corporate Vigilances Division. The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment. The causality assessment is one of the criteria used when determining regulatory reporting requirements.
Abbreviations: eCRF = electronic case report form; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; SAE = serious adverse event.

All events determined to be SAEs (irrespective of study intervention or causality) will be recorded and reported to the sponsor or designee immediately to facilitate the regulatory reporting requirements in Section 8.4.4. Under no circumstances should this exceed 24 hours.

The primary means for reporting SAEs to the sponsor's Corporate Vigilances Division is using the SAE Form (pdf extension) included into the eCRF. The study site personnel will enter the SAE data into this enterable pdf SAE Form and will send the completed pdf SAE Form to ensure the event is reported within 24 hours of awareness:

If the electronic system is unavailable, the paper SAE form available at site will be used.

E-mail is the preferred method to transmit SAE information to the sponsor's Corporate Vigilances Division. The paper SAE form (with all the available information about the event) should be sent to:

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 rare circumstances and in the absence of fax equipment, notification by telephone is acceptable with a copy of the SAE form sent by overnight mail or courier service.

Note: Initial notification to the sponsor by telephone does not replace the need for the investigator to complete the SAE form within the designated reporting timeframes.

8.4.3. Follow-up of Adverse Events and Serious Adverse Events

The investigator is obligated to proactively follow-up all adverse events and perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by sponsor or designee to elucidate the nature and/or causality of the event as fully as possible. This may include additional laboratory tests or investigations, histopathological

examinations or consultation with other health care professionals. If a participant dies during participation in the study or during the follow-up period, the investigator will provide the sponsor with a copy of any postmortem findings, including histopathology.

All SAEs will be followed until resolution, stabilization, the event is otherwise explained or the participant is lost to follow-up (as defined in Section 7.3).

The investigator will submit any new or updated SAE data to the sponsor's Corporate Vigilances Division within 24 hours receipt of the information. New or updated information will be entered on a new SAE form.

8.4.4. Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify the competent authority about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific requirements relating to safety reporting to the competent authority, Independent Ethics Committees (IEC) and investigators.

An SAE is determined to be a suspected unexpected serious adverse reactions (SUSAR) if it meets all the following criteria:

Unexpected (i.e. nature or severity of which is not consistent with the study intervention description [e.g. Investigator's Brochure for an unapproved investigational product or locally-approved Product Information for a marketed product]).

Serious.

Assessed to be related to study intervention.

Safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives a safety report describing a SAE or other specific safety information (e.g. summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IEC, if appropriate according to local requirements.

8.4.5. Pregnancy

Contraceptive requirements for female and male participants are specified in Section 5.3.1.

The investigator will attempt to collect pregnancy information on any female participant or male participant's female partner who becomes pregnant while the participant is in the study, during or after exposure to study intervention.

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy.

For female study participants only, the study site personnel will enter the pregnancy information into the eCRF as soon as it is available.

In addition, for female participants and male participants' female partners, the study personnel will enter the pregnancy information in a paper pregnancy form and will ensure the event is reported within 24 hours of awareness:

E-mail is the preferred method to transmit pregnancy information to the sponsor's Corporate Vigilances Division. The paper pregnancy form (with all the available information about the event) should be sent to:

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 rare circumstances and in the absence of fax equipment, notification by telephone is acceptable with a copy of the pregnancy form sent by overnight mail or courier service.

Note: Initial notification to the sponsor by telephone does not replace the need for the investigator to complete the pregnancy form within the designated reporting timeframes.

Additional informed consent will be sought (required within 72 hours) from female study participants to follow the pregnancy to outcome. Likewise, informed consent to follow the pregnancy will be sought from a pregnant female partner of a male study participant) (see Appendix 10.1.4). Once informed consent is provided, additional pregnancy information will be submitted to the sponsor on the paper pregnancy form following the process above.

The pregnant female will be followed until the completion/termination of the pregnancy. Information on the status of the mother and the neonate will be forwarded to the sponsor using pregnancy form. Follow-up will be performed for as long as necessary beyond the delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Abnormal pregnancy outcomes (e.g. spontaneous abortion [occurring at <22 weeks gestational age], stillbirth (occurring at >22 weeks gestational age), fetal death, congenital anomalies, ectopic pregnancy) are always considered to be an SAEs (see Appendix 10.8.2).

Any poststudy pregnancy-related SAE considered related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.4.2. While the investigator is not obligated to actively seek this information in former study participants, he/she or she may learn of an SAE through spontaneous reporting.

If pregnancy is suspected during treatment period, the study intervention(s) should be temporarily discontinued (see Section 7.1.1) immediately until the result of the pregnancy testing is known. If pregnancy is confirmed, then the study intervention should be permanently discontinued (see Section 7.1.2) in an appropriate manner and the participant discontinued from the study.

8.4.6. Cardiovascular and Death Events

Cardiovascular and death events will be recorded and reported as specified in Section 8.4.1 to Section 8.4.4.

8.4.7. Disease-related Events and/or Disease-related Outcomes Not Qualifying as Adverse Events or Serious Adverse Events

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 endpoint, as part of efficacy assessment) and should NOT be reported as an SAE unless a causal relationship to study treatment is suspected (see definition of an adverse event in Appendix 8).

8.4.8. Adverse Events of Special Interest

Adverse events of special interest are listed in appendix 10.11.

8.5. Overdose

For this study, any dose of study intervention greater than the participant's assigned dose according to protocol recommendations will be considered an overdose. The sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator or designated physician should:

1. Contact the medical monitor immediately.

Closely monitor the participant for any adverse event/SAE and laboratory abnormalities until study intervention can no longer be detected systemically (at least 7 days). In the absence of seriousness criteria, the overdose, and associated adverse events if any, are reported only on the adverse event eCRF page. **If the definition of any of the seriousness criteria is met**, the SAE Form must be also completed and transmitted to the sponsor.

Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

8.6. Pharmacokinetics

8.6.1. Pharmacokinetic Samples

For participants receiving the doublet only (SLI phase and doublet arm of the randomized phase), blood samples for characterization of the PK of encorafenib and cetuximab will be collected on the first day of treatment (Cycle 1 Day 1) and at steady state after 1 month treatment (Cycle 2 Day 1).

Serial blood samples will be collected from a subset of 24 participants treated at the recommended dose at selected sites (all nine participants in the SLI phase and the first 15 participants at the selected sites in the doublet arm of the randomized phase). Sparse sampling will be performed in all remaining participants in the doublet arm.

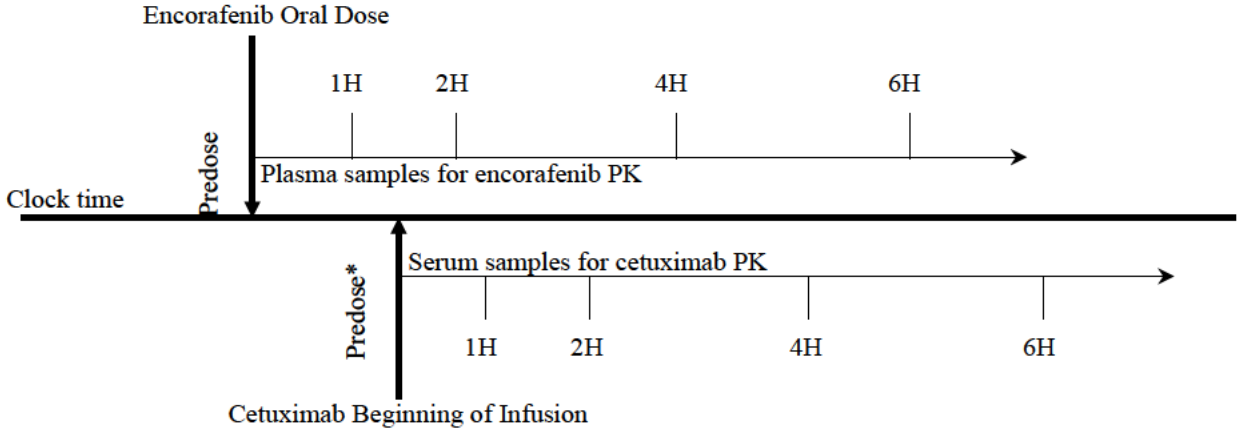
The timepoints for the serial and sparse sampling schedules are shown in Table 15.

Table 15: Sampling for Serial and Sparse Pharmacokinetic Schedules

	N	Cycle 1 Day 1					Cycle 2 Day 1				
		Pre	1 H	2 H	4 H	6 H	Pre	1 H	2 H	4 H	6 H
SLI Phase – Serial Sampling											
Encorafenib sampling[a]	9	X	X	X	X	X	X	X	X	X	X
Cetuximab sampling[b]		X	X	X	X	X	X	X	X	X	X
Randomized Phase – Doublet Arm Serial Sampling											
Encorafenib serial sampling[a]	15	X	X	X	X	X	X	X	X	X	X
Cetuximab sampling[b]		X	X	X	X	X	X	X	X	X	X
Randomized Phase – Doublet Arm Sparse Sampling											
Encorafenib sparse sampling[a]	48			X		X	X		X		
Cetuximab sparse sampling[b]				X		X	X		X		

Abbreviations: H = hours postdose; pre = predose; SLI = safety lead-in, N = number of participants.
[a] Timepoints are in relation to the encorafenib dose.
[b] The timepoints are in relation to the start of the cetuximab infusion.

Figure 3: Graphic Representation of Pharmacokinetic Sampling Plan



**Predose PK samples for cetuximab analysis should be collected just prior the beginning of the cetuximab infusion*
Abbreviations: H = hours postdose; PK = pharmacokinetics

Two blood samples of approximately 4 mL (one for analysis of the concentration of encorafenib in plasma and one for analysis of the concentration of cetuximab in serum) will be collected at each nominal timepoint. The sampling times will be in relation to the encorafenib dose or cetuximab start of infusion as shown in Figure 3. The exact date and time of each sample will be recorded.

Predose sampling information should include the dose amount taken and the date and approximate time of the most recent previous dose of encorafenib, or cetuximab (except for Cycle 1 Day 1). Postdose sampling information for encorafenib should include the exact date and time of the morning dose, including the dose amount taken. Postdose infusion information for cetuximab should include dose, start time, and infusion duration. Infusion interruptions should also be documented.

The total number of blood samples for PK analytical determination per participant will be either 20 for serial sampling or eight for sparse sampling (total volume of blood 80 mL or 32 mL, respectively).

If a participant experiences an adverse event that results in an unscheduled visit or meets the criteria for an SAE, a further blood sample should be collected (if feasible and if less than 24 hours have elapsed since the last dose). On Cycle 1 Day 1 and Cycle 2 Day 1, if vomiting occurs within the first 4 hours postdose, the exact time of the first vomiting episode on that day must be noted. If a vomiting episode occurs within the first 4 hours postdose on the day of the last encorafenib dose prior to collection of PK samples (on Cycle 2 Day1), the exact time (whenever possible) must be noted in the e-CRF.

Study visits for PK sampling should be scheduled in the morning so that correct predose and postdose PK blood samples can be collected. The encorafenib dose on PK visit days **should be taken at the study site, only after collecting the predose PK sample**.

The following must be considered when taking PK blood samples:

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.

Each plasma or serum sample will be divided into aliquots (primary aliquots for PK analysis and back-ups). Samples will be stored at the study site at -20°C. Primary aliquots will be shipped to central laboratory on the day of collection or the day after, at the latest, and back-ups within 28 days of collection. Samples may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Complete information regarding blood sample collection and processing, handling and shipment will be provided in the Laboratory Manual. The primary and back-up aliquots will be shipped separately. The samples will be stored at the central laboratory at -70°C until transfer to the third-party bioanalytical laboratory for analytical determination.

8.6.2. Analytical Determination

Analytical determination of plasma concentrations of encorafenib and serum concentrations of cetuximab will be carried out at a designated third-party bioanalytical laboratory using validated liquid chromatography tandem mass spectrometry (LC/MS-MS) and immunoassay methods.

8.6.3. Pharmacokinetic Analysis

Encorafenib and cetuximab concentrations will be transmitted by the bioanalytical laboratory to the subcontractor in charge of PK analysis. Non-compartmental and population PK analyses will be performed, as appropriate (see Section 9.4.3.9).

8.7. Pharmacodynamics

Not applicable. Pharmacodynamics will not be assessed in the study.

8.8. Pharmacogenomics

Not applicable. Pharmacogenomics will not be assessed in the study.

8.9. Other Exploratory Biomarker Assessment

Collection of samples for exploratory biomarker research is also part of this study. Blood and tumor tissue will undergo further exploratory assessments as described in Section 8.9.1 to Section 8.9.4. Blood sampling requirements for biomarkers are summarized in Table 16.

Table 16: Estimated Blood Sampling for Biomarker Assessments

Sample Type	Sample Volume (mL)	Number of Samples				Total Biomarker Blood Volume (mL)
		Screening	Treatment Phase			
			Baseline0	During Treatment	EOT Visit	
SLI Phase and Randomized Phase: Doublet Arm						
CRP	2.5	1	0	0	0	2.5
CCI	5	1	1[b]	1 per cycle	1	15+5 per cycle
MSI biomarker	2	0	1	0	0	2
					TOTAL	17 +5 per cycle
Randomized Phase: Control Arm						
CRP	2.5	1	0	0	0	2.5
CCI	5	1	1[b]	1 per cycle	1	15+5 per cycle
MSI biomarker	2	0	1	0	0	2
					TOTAL	19.5+5 per cycle

Abbreviations: CRP = C-reactive protein; EOT = end of treatment; MSI = microsatellite instability.

Cycle 1 Day 1 predose.

If not performed within 72 hours before C1D1 (i.e.first dose of study intervention)

Blood samples sent to the local laboratory for analysis will be collected, handled and analyzed according to the study site's standard procedures.

For blood and tumor samples sent to the central laboratory or third-party bioanalytical laboratory for analysis, information regarding tissue specimen and blood sample collection and processing, handling and shipment will be provided in the Laboratory Manual.

8.9.1. RAS Mutation Status

The FFPE tumor tissue source collected for central determination of *BRAF* V600E status at molecular prescreening or screening (see Section 8.1 will also be used to retrospectively test *RAS* wt status by the central laboratory.

8.9.2. Microsatellite Instability Status

The Microsatellite Instability Status (MSI) is a common test done for colorectal cancer patients in order to assess the disease subtype (MSI-H vs MSS) and prognosis. The results from this test will help analyse and interpret the clinical outcomes of patients in the study. The following samples will be used to test MSI status at the central laboratory:

FFPE tumor tissue source collected for central determination of *BRAF* V600E status at molecular prescreening or screening (see Section 8.1.1). The MSI test will analyze mutations in only five mononucleotide repeat markers (BAT-25, BAT-26, NR-21, NR-24 and MONO-27). This analysis will be compared to the same test done in DNA obtained from normal cells in a blood sample (below).

A blood sample at baseline (Cycle 1 Day 1 predose) to assess germline (normal DNA) as control for the same test done in the tumor sample. (see Table 16). This control is necessary to validate the MSI status of the tumor. The test in this study is a standard test that only targets five mononucleotide repeat markers (BAT-25, BAT-26, NR-21, NR-24 and MONO-27). No exploration of the patient's genetics will be done.

8.9.3. C-reactive Protein

A blood sample will be collected at screening for analysis of CRP, a marker of inflammation, at the central laboratory (see Table 16).

CCI

[redacted]

8.9.5. Sample collection for companion diagnostic validation

The FFPE tumor tissue source collected for central determination of BRAF V600E status at molecular prescreening or screening (See section 8.1.2 and 8.1.3) will also be used to retrospectively perform a comparison analysis between the BRAF V600E mutation as determined centrally in this clinical study with a companion diagnostic candidate.

8.10. Immunogenicity Assessments

Not applicable, immunogenicity will not be assessed in this study.

8.11. Health Economics

Not applicable, health economics will not be assessed in this study.

9. Statistical Considerations

This section presents a summary of the planned statistical analyses. Statistical analysis will be performed under the supervision of the study statistician at the Biometry Department, IRPF.

9.1. Statistical Hypotheses

Because of the exploratory nature of the SLI phase, all data will be analyzed descriptively and not as inferential issues. No formal statistical testing will therefore be performed.

The main aim in the randomized phase is to compare the efficacy of the doublet arm versus the control arm, as measured by the primary endpoint of PFS by BICR where $HR_{PFS\ (doublet\ vs\ control)}$ is the hazard ratio for PFS of the doublet arm versus the control arm. The following statistical hypotheses will be tested to address the primary objectives:

$$H_0: HR_{PFS}\ (\text{doublet vs control}) \geq 1 \text{ vs } H_1: HR_{PFS}\ (\text{doublet vs control}) < 1$$

which corresponds to the rejection of the null hypothesis (the PFS time for the doublet arm is less than or equal to the PFS time of the control arm).

9.2. Sample Size Determination

The planned sample size is of 103 participants (nine treated in the SLI phase and approximately 94 randomized in the Phase II part). Additional participants may be included in SLI phase if deemed necessary. The definition of a screen failure is provided in Section 5.4. Approximately 147 participants will be screened to achieve an estimated total of 103 participants.

9.2.1. Safety Lead-in Phase

Participants will be assigned to the starting dose of encorafenib 300 mg QD and cetuximab 400 mg/m^2 initial dose then 250 mg/m^2 once weekly thereafter. The dose for encorafenib and cetuximab will be considered acceptable if the observed Cycle 1 DLT rate is <33% (i.e. less than three participants with DLTs) out of nine evaluable participants (see Section 4.1.3 for the definition of a DLT). To be evaluable participants must meet the criteria for the Dose-determining Set (DDS) in Section 9.3**.**

A comparison of the operating characteristics for this dose-testing rule with nine participants and traditional 3+3 rules is shown in Table 17. The results illustrate the benefit of the additional participants as the probability of falsely declaring a dose to be toxic is lowest with a nine-participant cohort when the true DLT rate is ≤20%. Similarly, the probability of correctly declaring a dose to be toxic is higher with the nine-participant cohort when the true DLT rate is ≥40%. In addition,

observing no Cycle 1 DLTs in nine participants would be expected to occur with probability 0.040 if the true DLT rate is 30%.

Table 17: Operating Characteristics of Safety Lead-In Criteria for Nine Participants Compared To 3+3 Rules

True Cycle 1 DLT Rate	Probability of Dose Declared Toxic using 3+3 Rules	Probability of Observed Cycle 1 DLT rate ≥33% in Nine Participants
10%	0.094	0.053
20%	0.291	0.262
30%	0.506	0.537
40%	0.691	0.768
50%	0.828	0.910
Abbreviations: DLT = dose limiting toxicity.		

If the independent DMC determines the doses to be tolerable in the nine evaluable participants based on observed DLTs and the evaluation of the overall toxicity profile based on accumulated safety data, then the study will proceed to the randomized phase of the study.

9.2.2. Randomized Phase

The objective is to evaluate the consistency of the ARRAY-818-302 study data in the Chinese population. The study design therefore aims to detect a difference between the two arms (doublet arm and control arm) in terms of PFS. In the control arm, the median PFS is estimated to be 2 months[De Roock 2010, Saridaki 2013, Ulivi 2012]. The present study is powered to detect a PFS benefit that would result in a 2 months median difference between arms, i.e. from 2 to 4 months; this corresponds to a hazard ratio of 0.5.

A one-sided log-rank test will be used, with the following parameters: alpha=0.025, beta=0.2

Applying a 2:1 randomization and considering 10% of lost to follow-up a total number of 94 participants (63 participants in the doublet arm and 31 in the control arm) will be randomized in the study. With a monthly accrual rate of five participants, the duration of recruitment will be approximately 18.8 months. Under these hypotheses, 74 events should occur 21 months after the first randomized participants. The cut-off date for the main analysis will be set at the occurrence of the 74th event or when all participants without PFS event (disease progression per BICR or death) will have had the opportunity to perform their tumor assessment planned at week 36, whichever comes first.

Note that the power will depend on the number of PFS events that will be observed at the time of the main analysis (for example: if only 65 events are observed at the cut-off date due to high number of censored patients, power is estimated at 75%). The number of participants and timing of the analyses were determined using EAST6.4

9.3. Populations for Analyses

The following populations will be analyzed:

Population	Description
Screened Patients Set	All participants who signed the main (screening) ICF for the study.
Full Analysis Set (FAS)	For the SLI phase: all participants who receive at least one dose of study intervention. For the randomized phase: all randomized participants. Participants will be analyzed according to the study intervention assigned at randomization.
Safety Set	All participants who receive at least one dose of study intervention. Participants will be analyzed according to treatment received. There will be separate Safety Sets for the SLI phase and the randomized phase.
Dose-determining Set (DDS)	All SLI phase participants from the Safety Set who either completed a minimum exposure requirement and have sufficient safety evaluations or experienced a DLT. A participant is considered to have met the minimum exposure requirement if they received at least 75% of the planned dose of each study intervention during Cycle 1. Participants who do not experience a DLT during the first cycle will be considered to have sufficient safety evaluations if they have been observed for ≥28 days following the first dose, and are considered by both the sponsor and investigator to have enough safety data to conclude that a DLT did not occur.
Efficacy Set (ES)	All participants in the randomized phase and included in the FAS with a centrally confirmed mCRC *BRAF* V600E mutation.
Per-protocol Set (PPS)	All participants in the FAS who are considered sufficiently compliant with the protocol requirements. A precise definition of the criteria required for inclusion in the PPS will be provided in the SAP.
PK Set	All participants who receive at least one dose of encorafenib or cetuximab, and who have at least one postdose PK blood collection with associated bioanalytical results.

9.4. Statistical Analyses

A SAP will be prepared by the sponsor (or designee) and finalized prior to first participant first visit. This plan will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints. Any major modifications related to the primary endpoint definition or analysis will also be described in a protocol amendment.

The primary Clinical Study Report will be based on the data generated prior to the data cutoff date for the main analysis (see Section 9.2.2). An addendum to the Clinical Study Report will be written for the final analysis once all participants have been followed for at least 1 year after the start of study intervention of the last participant randomized, and when 70% of randomized patients died. As no statistical analysis will be conducted on data captured after final analysis, no additional addendum to CSR will be written and data summaries will be available upon request.

9.4.1. General Considerations

All analyses will be performed for the SLI and by treatment arm for the randomized phase of the study separately. All efficacy analyses will be performed using the FAS, and all safety analyses will be performed using the Safety Set unless otherwise specified. All data will be listed. This section summarizes the analyses planned on these data.

In general, following descriptive methods will be used to present all relevant data:

Continuous data will be presented using number of observations, number of missing, mean, standard deviations, median, lower and upper quartiles, minimum and maximum. 95% confidence intervals (CI) will be presented if relevant.

Categorical data will be summarized using number of observations, frequencies, percentages and number of missing. Unless otherwise specified, the calculation of proportions will be based on the non-missing data. Counts of missing observations will be excluded from the denominator if not otherwise specified in the SAP.

Formal statistical testing will be performed on the primary endpoint in the randomized phase for the main analysis. The overall significance level will be 0.025 (1-sided) and all statistical testing will be performed as 1-sided. Confidence intervals will be 2-sided with a confidence level of 95%, if not otherwise specified. The SLI phase results, the secondary and exploratory endpoints, supportive analyses and subgroup analyses in the randomized phase will be reported with descriptive statistics only.

The statistical analysis will be performed after the database lock using statistical analysis software (SAS®).

9.4.1.1. Pooling of Centers

In order to provide overall estimates of treatment effects, data will be pooled across study centers. The “center” factor will not be considered in statistical models or for subgroup analyses due to the high number of participating centers in contrast to the anticipated small number of participants randomized at each center.

9.4.1.2. Stratification Factors

The analysis of the randomized phase will be stratified using stratification factors collected via the IRT: ECOG performance status (0 versus 1) and prior use of irinotecan (yes versus no).

9.4.1.3. Baseline Definition

For all endpoint’s assessments in the SLI phase and all safety assessments in the randomized phase of the study, baseline is defined as the last completed and available assessment prior to date of first dose in the SLI phase and randomized phase, respectively. If an assessment that is planned to be performed prior to the first dose of study intervention in the protocol is performed on the same day as the first dose of study intervention and the time is unknown, it will be assumed that it was

performed prior to study intervention administration and will be considered as the baseline assessment.

For efficacy assessments in the randomized phase of the study, baseline is defined as the last assessment prior to randomization. If the assessment that is planned to be performed prior to randomization in the protocol is performed on the same day as the date of randomization and assessment time point is missing, it will be assumed that it was performed prior to randomization and will be considered as the baseline assessment. If such a value is missing, the last measurement prior to the first dose of study intervention will be used as the baseline measurement for the efficacy analysis, except for analyses of tumor assessments data where the baseline assessment would be considered missing.

Unscheduled assessments will be used in the determination of baseline. Data reported at the end of treatment visit are not eligible for baseline selection.

9.4.1.4. Definition of Treatment Period

The treatment period is defined as the time from the first dose of study intervention to last dose of study intervention + 30 days unless otherwise described in the SAP.

9.4.2. Primary Endpoint

9.4.2.1. Safety Lead-in Phase

The primary endpoints are described in Table 7.

The primary endpoint in the SLI is assessment of safety and tolerability of the doublet. The number and proportion of participants experiencing DLTs during the DLT evaluation period will be summarized and listed for the DDS. Analysis of other safety parameters will be performed as described in Section 9.4.3.8.

9.4.2.2. Randomized Phase

9.4.2.2.1. Primary Analysis

The primary endpoint is described in Table 8. The primary estimand is built to answer to the primary objective and evaluate PFS by BICR. The intercurrent events will be taken into account for the primary analysis as defined in Table 8.

Progression-free survival (PFS) is defined as the time from the date of randomization to the earliest documented date of disease progression per RECIST Version 1.1, or death due to any cause. PFS will be calculated in months.

If no event (disease progression or death) is observed or if an event is observed more than 12 weeks (for the first 24 weeks after randomization) or 24 weeks (after the first 24 weeks of randomization) after the last adequate tumor assessment (corresponding to two or more missing assessments), the

participant will be censored on the date of the last adequate tumor assessment that documented no progression. In addition, if a new anticancer therapy (medications or procedures) is started prior to an event, the participant will be censored on the date of the last adequate tumor assessment that documented no progression prior to the start of the new anticancer therapy.

An adequate post-baseline assessment is defined as an assessment where a response of complete response (CR), partial response (PR), stable disease (SD), non-CR/non-PD, or PD can be determined. Timepoints where the response is not evaluable or no assessment was performed will not be used for determining the censoring date.

Participants with no baseline tumor assessment (including participants with an inadequate baseline assessment) or with no adequate postbaseline tumor assessments within 12 weeks after the date of randomization will be censored on the day of randomization, unless the participant dies within 12 weeks of randomization, in which case, death will be an event on date of death.

The censoring and event date options to be considered for the PFS primary analysis are presented in Table 18.

If a PFS event is observed after a single missing or non-adequate tumor assessment, the actual date of event will be used. Participants without postbaseline tumor assessments but known to be alive will be censored at the time of the first administration of the study intervention.

Progression-free survival will be described in tabular and graphical format using Kaplan-Meier methods, reporting estimated median (in months) with 95% confidence intervals (CI), 25^{th} and 75^{th} percentiles [Brookmeyer and Crowley 1982, Klein and Moeschberger 1997] and Kaplan-Meier estimated probabilities with corresponding 95% CIs [Kalbfleisch and Prentice 2002] at selected timepoints. A Cox regression model stratified by randomization strata will be used to estimate the hazard ratio and the corresponding 95% CI based on the Wald test. The distribution of PFS will be compared using a stratified log-rank test.

Formal statistical testing will be performed as described in Section 9.4.1 to test the hypothesis in Section 9.1.

Table 18: PFS Outcome and Event Dates – Primary Analysis

Situation	Date of Progression/Censoring	Outcome
No adequate baseline assessment.	Date of randomization[a].	Censored[a]
PD or death ≤12 (or 24)[b] weeks after last adequate tumor assessment or ≤12 weeks after date of randomization.	Date of PD or death.	Event
PD or death >12 (or 24)[b] weeks after the last adequate tumor assessment[c] (two or more missing assessments).	Date of last adequate tumor assessment[c] documenting no PD, prior to new anticancer therapy or missed assessments.	Censored
No PD.		
New anticancer therapy given.		
Treatment discontinuation due to other reason than documented progression (e.g. toxicity, clinical progression based on investigator claim).	N/A (not considered as an event, patient without documented PD should be followed for progression after discontinuation of treatment).	Ignored

Abbreviations: N/A = not applicable; PD = progressive disease.

[a] If the participant dies ≤12 weeks after date of randomization, the death is an event with date on death date.

[b] Durations are equal to two times the length of the tumor assessment interval, which is 12 weeks for the first 24 months after randomization, and 24 weeks thereafter.

[c] If there are no adequate post-baseline assessments prior to the PD or death, then the time without adequate assessment should be measured from the date of randomization; if the criteria is met, the censoring will be on the date of randomization.

9.4.2.2.2. Sensitivity Analyses

The following sensitivity analyses will be performed to further assess the comparisons described by the primary objective. Additional sensitivity analyses may be specified in the SAP.

The PFS analysis will be repeated in the ES.

The PFS analysis will be repeated in the PPS.

The distribution of PFS in FAS will be compared between the treatment arms using an unstratified log-rank test and the hazard ratio (together with associated 95% CI) resulting from an unstratified Cox model will be presented.

Treatment policy estimand strategy will be used for intercurrent event of starting new anticancer therapy. PDs or deaths that occur after the start of new anticancer therapy will be considered as events.

Treatment policy estimand strategy will be used for intercurrent event of missing two or more tumor assessments (see Table 18). PDs or deaths that occur after two or more missing assessments will be considered as events.

The distribution of PFS in the FAS will be compared by adjusting with potential prognostic factors. As this comparison is not part of the testing strategy, no formal testing will be performed.

9.4.3. Secondary Endpoints

The secondary endpoints are described in Table 7 and Table 8.

The following analyses will be performed on the FAS and ES unless otherwise specified.

9.4.3.1. Progression-free Survival based on Investigator Assessments

The primary analysis will be repeated based on investigator assessments using the same analysis method and the same censoring rules described in Section 9.4.2.2**.** However, as these comparisons are not part of the testing strategy, no formal testing will be performed to compare these two treatment arms. The PFS will be described for the randomized phase only.

9.4.3.2. Overall Survival

Overall survival (OS) is defined as the time from randomization until date of death due to any cause. If a participant is not known to have died, survival will be censored at the date of last known date the participant was alive or at their last contact date whatever is earlier.

The Kaplan-Meier method will be used to estimate OS time. The median OS and its 95% CIs will be presented by treatment arm. Overall survival rates at different time points will be estimated with corresponding 2-sided 95% CIs. The OS of the doublet arm versus the control arm will also be analyzed using the same analysis method described for PFS. However, as this comparison is not part of the testing strategy, no formal testing will be performed to compare OS of these two treatment arms.

The Overall survival (OS) for doublet arm vs. control will be analyzed in a descriptive manner for the randomized phase only. According to the PMDA guidelines Method 1, a positive OS trend could be defined as observing at least half of the treatment effect obtained in BEACON study. Based on De Roock 2010, Ulivi 2012 and Saridaki 2013, a 6 months median OS is expected to be observed in the control arm (value also supported by BEACON study results), and a 9.3 months median OS was observed for Doublet in BEACON study. With limited survival data, OS analysis will be performed 21 months after the first randomized subject. With 94 randomized patients, the probability to observe a positive OS trend, i.e. an HR less than 0.8225, knowing that the true HR is 0.645 (6 months vs 9.3 months) and based on 56 deaths observed, is 80.3%.

9.4.3.3. Objective Response rate

Objective response rate (ORR) (for confirmed and unconfirmed responses) is defined as the proportion of participants with a best overall response of either CR or PR, as determined by BICR and investigator assessment per RECIST Version 1.1. The ORR will be described for the SLI phase and randomized phase.

Best Overall Response (BOR) is the best response obtained among all tumor assessment visits after the date of first dose (SLI) or the date of randomization (Phase II) until documented disease progression, death, start of subsequent antineoplastic therapy, and performed not later than 30 days after last dose intake. Clinical deterioration or clinical progression noted on the end of treatment visit eCRF will not be considered as documented disease progression. For confirmed BOR,

confirmation of the response will be performed per RECIST Version 1.1, preferably at the regularly scheduled assessment interval, but no sooner than 4 weeks after the initial documentation of CR or PR. Confirmation of PR or CR can be confirmed at an assessment later than the next assessment after the initial documentation of PR or CR, respectively (see Appendix 10.7).

Two sets of BOR will be considered, one for confirmed and one for confirmed + unconfirmed responses. BOR will be assessed based on BICR and investigator assessment.

The ORR will be provided with a corresponding Clopper-Pearson (exact) binomial 95% CI [Clopper and Pearson 1934].

9.4.3.4. Disease Control rate

The disease control rate (DCR) is defined as the proportion of participants with a confirmed BOR of CR, PR or SD, as determined by BICR and investigator assessment per RECIST Version 1.1. The DCR will be described for the randomized phase only.

9.4.3.5. Duration of Response

Duration of response (DOR) is defined for responders (CR or PR) only, as the time from the date of the first documented response to the earliest date of disease progression as determined by BICR and investigator assessment per RECIST Version 1.1, or death due to any cause.

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 before the cutoff date. The DOR of the doublet arm versus the control arm will be analyzed using the same censoring rules specified for PFS in Section 9.4.2.2.1. The Kaplan-Meier method will be used to estimate DOR time. The median DOR and its 95% CIs will be presented by treatment arm. DOR rates at different timepoints will be estimated with corresponding 2-sided 95% CIs. The DCR will be described for the SLI phase and randomized phase.

9.4.3.6. Time to Response

Time to response (TTR) (for confirmed and unconfirmed responses) is defined for responders (CR or PR) as the time between the date of randomization until the first documented response of CR or PR per RECIST Version 1.1. Participants who do not have a CR or PR by the data cutoff date will be censored for time to response at their last radiological assessment. Participants who receive subsequent anticancer therapy prior to response will be censored at their last radiological assessment prior to initiation of subsequent anticancer therapy. The Kaplan-Meier method will be used to estimate TTR. The median TTR and its 95% CIs will be presented by treatment arm. TTR rates at different timepoints will be estimated with corresponding 2-sided 95% CIs. The TTR will be described for the randomized phase only.

9.4.3.7. Patient Reported Outcomes

Detailed methodology for summary and statistical analyses of the data on PROs will be further detailed in the SAP. All PRO analyses will be performed on the FAS and provided for the randomized phase only.

The QoL questionnaires (EORTC QLQ-C30, FACT-C, EQ-5D-5L, PGIC) will be scored according to their respective user guides/scoring manuals. The number and percentage of participants who complete each questionnaire will be summarized at each timepoint by treatment arm, as will the reasons for non-completion of these measures.

Descriptive statistics will be used to summarize the scored scales at each scheduled assessment. Additionally, change from baseline in the domain scores at the time of each assessment will be summarized. Patients with an evaluable baseline score and at least one evaluable postbaseline score during the treatment period will be included in the change from baseline analyses. In addition, a repeated measurement analysis model may be used to compare the two treatment arms with respect to changes in the domain scores longitudinally over time. Full details of the modelling analysis will be provided in the SAP.

Time to definitive deterioration in the QoL domains will be assessed in the treatment arms. The time to definitive deterioration is defined as the time from the date of randomization to the date of event, which is defined as at least 10% worsening relative to baseline of the corresponding scale score with no later improvement above this threshold observed during the course of the study or death due to any cause. If a participant has not had an event prior to analysis cutoff or start of another anticancer therapy, time to deterioration will be censored at the date of the last adequate QoL evaluation. The distribution will be presented descriptively using Kaplan-Meier curves. Median time to definitive deterioration along with 2-sided 95% CI will be provided. Additionally, time to definitive deterioration with different cutoff definitions (e.g. 5%, 15%) may be specified in the SAP as deemed appropriate. A Cox model will be fit with treatment arm and stratification factors as the covariates to obtain a hazard ratio estimate of the treatment effect along with 95% CI. The stratification factors used in the test will be precisely those used for randomization and will be based on the actual randomization (IRT) information.

Further analysis will be detailed in the SAP.

9.4.3.8. Safety

All safety analyses will be performed on the Safety Set. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate. Key safety analyses will also be conducted at the time of the final analysis.

9.4.3.8.1. Study Intervention Exposure

Exposure to the study intervention is defined as the time interval between the actual date of first study intervention administration (included) and the actual date of last study intervention administration (included), i.e., as the quantity “date of last study intervention administration–date of first study intervention administration + 1 day”.

The duration of study intervention exposure, actual and relative dose intensity will be summarized by study intervention and treatment arm. The number of participants with dose modifications (reduction, interruption, both) will be presented by study intervention and treatment arm, along actual daily doses and reasons for dose modification. All exposure data will be listed.

Further details will be provided in the SAP.

9.4.3.8.2. Adverse Events

All analyses of adverse events will be further detailed in the SAP.

The occurrence of an adverse event is 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). All adverse events will be coded according to MedDRA (Appendix 10.1.8.3.4).

A treatment emergent adverse event (TEAE) is defined as:

- any event that first occurred during the treatment phase (i.e. from first treatment administration date up to last administration date+30 days) or that worsened during that study period,

- any event that first occurred > 30 days after the last dose of study treatment or that worsened during that study period AND assessed by the Investigator as related to study treatment.

Incidence tables will display the number and percentage of participants with TEAEs and number of TEAEs by SOC and preferred term. Further summaries will be provided by maximum severity (based on NCI CTCAE grades Version 4.03, where applicable) and relationship to study intervention. A participant with multiple occurrences of an adverse event will only be counted under the maximum NCI CTCAE grade or worse relationship for this event.

Serious adverse events, adverse events resulting in study intervention discontinuation, study intervention modification or study discontinuation and adverse events leading to additional therapy will also be separately presented.

Additional analyses, including time to onset and duration, may be estimated.

Summaries for deaths on-study treatment and off-treatment will be provided on Safety Set.

Serious adverse events will also be described on an individual basis: participant's code, sex and age, verbatim term, preferred term, date of the first study intervention administration, duration of treatment, action taken with study intervention, use of a corrective treatment, outcome and relationship to the study intervention in the investigator's opinion.

Adverse events of special interest of encorafenib will be identified, described and defined in the SAP. 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 intervention. For each specific category, the number and percentage of participants with at least one event will be reported. Additional analyses may be defined.

9.4.3.8.3. Clinical Safety Laboratory Evaluation

For each clinical safety laboratory parameter, data will be summarized over time and plots of measurements over time will be generated for selected parameters.

The absolute changes poststudy intervention administration – baseline (the baseline value being the value measured on the last blood sample collected before the first study intervention administration) will be calculated and tabulated. Results of retests performed poststudy intervention administration will not be analyzed and tabulated. They will only be displayed in individual data listings.

For clinically relevant preselected parameters, scatter plots highlighting individual results before and after study intervention administration will be produced. Plots representing the cumulative frequency distribution of the relative changes from baseline by treatment group will be generated for clinically relevant preselected parameters.

For laboratory tests covered by NCI CTCAE Version 4.03 [NCI CTCAE 2010], laboratory data will be graded accordingly. Grade 0 will be assigned for all non-missing values not graded as ≥1. Grade 5 will not be used. Shift tables of baseline grade versus maximum grade on study will be presented.

For other laboratory parameters that cannot be graded using NCI CTCAE, shift tables of normal-abnormal will be presented.

9.4.3.8.4. Other Safety Data

Vital signs, physical examination and body weight, dermatological examination, ECG and ECOG performance status 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.

9.4.3.9. Pharmacokinetics

PK analyses will be performed of the PK Set.

Descriptive statistics of encorafenib plasma concentrations and cetuximab serum concentrations will be reported and presented graphically. A non-compartmental analysis will be performed in participants with serial blood sampling including the patients from the SLI part. Descriptive statistics of non-compartmental PK parameters (e.g. area under the curve [AUC], minimum concentration [C_{min}] and maximum concentration [C_{max}]) of encorafenib and cetuximab will be reported. Details of the analyses will be included in the SAP or in a PK Analysis Plan.

A population PK analysis will be performed, pooling all data from this study with data from at least the ARRAY-818-302 study (see Section 2.1.4). Ethnicity/Race as a covariate for encorafenib and the potential interaction between encorafenib and cetuximab in the Chinese population will be explored. Individual PK parameters (AUC, C_{min} and C_{max}) of Chinese participants enrolled in the current study will be calculated using the population PK model mentioned above. If appropriate, exploratory and descriptive exposure-response relationships will be performed. Details of these

analyses will be provided in a specific standalone modelling plan. The modelling results will be reported in a separate report.

9.4.4. Exploratory Endpoints

Details of all exploratory analyses will be provided in the SAP.

9.4.5. Other Analyse(s)

The summaries of disposition of participants, demographics and baseline characteristics and important protocol deviations will be described in the SAP. All data will be presented by treatment arm, and overall if appropriate, unless otherwise specified in the SAP.

Prior and concomitant therapies will be described separately for antineoplastic therapy and non-antineoplastic therapy. Subsequent therapies will be summarized for the antineoplastic therapies only. Concomitant medications/therapies will be summarized by Anatomical Therapeutic Classification System term and preferred term. Analyses will be performed on the FAS unless otherwise specified in the SAP. The number of participants with at least one concomitant procedure will be tabulated by summarized by SOC and preferred term. Summaries will include those medications/therapies and therapeutic/diagnostic procedures starting on or after the start of study intervention or starting before the start of study intervention and continuing after the start of study intervention.

Any other medication or procedure starting and ending before the first study intervention administration will be listed but not summarized.

9.4.5.1. Subgroup Analyses

Selected safety analyses may be performed on various subgroups. The effects of the primary endpoint will be displayed using a forest plot of the treatment effect hazard ratios by subgroups, including stratum. Further details including the precise subgroups used will be detailed in the SAP.

9.5. Interim/Initial Analyses

There are no interim analyses planned.

9.6. Data Monitoring Committee

An independent DMC will review the available safety information in the SLI phase in order to evaluate the tolerability of the doublet prior to the start of the randomized phase. If the independent DMC determines the doses to be tolerable in the evaluable participants, the study will proceed to the randomized phase. The independent DMC will make a recommendation if the doses are not deemed tolerable (see Section 4.1.3).

The independent DMC will further review the available safety information after the first 15 participants of the randomized phase treated with encorafenib and cetuximab have completed at least one cycle of treatment to confirm tolerability and will then be responsible for reviewing all safety data at regular intervals (every 6 months at a minimum).

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

The independent DMC will maintain written records of all its meetings.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

Consensus ethical principles derived from international guidelines including the Declaration of Helsinki.

Applicable International Council on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines.

Applicable laws and regulations.

The protocol, protocol amendments, ICF, Investigator's Brochure and other relevant documents (e.g. advertisements) must be submitted to an IEC by the investigator and reviewed and approved by the IEC before the study is initiated.

Any amendments to the protocol will require IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants. In that case, amendment will be submitted within the period defined by local regulations.

The investigator will be responsible for the following:

Providing written summaries of the status of the study to the IEC annually or more frequently in accordance with the requirements, policies and procedures established by the IEC.

Notifying the IEC of SAEs or other significant safety findings as required by IEC procedures.

Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR) ICH guidelines, the IEC, European regulation 536/2014 for clinical studies (if applicable) and all other applicable local regulations.

The screening of participants does not start before the approval of the IEC has been obtained and the study authorized by the competent authority (or notified to the competent authority, depending on the national regulations).

10.1.2. Early Study Termination

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs, the competent authorities and any contract research organizations CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.2.1. Early Study Termination decided by the Sponsor

The sponsor may discontinue the study at any time for any of the following reasons:

Emerging adverse events of such a serious nature that continuation of the study becomes unacceptable.

Recruitment rate too low to expect completion of the study in its present form within the period foreseen for inclusions.

Deviations from ICH GCP and/or regulations.

Decision to stop development of the study intervention.

If the study is prematurely discontinued, all study data must be returned to IRPF. In addition, the study site must conduct final disposition of all unused study interventions in accordance with study procedures.

10.1.2.2. Early Study Termination decided by the Competent Authorities

The competent authorities may suspend or prohibit a 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.

10.1.3. Financial Disclosure

Investigators and co-investigators will provide the sponsor with sufficient, accurate financial information (as requested) to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate competent authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

The funding of research is supported by the sponsor (e.g. investigator fees, study costs, participant compensation for travel expenses).

By signing the protocol, the investigator declares no conflict of interest.

10.1.4. Informed Consent Process

Written information about the study must be given to each participant and/or their legally authorized representative 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. It must also describe the measures taken to safeguard participant's privacy and protection of personal data, according to EU General Data Protection Regulation (2016/679).

The investigator or designated study site personnel will explain the nature of the study, including the restraints and risks, to the participant or his/her legally authorized representative and answer all questions regarding the study. They will be given a sufficient time to consider the study before consenting.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, the IEC or study site and European Union General Data Protection Regulation (2016/679):

Participants undergoing molecular prescreening will initially provide written informed consent for molecular prescreening only (molecular prescreening ICF).

All participants will provide written informed consent for screening, study intervention and assessments (screening ICF) before any study-specific procedures are carried out.

Separate informed consent must also be provided by participants if there is discordance between the local assay and central laboratory *BRAF* V600E status results or if the central laboratory is not able to confirm presence of a *BRAF* V600E mutation and the participant is willing to continue treatment. Participant can only continue treatment if there is no clinical indication of deterioration or disease progression and the investigator determines that the participant is deriving benefit. The ICF will inform the participant that their *BRAF* V600E status is unconfirmed and will describe alternative treatment options. The medical records must include statements that the applicable written informed consent was obtained for molecular prescreening, at screening (and for continued treatment if the *BRAF* V600E status is unconfirmed, if applicable) and the dates obtained. The investigator or his/her designee obtaining the informed consent must also sign the ICFs.

The participant must be reconsented to confirm his/her agreement to continue participating if the written information is amended during the study due to new information becoming available that may be relevant to the participant's willingness to continue participating or due to amendments to the protocol.

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 participant.

As soon as consent is signed, the participant will be given a personal card to be kept all along the study duration and providing the following information: participant's name, sponsor's name, study code, (if applicable), date of start and expected date of end of the study (if applicable), complete address of the study site with the name and emergency phone number of the Investigator.

In the event of pregnancy during the study, additional informed consent will be sought (required within 72 hours) from the pregnant female (female study participant or partner of a male study participant) to allow the investigator to follow the pregnancy to outcome and to provide pregnancy information to the sponsor.

10.1.5. Data Protection

Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law and European Union General Data Protection Regulation (2016/679). The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the ICF.

The participant must be informed that his/her medical records may be examined by clinical quality assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IEC members and by inspectors from competent authorities.

10.1.6. Communication with Sites

Sites will be updated regularly about study status. Relevant information and important decisions regarding the study will be communicated to all sites in parallel in writing in a timely manner.

In case of emergency requiring implementation of urgent measures with regards to participant safety, the sites will first be contacted by telephone by the sponsor medical monitor or designee, with the information confirmed in writing. A Safety Monitoring Plan will be also written with regards to SAE management and communication.

10.1.7. Dissemination of Clinical Study Data

Any inventions or discoveries (whether patentable or not), work product, results and reports from the Study shall be promptly disclosed by Institution or Investigator to Sponsor and shall become, be and remain the sole and exclusive property of Sponsor.

However, any patents or patent applications regarding to inventions made or developed within the framework of exploratory biomarker testing (RAS, CCI, CRP, CCI) during the course of the Study, shall be jointly owned by Sponsor, Institution and the Sponsor's partner providing the product cetuximab.

Institution shall not:

- use the results of the exploratory biomarker testing without a prior written consent of Sponsor;
- file a patent application without a prior written consent of Sponsor;

- sublicense the patents and the results of the Study to a third party without prior written consent of Sponsor.

Clinical Study Report:

Data analysis and Clinical Study Report 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, statistical and PK integrated report. It must be signed by the sponsor's medically qualified representative signatory and the co-ordinating investigator.

Study Results Communication:

Within a maximum period of 12 months after study completion, global results of the research are communicated to the investigator.

The participant can ask the investigator for the results, according to local regulations.

For clinical studies that are part of a marketing authorisation application, the results have to be published on the Chinese website www.chinadrugtrials.org.cn within 12 months of completion of the study (at minima, the clinical study results information shall include synopsis content of the Clinical Study Report as specified in ICH E3) according to CDE regulation < regulations for the registration and information publicity of drug clinical trials > (2020 NO. 9). The results will also be published on ClinicalTrials.gov website (www.clinicaltrials.gov). The documents will be anonymized to ensure data protection of individuals according to legislation.

10.1.8. Data Quality Assurance

All participant data relating to the study will be recorded in an eCRF unless transmitted to the sponsor or designee electronically (e.g. central laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

The sponsor assumes accountability for actions delegated to other individuals (e.g. CROs).

10.1.8.1. Audit

The investigator must permit study-related monitoring, audits, IEC review and competent authority inspections.

The purpose of a sponsor's audit, independent of and separate from monitoring or quality control activities, is to evaluate study conduct and compliance with the protocol, sponsor's standard operating procedures, ICH GCP and the applicable regulatory requirements. Audits may be conducted by the sponsor's Clinical Quality Assurance Department or designee at each relevant location where activities dedicated to the clinical study 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 designee.

10.1.8.2. Inspection

The competent authority may inspect any study 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 agree to provide direct access to source documents.

10.1.8.3. Data Management

The sponsor or designee is responsible for the data management of this study, including quality checks of the data. Data management will be subcontracted to a CRO under the supervision of the sponsor's data manager. All clinical data related to the study will be collected and saved in a computerized database according to the procedures in Appendix 10.1.8.3.1 to Appendix 10.1.8.3.6. Full details are provided in the Data Management Plan.

10.1.8.3.1. Electronic Case Report Form

An eCRF will be developed for this study. The eCRF (Medidata Rave®) will be used to record all participant data required by the protocol. The hosting of this web-based electronic data capture will be subcontracted to Medidata Solutions, Inc.

The eCRF should be compliant with local regulations, compliant with 21CFR Part 11, fully validated and include an access control and a traceability system for data corrections (audit trail).

Before the start of the study, the investigator will complete a Delegation of Significant Study-related Duties Form. The signature and initials of all persons in charge of eCRF completion should be recorded on this form. Each person involved in eCRF completion, review, correction and/or validation will be trained and then will have an individual login and access code to the eCRF. An eCRF user guide will be available for investigators/study site personal involved in eCRF completion and CRAs.

Data from study assessments and procedures outlined in Section 8 will be recorded in the source documents and the eCRF by the investigator and designated study site personnel. All information entered into the eCRF will be recorded from source documents. The investigator is responsible for the management and accuracy of the information entered into the eCRF.

An eCRF must be completed for each participant enrolled in the study (i.e. ICF signed).

10.1.8.3.2. Central/External Data

Results of local laboratory testing (e.g. CCI [redacted] will be entered into the eCRF at the study site.

The following electronic data are not reported in the eCRF by the investigator and will be transferred to the CRO data management for validation and integration into the study database according to the specifications given by the data manager. These data will be captured and handled in accordance with ICH GCP guidelines:

- Central review assessment of tumor response.

  Central review assessment of tumor response will be determined by the Blinded (to treatment received) Independent Central Review (BICR) according to RECIST v1.1. The data of the BICR will not be provided to investigators for decisions regarding participant's treatment. These data will be reconciled with eCRF data then imported in the Clinical Study Database as external data.

- Centrally analyzed biomarker samples:

  Actual dates and times of biomarker samples will be entered in both the eCRF and the requisition form. The samples will be sent to a designated central laboratory/third-party bioanalytical laboratory for analysis. *BRAF* V600E status results will be entered in the eCRF. If any of the biomarker analysis results are intended to form part of the Clinical Study Report, they will be transferred to the CRO data management for validation and integration into the study database.

- Centrally analyzed PK samples:

  Actual dates and times of blood collections will be entered in the eCRF. Validated results from bioanalysis of encorafenib concentrations in plasma and cetuximab concentrations in serum will be transmitted by the third-party bioanalytical laboratory to the subcontractor in charge of PK analysis. The encorafenib and cetuximab concentrations and final PK parameters will be uploaded in the final database from an electronic data file respectively provided by the bioanalytical laboratory and the subcontractor.

10.1.8.3.3. Data Cleaning

Manual and electronic edit checks used for data cleaning are described in the study Data Validation Plan. Upon approval, the edit checks and listings will be programmed. The data management 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 eCRF. The system's automatic audit trail will record the date, time and author of the changes.

Data entered into the eCRF will be validated as defined in the Data Validation Plan. Validation includes, but is not limited to, validity checks (e.g. range checks), consistency checks and customized checks (logical checks between variables to ensure that study data are accurately reported) for eCRF data and central/external data (e.g. laboratory data). A majority of edit checks will be triggered during data entry and will therefore facilitate efficient 'point of entry' data cleaning.

The data management will perform both manual eCRF review and review of additional electronic edit checks to ensure that the data are complete, consistent and reasonable. The electronic edit checks will run continually throughout the course of the study and the issues will be reviewed manually online to determine what action needs to be taken.

Manual queries may be added to the system by the data management or CRA. Clinical data managers and CRAs are able to remotely and proactively monitor the participant eCRFs to improve data quality.

Central/external data will be transferred electronically to data management (see Section 10.1.8.3.2). Discrepancies will be queried to the study site and/or the laboratory until the electronic data and the database are reconciled.

All updates to queried data will be made by authorized study site personnel only and all modifications to the database will be recorded in an audit trail.

10.1.8.3.4. Data Coding

Adverse events, concomitant diseases, concomitant therapeutic/diagnostic procedures and medical/surgical histories will be coded using MedDRA (latest version in use) and prior and concomitant medications will be coded using the World Health Organization (WHO) DRUG GLOBAL dictionary (latest version in use), plus the respective user guides and sponsor specific guidelines. The coding will be validated by a CRO physician and the sponsor's medical monitor.

10.1.8.3.5. Database Lock

Analysis will be based either on database lock or database snapshot.

A snapshot consists of a stable view of the data i.e. an extract of the database done at a specific timepoint. The specific timepoint will be defined in the DMC Charter as well as the list of critical variables:

Critical variables will be entered, source data verified and cleaned (without remaining open queries).

Non-critical variables will be entered, source data verified and cleaned as much as possible.

As data will not be locked in the eCRF, entry of additional data and changes in eCRF will be deemed possible.

All snapshots will be stored in SAS® format on a sponsor -dedicated secured server.

The validated database will be locked upon request of the sponsor's data manager following the completion of all steps required, i.e. entry, reception and check of all data, resolution of all queries, validation of the coding, clinical and safety databases reconciliation and data review/Validation Committee meeting performed.

Subsequent changes to the database will then only be made by written agreement of the sponsor.

10.1.8.3.6. Data Storage

Data, as well as their 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 eCRFs will be sent in portable document format (PDF) format to the sponsor and then stored on a dedicated secured server by the sponsor.

A CD-ROM (or similar storage support) containing the PDF version of all eCRFs of the site (including audit trail) will be archived by the study site.

10.1.8.4. Study Monitoring

Monitoring details describing strategy (e.g. risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities and requirements, including handling of non-compliance issues and monitoring techniques (central, remote or on-site monitoring) are provided in Monitoring Plan.

Representatives of the sponsor will perform ongoing source data verification to confirm that data entered into the eCRF by authorized study site personnel are accurate, complete and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP and all applicable regulatory requirements.

On-site visits will be carried out by a representative of the sponsor (CRA and/or study manager) before study initiation and at regular intervals (as defined in the Monitoring Plan) throughout the study. Additional visits and communication by telephone, fax or meeting may be performed if necessary. Any site visit performed by representatives of the sponsor will be recorded in the investigator's site file.

10.1.8.4.1. Site Pre-selection Visit

Before selecting a study site 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, recruitment, environment), technical means and study site personnel to carry out the study. This includes a check that the study site has all the necessary equipment to conduct the study (e.g. sample processing and storage, study intervention storage, ECGs) and where applicable, appropriate calibration has been performed.

10.1.8.4.2. Initiation Visit

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

The investigator has received:

The protocol, administrative and financial agreement signed by all parties.

The written statement of IEC approval and the list of its members and their functions.

The written statement of competent authority approval.

The original signed and dated curriculum vitae of the investigator(s) has been collected.

Local laboratory normal ranges have been collected.

All study materials are available at 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 will also provide training on the study protocol requirements and study specific procedures.

10.1.8.4.3. Routine Monitoring Visits

Throughout the study, regular monitoring visits will be carried out by the CRA to check compliance with ICH GCP, participant informed consent, strict application of the protocol, conformity of the data entered in the eCRF with the source documents and ensure its correct completion, adverse event reporting, proper retention, storage and management of the study intervention as well as the source and other study-related documents.

10.1.8.4.4. Close-out Visit

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

Verify that the eCRFs are complete and all queries are resolved.

Control the accountability of intact and used study intervention units and their destruction or their return to local China depot). For further details, see section 6.2.1.

Make an on-site review of all study documentation and complete it if necessary.

Remind the investigator of his regulatory obligations, study document archiving process and duration.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator at least 5 years after the drug is approved for marketing or at least 5 years after the termination of the clinical trial (whichever occurs last), as per local regulations, unless study site policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.9. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the study site.

Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Current medical records must also be available.

Definition of what constitutes source data can be found in the Source Data Identification Form.

In accordance to the requirements of ICH GCP, all sponsor representatives (study manager, CRA and auditors) have to be given a 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 keep professional confidentiality with regards to the participant data.

10.1.10. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the date of the first participant's first visit and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed (see Appendix 10.1.8.4.4).

The investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice to the sponsor or designee is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

Failure of the investigator to comply with the protocol, the requirements of the IEC or local health authorities, the sponsor's procedures or ICH GCP guidelines.

Inadequate recruitment of participants by the investigator.

Poor product safety, lack of efficacy

New information that could jeopardise the participant' safety

Discontinuation of study intervention development

10.1.11. Publication Policy

The results of this study, which are the property of the sponsor, and exclusively for the exploratory biomarkers co-owned by the Sponsor, Institution and the Sponsor's partner and considered as confidential, may be published or presented at scientific meetings.

The investigator must agree to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments. Publication or communication relating to results of the study, in written or oral form, shall comply with the following provisions:

Any communication or publication project must be provided to the sponsor for review at least 60 days before 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 he deems appropriate to establish and preserve his proprietary rights.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a co-ordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. In case of a multicentre study, the sponsor shall determine the author's list and their appearance order within the publication project according to their participation in the design of the protocol as well as their recruitment of eligible and analyzable participants.

10.1.12. Insurance Policy

In accordance with the provisions of the law and ICH GCP, the sponsor 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 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 the sponsor's insurance**.**

10.2. Appendix 2: Contraceptive Guidance

Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. The following guidance is adapted from the guidelines of the Clinical Trials Facilitation Group [CTFG 2014].

10.2.1. Definition of a Woman of Childbearing Potential and Fertile Men

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (e.g. amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with one of the following:
- Documented hysterectomy.
- Documented bilateral salpingectomy.
- Documented bilateral oophorectomy.

For participants with permanent infertility due to an alternate medical cause other than the above, (e.g. mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the study site personnel's: review of the participant's medical records, medical examination or medical history interview.

- Postmenopausal female:

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

High FSH (and LH and estradiol) levels in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one measurement is required.

Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

For the purpose of this guidance, a man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

10.2.2. Contraceptive Guidance

For the purpose of this guidance, methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods. Such methods include:

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.
- Intrauterine hormone-releasing system.
- Bilateral tubal occlusion.
- Vasectomized partner.
- Sexual abstinence.

Acceptable birth control methods that result in a failure rate of more than 1% per year 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.

10.3. Appendix 3: Recommended Guidelines for the Management of Cetuximab-induced and/or Encorafenib-induced Toxicity

10.3.1. Skin Toxicity

Clinical judgment and experience of the treating physician should guide the management plan of each participant.

10.3.1.1. Initial Rash Treatment Regimen:

The Initial Rash Treatment regimen may be initiated as prophylactic treatment 24 hours before the first dose of study intervention or later to treat mild rash (NCI CTCAE Grade 1), as needed.

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 (para-aminobenzoic acid-free, sun protection factor ≥30, ultraviolet A/ultraviolet B protection).

Topical steroids, preferably mometasone cream (e.g. Elocon®).

Topical erythromycin (e.g. Eryaknen®).

Topical pimecrolimus.

> Note: Topical agents should be applied on a daily basis starting on Day 1 of study intervention (or 24 hours before first dose) and more often, as needed.

Possibly oral doxycycline (100 mg daily) for the first 2 to 3 weeks of study intervention.

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:

<u>Mild Rash (Grade 1) Treatment Regimen:</u>

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 participant should be reassessed within a maximum of 2 weeks, or according to investigator opinion.

<u>Moderate Rash (Grade 2) Treatment Regimen:</u>

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 twice daily) or minocycline (50 to 100 mg twice daily).

Use of acitretin is not recommended.

Severe Rash (Grade 3 or 4) Treatment Regimen:

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 2017, Lacouture 2011].

Use of acitretin is not recommended.

Grade 4:

Immediately discontinue the participant from study intervention and treat with oral or topical medications (see recommendation Grade 3).

10.3.1.2. Symptomatic Treatment Regimen:

It is strongly recommended that participants 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.

10.3.2. Hand-foot Skin Reactions

Clinical judgment and experience of the treating physician should guide the management plan of each participant. The algorithm in Table 19 is recommended for the management of HFSR based on the severity of HFSR.

Table 19: Algorithm for the Management of Hand-foot Skin Reactions Based on Severity

HFSR Severity (NCI CTCAE Grade)	Intervention
No HFSR	**Maintain frequent contact with treating 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 participant 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 to 40% urea, salicylic acid 3 to 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 participant 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 to 4% lidocaine, opiates, NSAIDS or GABA agonists for pain; follow dose modifications listed in Table 29.
	If no improvement within 15 days, proceed to next steps.
	⬇

HFSR severity	Intervention
Grade 3	**Interrupt dose until improvement to Grade 0 or 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 29
Abbreviations: ADL = activities of daily living; BRAF = B-raf murine sarcoma viral oncogene homolog B1; GABA = gamma-aminobutyric acid; HFSR = hand-foot skin reaction; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NSAID = non-steroidal anti-inflammatory drug. Table adapted from Nardone 2012.	

The supportive care measures for the prevention and/or management of HFSR summarized in Table 20 should be followed, in addition to proper participant education.

Table 20: Supportive Care for the Prevention and Management of Hand-foot Skin Reactions

Stage	Recommendations
Before initiation of study intervention	Educate the participant about the early signs and symptoms of HFSR and discuss the importance of early reporting. HFSR could start as early as 2 to 5 days after study intervention 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 participant for signs and symptoms of HFSR. Instruct the participant to: Apply emollient cream regularly to hands and feet: use 20 to 40% urea, salicylic acid 3 to 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 moisturizing and keratolytic creams to control existing palmar and plantar hyperkeratosis.
Treatment of HFSR	Ensure that the participant follows dose modification guidelines (Table 29). Monitor the participant for worsening/resolution of HFSR (normal frequency monthly, except if participant has Grade 2 or 3 HFSR, where bi-weekly visits are recommended). Prescribe analgesics if necessary.

Stage	Recommendations
	Instruct the participant to: Continue the use of prevention strategies. Cushion sore skin. For control or relief of pain symptoms, participant may submerge hands and feet in cool water baths or apply cold compresses for relief.
Wear loose-fitting clothing made of soft, natural fabrics and shoes that are wide and comfortable. Avoid tight belts, panties and bras. Table adapted from Van Moos 2008.	

10.4. Appendix 4: List of Concomitant Medications

10.4.1. Concomitant Medications to be Used with Caution

Table 21: List of Cytochrome P450 Substrates to be Used With Caution (CYP2C8, CYP2C9, CYP2C19 and CYP3A)

CYP2C8	CYP2C9	CYP2C19	CYP3A	
Amodiaquine	Acenocoumarol	Clopidogrel	Alfentanil [1, 2]	Isavuconazole [1]
Cerivastatin	Celecoxib	Diazepam	Alpha-dihydroergocryptine	Ivabradine [1]
Repaglinide	Diclofenac	Esoprazole	Alprazolam [2]	Lemborexant [1]
Rosiglitazone	Glipizide	Lansoprazole	Amiodarone [2]	Lomitapide [1]
Torasemide	Irbesartan	Moclobemide	Amlodipine	Lopinavir
	Losartan	Omeprazole	Apixaban [2]	Lovastatin [1]
	Phenytoin	Pantoprazole	Aplaviroc	Lurasidone [1]
	Piroxicam	Phenobarbitone	Aprepitant	Maraviroc [1]
	S-ibuprofen	Phenytoin [2]	Aripiprazole	Methadone
	Sulfamethoxazole	Proguanil	Astemizole	Midazolam [1, 2]
	Tolbutamide	Rabeprazole	Atorvastatin [2]	Mobocertinib [1, 2]
	Torasemide	S-mephenytoin	Boceprevir	Naloxegol [1]
			Avanafil [1]	Nifedipine
			Brecanavir	Nisoldipine[1]
			Brotizolam	Nitrendipine
			Budesonide [1]	Pimozide [2]
			Buspirone [1]	Perospirone
			Capravirine	Quetiapine [1]
			Casopitant	Quinine
			Cisapride [2]	Quinidine [2]
			Clarithromycin	Ritonavir
			Conivaptan [1]	Rivaroxaban [2]
			Cyclosporine [2]	Saquinavir [1]
			Darifenacin [1]	Sildenafil [1]

CYP2C8	CYP2C9	CYP2C19	CYP3A	
			Darunavir [1]	Simvastatin [1, 2]
			Diazepam	Sirolimus [1, 2]
			Diergotamine [2]	Tadalafil [2]
			Diltiazem	Tacrolimus [1, 2]
			Disopyramide [2]	Telaprevir
			Dasatinib [1,2]	Telithromycin
			Dronedarone [1]	Temsirolimus [2]
			Ebastine	Terfenadine [2]
			Eletriptan [1]	Ticagrelor [1]
			Eplerenone [1]	Tipranavir [1]
			Ergotamine [2]	Tolvaptan[1]
			Erythromycine	Trazadone
			Everolimus [1, 2]	Triazolam [1]
			Felodipine [1]	Vardanefil [1, 2]
			Haloperidol	Venotoclax [1]
			Fentanyl [2]	Verapamil
			Fluticasone [1]	Vinca alkaloids (vincristine)[2]
			Ibrutinib [1, 2]	Zolpidem [2]
			Ifosfamide [2]	Zopiclone [2]
			Indinavir [1]	

Abbreviations: CYP = cytochrome P450; FDA = Food and Drug Administration; US = United States.

Table was compiled from the Indiana University School of Medicine's "Clinically Relevant" table, a list by the US FDA (https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers), the University of Washington's Drug Interaction Database and https://ansm.sante.fr/documents/reference/thesaurus-des-interactions-medicamenteuses-1. The list is not necessarily exhaustive of every possible substrate.

[1] Sensitive substrates: Drugs whose plasma area under concentration-time curve 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: 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. Torsade de Pointes).

Table 22: List of Cytochrome P450 Substrates to be used with Caution (CYP2B6)

CYP2B6*
Bupropion[1]
Cyclophosphamide
Efavirenz[1]
Ifosfamide
Methadone
Thiotepa

Abbreviations: CYP = cytochrome P450; FDA = Food and Drug Administration; US = United States.

*Table was compiled from the Indiana University School of Medicine's "Clinically Relevant" table, a list by the US FDA (https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers) and the University of Washington's Drug Interaction Database. The list is not necessarily exhaustive of every possible substrate.

[1]-Sensitive substrates: The area under the concentration-time curves 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 23: List of Inhibitors of Uridine Diphosphate-glucuronosyl Transferase 1A1 to be used with Caution

Inhibitors of UGT1A1	Atazanavir, erlotinib, flunitrazepam, gemfibrozil, indinavir, ketoconazole, nilotinib, pazopanib, propofol, regorafenib, sorafenib
Abbreviations: UGT1A1 = Uridine diphosphate-glucuronosyl transferase.	

Table 24: Moderate Cytochrome P450 3A4 Inhibitors to be Administered with Caution when Co-administered with Encorafenib

Aprepitant	Erythromycin
Ciprofloxacin	Fluconazole
Conivaptan	Fluvoxamine
Crizotinib	Grapefruit juice
Cyclosporine	Imatinib
Diltiazem	Isavuconazole
Dronedarone	Verapamil
Reproduced from https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers	

Table 25: Breast Cancer Resistance Protein and P-glycoprotein Inhibitors/Inducers to be used with Caution

Transporter	Gene	Inhibitor[1)]	Inducer[2)]
BCRP	ABCG2	Cyclosporine, elacridar (GF120918), eltrombopag, gefitinib	Not known
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

Abbreviations: BCRP = breast cancer resistance protein; P-gp = P-glycoprotein.

Reproduced from http://.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 or otherwise indicated if substrate is other than digoxin.
2) Inducers listed for P-gp are those that showed >20% decrease in digoxin area under the concentration-time curveor otherwise indicated if substrate is other than digoxin.

Table 26: Substrates of Breast Cancer Resistance Protein, Organic Anionic Transporters, Organic Anion Transporting Polypeptides, Organic Cationic Transporters and P-glycoprotein, to be administered with Caution

BCRP	Imatinib, irinotecan, 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

Abbreviations: BCRP= breast cancer resistance protein; OAT = organic anionic transporter, organic anion transporting polypeptide; organic cationic transporter; P-gp = P-glycoprotein.

Reproduced from http://.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm

Table 27: List of Potential QT Prolonging Drugs

Drug	QT Risk0	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	Substrate for CYP3A4
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	Substrate for CYP3A4
Citalopram	Known risk	
Clarithromycin	Known risk	Substrate for CYP3A4
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	
Doxepin	Conditional risk	
Dronedarone	Possible risk	Substrate for CYP3A4
Droperidol	Known risk	
Eribulin	Possible risk	
Erythromycin	Known risk	Females>Males. Substrate for CYP3A4
Escitalopram	Possible risk	
Famotidine	Possible risk	
Felbamate	Possible risk	
Fingolimod	Possible risk	
Flecainide	Known risk	

Drug	QT Risk0	Comment
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 CYP3A4
Ibutilide	Known risk	Females>Males
Imipramine	Conditional risk	Risk of TdP in overdosage
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	
Lithium	Possible risk	
Mesoridazine	Known risk	
Methadone	Known risk	Females>Males. Substrate for CYP3A4
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 CYP3A4

Drug	QT Risk0	Comment
Probucol	Known risk	
Procainamide	Known risk	
Protriptyline	Conditional risk	
Quetiapine	Possible risk	Substrate for CYP3A4
Quinidine	Known risk	Females>Males. Substrate for CYP3A4
Ranolazine	Possible risk	
Risperidone	Possible risk	
Ritonavir	Conditional risk	Substrate for CYP3A4
Roxithromycin	Possible risk	
Sertindole	Possible risk	
Sertraline	Conditional risk	
Solifenacin	Conditional risk	
Sotalol	Known risk	Females>Males
Sparfloxacin	Known risk	
Tacrolimus	Possible risk	Substrate for CYP3A4
Telithromycin	Possible risk	Substrate for CYP3A4
Terfenadine	Known risk	Substrate for CYP3A4
Thioridazine	Known risk	
Tizanidine	Possible risk	
Trazodone	Conditional risk	Substrate for CYP3A4
Trimethoprim-Sulfa	Conditional risk	
Trimipramine	Conditional risk	
Vandetanib	Known risk	
Vardenafil	Possible risk	Substrate for CYP3A4
Venlafaxine	Possible risk	
Voriconazole	Possible risk	
Ziprasidone	Possible risk	

Abbreviations: CYP = cytochrome P450; TdP = Torsade de Pointes

Additional agents can be found at https://www.crediblemeds.org

Classification according to the Qtdrugs.org Advisory Board of the Arizona CERT.

10.4.2. Prohibited Concomitant Medications

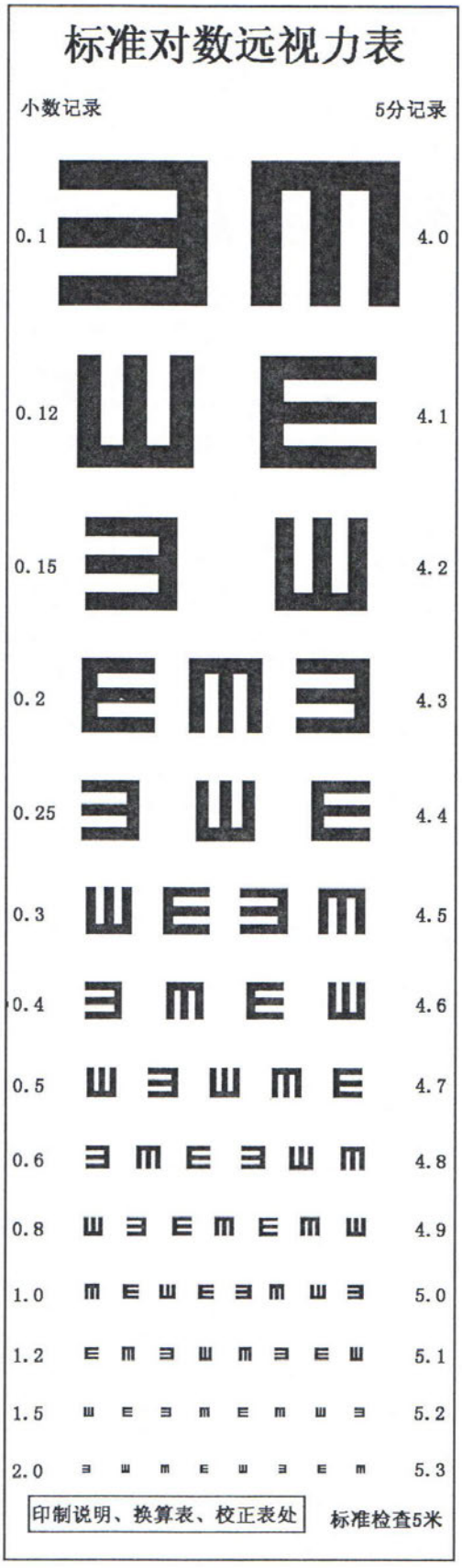
Table 28: Strong Cytochrome P450 3A4 Inhibitors and Strong Cytochrome P450 Inducers to be Prohibited when Co-administered with Encorafenib

Strong Inhibitors	
Ceritinib	Lopinavir
Clarithromycin	Nefazodone
Cobicistat	Nelfinavir
Conivaptan	Ombitasvir
Dasabuvir	Paritaprevir
Elvitegravir	Posaconazole
Idelalisib	Ritonavir
Indinavir	Saquinavir
Itraconazole	Telithromycin
Ketoconazole	Tipranavir
	Voriconazole
Strong Inducers	
Apalutamide	Lumacaftor
Carbamazepine	Mitotane
Enzalutamide	Phenytoin
Ivosidenib	Rifampin
Ivacaftor	St. John's wort
Reproduced from https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers	

10.5. Appendix 5: Standard Logarithmic Visual Acuity Chart

Taken from Holladay 2004.

The score value (between 4.0 and 5.3) needs to be entered into eCRF, as mostly used by ophthalmologists.


标准对数远视力表
小数记录
5分记录
0.1
4.0
0.12
4.1
0.15
4.2
0.2
4.3
0.25
4.4
0.3
4.5
0.4
4.6
0.5
4.7
0.6
4.8
0.8
4.9
1.0
5.0
1.2
5.1
1.5
5.2
2.0
5.3
印制说明、换算表、校正表处
标准检查5米

10.6. Appendix 6: Dose Modifications

10.6.1. Dose Modifications for Encorafenib-related Adverse Events

Table 29: Recommended Dose modifications for Encorafenib-related Adverse Events

Worst Toxicity **NCI CTCAE Version 4.03 Grade (unless otherwise specified)**	**Dose Modification for Encorafenib**
Eye disorders - Posterior uveitis (including iritis and iridocyclitis) **Any visual acuity impairment at screening should be documented and should be considered as baseline.**	
Grade 1 or 2	Treat with specific (e.g. topical) ocular therapy. If uveitis does not respond, interrupt dosing of encorafenib and repeat ophthalmic monitoring including visual acuity assessment within 10 days. If resolved to baseline or ≤Grade 1 resume study intervention at the same dose. If posterior uveitis lasts >6 weeks, permanently discontinue encorafenib.
Grade 2	Treat with specific (e.g. topical) ocular therapy. If uveitis does not respond, interrupt dosing of encorafenib and repeat ophthalmic monitoring including visual acuity assessment within 10 days. If resolved to ≤Grade 1, resume study intervention at one reduced dose level of encorafenib0. If posterior uveitis lasts >6 weeks, permanently discontinue encorafenib and ophthalmic monitoring should be repeated.
Grade 3	Interrupt dosing of encorafenib and repeat ophthalmic monitoring including visual acuity assessment within 10 days. If resolved to ≤Grade 1, resume study intervention at one reduced dose level of encorafenib0. If posterior uveitis lasts >6 weeks, permanently discontinue encorafenib and ophthalmic monitoring should be repeated.
Grade 4	Permanently discontinue encorafenib and immediately follow-up with ophthalmic monitoring0
Liver-related adverse events	
Grade 1 AST or ALT >ULN to 3 × ULN	Maintain dose level of encorafenib.
Grade 2 AST or ALT >3 to 5.0 × ULN or 3 × baseline value0 **AND** **blood total bilirubin** **≤2.0 × ULN**	Maintain dose level of encorafenib. If not resolved in ≤14 days, interrupt dose of encorafenib until resolved to Grade≤1 (or Grade ≤2 in case of liver metastasis), then resume study intervention at current dose level of encorafenib. If additional occurrence: Interrupt dosing of encorafenib until resolved to Grade ≤1 (or Grade ≤2 in case of liver metastasis), then resume study intervention at one reduced dose level0 of encorafenib.
AST or ALT 3.0 to 5.0 × ULN **AND** **blood total bilirubin** **>2.0 × ULN**	Interrupt dosing of encorafenib until resolved to Grade ≤1, then: If resolved in ≤7 days, resume study intervention at one reduced dose level0 of encorafenib. If not resolved in ≤7 days, permanently discontinue encorafenib.

Worst Toxicity **NCI CTCAE Version 4.03 Grade** **(unless otherwise specified)**	**Dose Modification for Encorafenib**
Grade 3 AST or ALT >5.0 to 8.0 × ULN **AND** **blood total bilirubin** **≤2.0 × ULN**	Interrupt dosing of encorafenib until resolved to Grade ≤1 (or Grade ≤2 in case of liver metastasis), then: If resolved in ≤14 days, resume study intervention at current dose level of encorafenib. If not resolved in ≤14 days, resume study intervention at one reduced dose level0 of encorafenib. If additional occurrence: Interrupt dosing of encorafenib until resolved to Grade ≤1 (or Grade ≤2 in case of liver metastasis), then resume treatment at one reduced dose level0 of encorafenib.
AST or ALT >8 × ULN AND blood total bilirubin ≤2.0 × ULN	Permanently discontinue encorafenib.
AST or ALT >5.0 × ULN AND blood total bilirubin >2.0 × ULN	Permanently discontinue encorafenib.
Grade 4 AST or ALT >20.0 × ULN	Permanently discontinue encorafenib.
Cardiac investigation – Prolongation of QT interval QTcF value	
QTcF >500 ms during treatment and change from pre-intervention value remains ≤60 ms	Participants 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 until QTcF <500 ms. Then resume treatment at one reduced dose level0 of encorafenib. 2nd occurrence: Temporarily interrupt dosing of encorafenib until QTcF <500 ms. Then resume treatment at one reduced dose level0 of encorafenib. If a participant restarts encorafenib following resolution of Grade 3 QTcF prolongation event, the participant 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.
QTcF increase during treatment is both >500 ms and >60 ms change from pre-intervention values	Participants 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.

Worst Toxicity **NCI CTCAE Version 4.03 Grade** **(unless otherwise specified)**	**Dose Modification for Encorafenib**
Rash (see cetuximab dose modifications [Table 30] and Appendix 10.3.1).	
Grade 1	Maintain dose level of encorafenib. Initiate Initial Rash Treatment regimen if it was not already started and rash should be closely monitored.
Grade 2	Maintain dose level of encorafenib. 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 until resolved to Grade ≤1. Then resume study intervention at current dose level of encorafenib. 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.
Grade 3	1st occurrence: Interrupt dosing of encorafenib until resolved to Grade ≤1. Reassess weekly. Then resume treatment at current dose level of encorafenib. Consider referral to dermatologist and manage rash per dermatologist's recommendation. 2nd occurrence: Interrupt dosing of encorafenib until resolved to Grade ≤1. Then resume study intervention at one reduced dose level0 of encorafenib unless in the judgment of the investigator, the rash is considered to be unrelated to encorafenib then study intervention can be resumed at the same dose level. Consider referral to dermatologist and manage rash per dermatologist's recommendation.
Grade 4	Permanently discontinue encorafenib0.
HFSR/Palmar-plantar erythrodysesthesia syndrome0 (Appendix 10.3.2)	
Grade 1	Maintain dose of encorafenib. Promptly institute supportive measures, such as topical therapy, for symptomatic relief. Give instruction on lifestyle 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 lifestyle 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 lifestyle 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 lifestyle modifications. If dosing is interrupted, interrupt until resolved to Grade ≤1. Resume study intervention at the same dose level or one reduced dose level0 of encorafenib at the investigator's discretion.

Worst Toxicity **NCI CTCAE Version 4.03 Grade** **(unless otherwise specified)**	**Dose Modification for Encorafenib**
Grade 3	1st to 3rd occurrence: Interrupt dosing of encorafenib until resolved to Grade ≤1. Promptly initiate supportive measures, such as topical therapy, for symptomatic relief. Give instruction on lifestyle modifications. Reassess the participant weekly. Then resume treatment at one reduced dose level0 of encorafenib. Consider referral to dermatologist and manage HFSR per dermatologist's recommendation. >3rd occurrence: Interrupt dosing of encorafenib until resolved to Grade ≤1, decision to resume treatment with encorafenib at one reduced dose level0 or permanently discontinue encorafenib should be based upon the investigator's discretion.
SCC, KA and any Other Suspicious Skin Lesion	
Grade ≤3	Maintain dose of encorafenib. Treatment of SCC, KA and any other suspicious skin lesion (e.g. new primary melanoma) should occur based upon study site standards.
Non-cutaneous malignancies	
	Permanently discontinue encorafenib in patients who develop RAS mutation-positive non-cutaneous malignancies
Diarrhea. Treatment should be based on study site practice (see Section 6.5.1.2).	
Uncomplicated Grade 1 or 2	Maintain dose of encorafenib.
Complicated Grade 1 or 2	Consider temporary interruption of encorafenib until resolved to Grade ≤1. Then resume treatment at current dose level.
Grade 3 or 4	Interrupt dosing of encorafenib 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 level0.
Nausea/vomiting	
Grade 1 or 2	Maintain dose level of encorafenib. Promptly institute antiemetic measure.
Grade 3	Interrupt dosing of encorafenib until resolved to Grade ≤1. Then resume treatment at one reduced dose level0 of encorafenib. Note: Interrupt dosing of encorafenib for ≥Grade 3 vomiting or Grade 3 nausea only if the vomiting or nausea cannot be controlled with optimal antiemetics (based on study site standards).
Grade 4	Permanently discontinue encorafenib0.
All other adverse events (suspected to be related to encorafenib)	
Grade 1 or 2	If the event is a persistent Grade 2 adverse event not responsive to a specific therapy, consider interruption or reduction of encorafenib, as applicable
Grade 3	Interrupt dosing of encorafenib until resolved to Grade ≤1 or to preintervention/baseline level. If the event resolves ≤21 days, then encorafenib may be resumed at one reduced dose level0 based upon the investigator's discretion.
Grade 4	Permanently discontinue encorafenib0.
Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CK = creatine kinase; HFSR = hand-foot skin reaction; KA = keratoacanthoma; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse	

Worst Toxicity NCI CTCAE Version 4.03 Grade (unless otherwise specified)	Dose Modification for Encorafenib
Events; QTcF = QT interval corrected for heart rate using Fridericia's formula; SCC = squamous cell carcinoma; ULN = upper limit of normal. Dose reduction below 150 mg QD is not allowed. Ophthalmic monitoring mandated for posterior uveitis: further evaluation with specialized retinal imaging in addition to basic assessment (e.g. best corrected visual acuity testing, slit lamp examination, intraocular pressure and dilated fundoscopy). Any diagnosis of retinal events must be supported by presence or absence of symptoms and visual acuity assessment as well as any other documented findings. For participants enrolled with liver metastases and baseline liver function test elevations. Disorder characterized by redness, marked discomfort, swelling and tingling in the palms of the hands or the soles of the feet. A participant with a Grade 4 adverse event may resume encorafenib at the lower dose level if the event recovers to Grade ≤1 within 28 days of discontinuing study intervention and, if in the opinion of the investigator and medical monitor, the event is not life-threatening and the participant can be managed and monitored for recurrence of the event. Any participants requiring a dose interruption of duration >28 days must discontinue encorafenib permanently.	

10.6.2. Dose Modifications for Cetuximab-related Adverse Events

Table 30: Recommended Dose Modifications for Cetuximab-related Adverse Events

Worst Toxicity NCI CTCAE Version 4.03 Grade	Dose Modification for Cetuximab during a Cycle
Infusion reaction: If an infusion reaction occurs while cetuximab is being infused, the infusion should be stopped immediately, and the participant 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 premedications such as antihistamines or low-dose systemic corticosteroids may be administered when the infusion is restarted per study site standards. All subsequent infusions must also be administered at the reduced rate.
Grade 3 or 4	Permanently discontinue cetuximab
Rash: see encorafenib dose modifications (Table 29)	
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 one 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 upon 4th occurrence.
Grade 4, despite skin toxicity therapy	Permanently discontinue cetuximab.
In case of interstitial lung disease, for all grades, cetuximab must be permanently discontinued.	
Abbreviations: NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.	

10.6.3. Dose Modifications for 5 Fluorouracil and Irinotecan-related Adverse Events during FOLFIRI Treatment

Table 31: Recommended Dose Modifications for 5 Fluorouracil and Irinotecan-related Adverse Events During FOLFIRI Treatment

Worst Toxicity NCI CTCAE Version 4.03 Grade	Dose Modification for 5-FU and Irinotecan During a Cycle of FOLFIRI Therapy	At Start of Next Cycles of FOLFIRI Therapy (After Adequate Recovery), Compared with Starting Dose in Previous Cycle
Dose modifications below are for both 5-FU and irinotecan unless otherwise noted.		
Hematologic Toxicities		
A new cycle of therapy should not begin until the ANC has recovered to ≥1500/mm^3 and the platelet count has recovered to ≥100,000/mm^3. Treatment should be delayed 1 to 2 weeks to allow for recovery from study intervention-related toxicities, unless otherwise noted. If the participant has not recovered after a 28-day delay, consideration should be given to discontinuing FOLFIRI.		
Neutropenia		
Grade 1 (1500 to 1999/mm^3)	Maintain dose level	Maintain dose level
Grade 2 (1000 to 1499/mm^3)	Decrease one dose level	Maintain dose level
Grade 3 (500 to 999/mm^3)	Omit dose until resolved to ≤Grade 10, then decrease one dose level	Decrease one dose level
Grade 4 (< 500/mm^3)	Omit dose until resolved to ≤Grade 10, then decrease two dose levels	Decrease two dose levels
Thrombocytopenia		
Grade 1 (<LLN to 75,000/mm^3)	Maintain dose level	Maintain dose level
Grade 2 (75,000 to 50,000/mm^3)	Decrease one dose level	Maintain dose level
Grade 3 (50,000 to 25,000/mm^3)	Omit dose until resolved to ≤Grade 2, then decrease one dose level	Decrease one dose level
Grade 4 (< 25,000/mm^3)	Omit dose until resolved to ≤Grade 2, then decrease two dose levels	Decrease two dose levels
Neutropenic Fever	Omit dose until resolved to ≤Grade 10 ANC and platelet count (for a maximum time of two, 2-week treatments [approx. 28 days]), then decrease two dose levels	Decrease two dose levels
Other Hematologic Toxicities	Dose modifications for leukopenia and anemia during a cycle of therapy and at the start of subsequent cycles of therapy are also based on NCI CTCAE toxicity criteria and are the same as those recommended for neutropenia as above.	
Diarrhea		
A new cycle of therapy should not begin until the study intervention-related diarrhea has recovered to ≤Grade 1. Treatment should be delayed 1 to 2 weeks to allow for recovery from study intervention-related toxicities. If the participant has not recovered after a 14-day delay, consideration should be given to discontinuing FOLFIRI.		
Grade 1 (2-3 stools/day >pretx)	Maintain dose level	**Both -** Maintain dose level

Worst Toxicity NCI CTCAE Version 4.03 Grade	**Dose Modification for 5-FU and Irinotecan During a Cycle of FOLFIRI Therapy**	**At Start of Next Cycles of FOLFIRI Therapy (After Adequate Recovery), Compared with Starting Dose in Previous Cycle**
Grade 2 (4-6 stools/day >pretx)	Decrease one dose level	**5-FU** - Decrease one dose level **Irinotecan** - Maintain dose level
Recurrent Grade 2 (4-6 stools/day >pretx)	Decrease one dose level	**Both –** Decrease one dose level
Grade 3 (7-9 stools/day >pretx)	Omit dose until resolved to ≤Grade 1, then decrease one dose level	**Both -** Decrease one dose level
Grade 4 (≥10 stools/day >pretx)	Omit dose until resolved to ≤Grade 1 (for a maximum time of two, 2-week treatments [approx. 28 days]), then decrease two dose levels	**Both -** Decrease two dose levels
Mucositis (Dose Adjustment for 5-FU ONLY)		
Grade 1	Maintain dose level	Maintain dose level
Grade 2	Decrease one dose level	Decrease one dose level
Recurrent Grade 2	Decrease one dose level	Decrease two dose levels
Grade 3	Omit dose until resolved to ≤Grade 1, then decrease one dose level	If unresolved to ≤Grade 1, omit dose for maximum of 28 days, then decrease two dose levels
Grade 4	Omit dose until resolved to ≤Grade 1 (for a maximum time of two, 2-week treatments [approx. 28 days]), then decrease two dose levels	If unresolved to ≤Grade 1, omit dose for maximum of 28 days, then decrease two dose levels
Nausea/Vomiting (Dose reductions should occur only if symptoms persist despite two treatments with adequate [combination] antiemetic treatment).		
Grade 1	Maintain dose level	Maintain dose level
Grade 2	Maintain dose level	Maintain dose level
Grade 3	**5-FU** - Maintain dose level **Irinotecan** - Decrease one dose level	**5-FU** - Maintain dose level **Irinotecan** - Decrease one dose level
Grade 4	**5-FU** - Decrease one dose level **Irinotecan** – Decrease one dose level	**5-FU** - Decrease one dose level **Irinotecan** - Decrease one dose level
Skin Toxicity (Including Palmar Plantar Erythrodysesthesia) (Dose Adjustment for 5-FU ONLY)		
Grade 1	Maintain dose level	Maintain dose level
Grade 2	Maintain dose level	Maintain dose level
Grade 3	Omit dose until resolved to ≤Grade 1 (for a maximum time of two, 2-week treatments [approx. 28 days]), then decrease one dose level	Decrease one dose level
Grade 4	Omit dose until resolved to ≤Grade 1 (for a maximum time of two, 2-week	Decrease two dose levels

Worst Toxicity NCI CTCAE Version 4.03 Grade	**Dose Modification for 5-FU and Irinotecan During a Cycle of FOLFIRI Therapy**	**At Start of Next Cycles of FOLFIRI Therapy (After Adequate Recovery), Compared with Starting Dose in Previous Cycle**
	treatments [approx. 28 days]), then decrease two dose levels	
Cardiac Toxicity (Dose Adjustment for 5-FU ONLY)		
Grade ≥2	Discontinue 5-FU	
Neurocerebellar Toxicity (Dose Adjustment for 5-FU ONLY)		
Any grade	Discontinue 5-FU	
Other Nonhematologic0 Toxicities		
Grade 1	Maintain dose level	Maintain dose level
Grade 2	Maintain dose level	Maintain dose level
Grade 3	Omit dose until resolved to ≤Grade 1, then decrease one dose level	Decrease one dose level
Grade 4	Omit dose until resolved to ≤Grade 1, then decrease one dose level	Decrease one dose level

Abbreviations: approx. = approximately, ANC = absolute neutrophil count, 5-FU = 5 fluorouracil; FOLFIRI = 5-fluorouracil/folinic acid+irinotecan; LLN = lower limit of normal, NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; pretx = pretreatment.

If a dose delay is required due to any grade of neutropenia prophylactic use of granulocyte colony-stimulating factor and granulocyte-macrophage colony stimulating factor prior to the next administration of FOLFIRI is permitted at the investigator's discretion [Smith 2015].

Excludes alopecia, anorexia or asthenia.

10.6.4. Dose Modifications Irinotecan-related Adverse Events when given without 5 Fluorourical and Folinic Acid

Table 32: Recommended Dose Modifications for Irinotecan-related Adverse Events when given without 5 Fluorouracil and Folinic Acid

Worst Toxicity NCI CTCAE Version 4.03 Grade	Dose Modification for Irinotecan During a Cycle of Therapy	At Start of Next Cycles of Therapy (After Adequate Recovery) Compared with Starting Dose in Previous Cycle
Hematologic Toxicities		
A new cycle of therapy should not begin until the granulocyte count has recovered to ≥1500/mm^3 and the platelet count has recovered to ≥100,000/mm^3. Treatment should be delayed 1 to 2 weeks to allow for recovery from study intervention-related toxicities. If the participant has not recovered after a 2-week delay, consideration should be given to discontinuing irinotecan.		
Neutropenia		
Grade 1 (1500 to 1999/mm^3)	Maintain dose level	Maintain dose level
Grade 2 (1000 to 1499/mm^3)	Decrease one dose level	Maintain dose level
Grade 3 (500 to 999/mm^3)	Omit dose until resolved to ≤Grade 20, then decrease one dose level	Decrease one dose level
Grade 4 (< 500/mm^3)	Omit dose until resolved to ≤Grade 20, then decrease two dose levels	Decrease two dose levels
Neutropenic Fever	Omit dose until resolved, then decrease two dose levels	Decrease two dose levels
Other Hematologic Toxicities	Dose modifications for leukopenia, thrombocytopenia and anemia during a cycle of therapy and at the start of subsequent cycles of therapy are also based on NCI CTCAE toxicity criteria and are the same as those recommended for neutropenia as above.	
Diarrhea		
A new cycle of therapy should not begin until the study intervention-related diarrhea has recovered to ≤Grade 1. Treatment should be delayed 1 to 2 weeks to allow for recovery from study intervention-related toxicities. If the participant has not recovered after a 14-day delay, consideration should be given to discontinuing irinotecan.		
Grade 1 (2-3 stools/day >pretx)	Maintain dose level	Maintain dose level
Grade 2 (4-6 stools/day >pretx)	Decrease one dose level	Maintain dose level
Recurrent Grade 2 (4-6 stools/day >pretx)	Decrease one dose level	Decrease one dose level
Grade 3 (7-9 stools/day >pretx)	Omit dose until resolved to ≤Grade 2, then decrease one dose level	Decrease one dose level
Grade 4 (≥ 10 stools/day >pretx)	Omit dose until resolved to ≤Grade 2 then decrease two dose levels	Decrease two dose levels

Worst Toxicity NCI CTCAE Version 4.03 Grade	Dose Modification for Irinotecan During a Cycle of Therapy	At Start of Next Cycles of Therapy (After Adequate Recovery) Compared with Starting Dose in Previous Cycle
Other Nonhematologic0 Toxicities		
Grade 1	Maintain dose level	Maintain dose level
Grade 2	Decrease one dose level	Decrease one dose level
Grade 3	Omit dose until resolved to ≤Grade 2, then decrease one dose level	Decrease one dose level
Grade 4	Omit dose until resolved to ≤Grade 2, then decrease two dose levels	Decrease two dose levels
Abbreviations: approx. = approximately; FOLFIRI =5-fluorouracil/folinic acid+irinotecan; NCI CTCAE = National Cancer Institute Common Terminology Critiera for Adverse Events pretx = pretreatment. If a dose delay is required due to any grade of neutropenia prophylactic use of granulocyte colony-stimulating factor and granulocyte-macrophage colony stimulating factor prior to the next administration of FOLFIRI is permitted at the investigator's discretion [Smith 2015]. Excludes alopecia, anorexia or asthenia.		

10.7. Appendix 7: Response Evaluation Criteria in Solid Tumors Version 1.1

Taken from Eisenhauer 2009.

10.7.1. Methods of Measurement

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 start of study intervention and never more than 28 days before the first dose.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during the treatment phase and follow-up phase (if applicable). 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 examination.

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 color 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 studies where 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 ULN, however, they must normalize for a participant to be considered in CR. 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.

10.7.2. Measurability of Tumor at Baseline

10.7.2.1. 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.

10.7.2.2. Special Considerations Regarding Lesion Measurability

Bone lesions, cystic lesions and lesions previously treated with local therapy require particular comments:

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 participant, 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 brid progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

10.7.3. Tumor Response Evaluation

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 (see Appendix 10.7.2.1).

10.7.3.1. 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 participants 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, sagittal or coronal). The smaller of these measures is the short axis.

For example, an abdominal node which is reported as being 20 mm × 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').

10.7.3.2. Response Criteria

Tumor Response for Target and Non-target Lesions

Evaluation of Target Lesions

This section provides the definitions of the criteria used to determine objective tumor response for 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 CR criteria are met, since a normal lymph node is defined as having a short axis of <10 mm. Case report forms 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 eCRF. If it is the opinion of the investigator 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 investigator 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'.

Evaluation of Non-target Lesions

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).

Progressive Disease (PD): *Unequivocal progression* of existing non-target lesions. The appearance of one or more new lesions is also considered progression.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

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 participant 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 participant has only non-measurable disease. This circumstance arises in some Phase III studies 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 participants 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 participant 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 participant's baseline lesions show PR or CR.

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 participant who has visceral disease at baseline and while on study has a CT or MRI brain scan ordered which reveals metastases. The participant'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:

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.

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.

Timepoint Response

It is assumed that at each protocol specified timepoint, a response assessment occurs. A summary of the overall response status calculation at each timepoint for participant who have measurable disease at baseline is shown in Table 33.

Table 33: Timepoint Response: Participants 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**

Abbreviations: CR = complete response; NE=not evaluable; PD=progressive disease; PR=partial response; SD=stable disease.

When no imaging/measurement is done at all at a particular timepoint, the participant is not evaluable at that timepoint. If only a subset of lesion measurements is made at an assessment, usually the case is also considered not evaluable at that timepoint, unless convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned timepoint response. This would be most likely to happen in the case of PD.

Evaluation of Best Overall Response

The BOR is the best response across all timepoints recorded from the start of the study intervention until the end of intervention (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 postintervention assessments are to be considered in determination of BOR. Protocols must specify how any new therapy introduced before progression will affect best response designation. The participant's BOR 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'.

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 participants with CR may not have total sum of 'zero' on the eCRF.

Participants with a global deterioration of health status requiring discontinuation of study intervention 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 study intervention. Symptomatic deterioration is *not* a descriptor of an objective response: it is a reason for stopping study intervention. The objective response status of such participants 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 CR depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of CR. 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.

10.8. Appendix 8: Adverse Event Definitions

10.8.1. Definition of an Adverse Event

Adverse Event Definition
An adverse event is any untoward medical occurrence from signature of informed consent in a patient or clinical study participant, whether or not considered related to the study intervention. NOTE: An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease (new or exacerbated).

Events Meeting the Adverse Event Definition
Any abnormal laboratory test results (e.g. haematology, clinical chemistry or urinalysis) or other safety assessments (e.g. ECG, radiological scans, vital signs measurements), including those that worsen from ICF signature, considered clinically significant in the medical and scientific judgment of the investigator (i.e. not related to progression of underlying disease). Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. New conditions detected or diagnosed after ICF signature even though it may have been present before the start of the study. Signs, symptoms or the clinical sequelae of a suspected drug-drug interaction. Signs, symptoms or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. The event of an overdose itself meets the definition of an adverse event and should be reported as an adverse event/SAE. Progression of malignancy (including fatal outcomes), if documented by use of appropriate method as part of the efficacy assessment will be designated as progression of disease in the eCRF and should not be reported as adverse events unless a causal relationship to study intervention is suspected. "Lack of efficacy", "disease progression" or "failure of expected pharmacological action" per se will not be reported as an adverse event/SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms and/or clinical sequelae resulting from disease progression will be reported as adverse event or SAE if they fulfil the definition of an adverse event/SAE. Adverse events specifically related to subsequent anticancer therapy and hospitalisations necessary for the administration of such therapy before the 30-day safety follow-up visit.

Events NOT Meeting the Adverse Event Definition
Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. The disease/disorder being studied or expected progression, signs or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. Medical or surgical procedure (e.g. endoscopy, appendectomy): the condition that leads to the procedure is the adverse event. Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.8.2. Definition of a Serious Adverse Event

If an event is not an adverse event according to the definition in Section 10.8.1, then it cannot be an SAE even if serious conditions are met (e.g. hospitalisation for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
f. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
g. Requires inpatient hospitalisation or prolongation of existing hospitalisation In general, hospitalisation signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalisation are adverse events. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the adverse event should be considered serious. Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an adverse event. Any hospitalization or prolongation of hospitalization due to the circumstances listed below will not be notified as a SAE to the sponsor by the investigator: Planned (according to the protocol) medical/surgical procedure including 24 hours hospitalization after the first treatment administration. Preparation for routine health assessment/procedure (e.g. routine colonoscopy). Planned medical/surgical admission (planned before entry into the study; appropriate documentation is required). Administrative or social reasons (e.g. lack of housing, economic inadequacy, care-giver respite, family circumstances).
h. Results in persistent disability/incapacity The term disability means a substantial disruption of a participant's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza and accidental trauma (e.g. sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
i. Is a congenital anomaly/birth defect

A SAE is defined as any untoward medical occurrence that, at any dose:
j. Other situations: Medical or scientific judgment should be exercized in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of drug dependency or drug abuse.

10.9. Appendix 9: Liver Safety: Suggested Actions and Follow-up Assessments and Study Intervention Rechallenge Guidelines

Guidelines for study intervention temporary and permanent discontinuation, follow-up and rechallenge are provided in Appendix 10.6.

10.10. Appendix 10: The percentage of total red marrow present at different skeletal sites in a healthy adult

Skeletal site	Percentage of red marrow
Cranium	7.6
Mandible	0.8
Scapulae	2.8
Clavicles	0.8
Sternum	3.1
Ribs	16.1
Cervical vertebrae	3.9
Thoracic vertebrae	16.1
Lumbar vertebrae	12.3
Sacrum	9.9
Os coxae	17.5
Femora, upper half	6.7
Femora, lower half	0
Tibiae, fibulae, patellae	0
Ankle and foot bones	0
Humeri, upper half	2.3
Humeri, lower half	0
Ulnae, radii	0
Wrist and hand bones	0

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10.11. Appendix 11 : Adverse Events of Special Interest

Adverse Event of Special Interest	MedDRA Preferred Term (From MedDRA 26.0)
Cutaneous non-squamous cell carcinoma	Basal cell carcinoma
Cutaneous non-squamous cell carcinoma	Carcinoma in situ of skin
Cutaneous non-squamous cell carcinoma	Dysplastic naevus syndrome
Cutaneous non-squamous cell carcinoma	Eccrine carcinoma
Cutaneous non-squamous cell carcinoma	Epidermal naevus syndrome
Cutaneous non-squamous cell carcinoma	Extramammary Paget's disease
Cutaneous non-squamous cell carcinoma	Hidradenocarcinoma
Cutaneous non-squamous cell carcinoma	Malignant sweat gland neoplasm
Cutaneous non-squamous cell carcinoma	Mastocytoma
Cutaneous non-squamous cell carcinoma	Neoplasm skin
Cutaneous non-squamous cell carcinoma	Neuroendocrine carcinoma of the skin
Cutaneous non-squamous cell carcinoma	Pilomatrix carcinoma
Cutaneous non-squamous cell carcinoma	Porocarcinoma
Cutaneous non-squamous cell carcinoma	Sebaceous carcinoma
Cutaneous non-squamous cell carcinoma	Skin angiosarcoma
Cutaneous non-squamous cell carcinoma	Skin cancer
Cutaneous non-squamous cell carcinoma	Skin cancer metastatic
Cutaneous non-squamous cell carcinoma	Skin neoplasm bleeding
Cutaneous non-squamous cell carcinoma	Trichoblastic carcinoma
Cutaneous squamous cell carcinoma	Atypical fibroxanthoma
Cutaneous squamous cell carcinoma	Basosquamous carcinoma of skin
Cutaneous squamous cell carcinoma	Bowen's disease
Cutaneous squamous cell carcinoma	Keratoacanthoma
Cutaneous squamous cell carcinoma	Marjolin's ulcer
Cutaneous squamous cell carcinoma	Skin squamous cell carcinoma metastatic
Cutaneous squamous cell carcinoma	Squamous cell carcinoma of skin
Cutaneous squamous cell carcinoma	Trichoblastic carcinoma
Melanomas	Acral lentiginous melanoma
Melanomas	Acral lentiginous melanoma stage I
Melanomas	Acral lentiginous melanoma stage II
Melanomas	Acral lentiginous melanoma stage III
Melanomas	Acral lentiginous melanoma stage IV
Melanomas	Desmoplastic melanoma
Melanomas	Lentigo maligna
Melanomas	Lentigo maligna recurrent
Melanomas	Lentigo maligna stage I

Adverse Event of Special Interest	MedDRA Preferred Term (From MedDRA 26.0)
Melanomas	Lentigo maligna stage II
Melanomas	Lentigo maligna stage III
Melanomas	Lentigo maligna stage IV
Melanomas	Malignant blue naevus
Melanomas	Malignant melanoma
Melanomas	Malignant melanoma in situ
Melanomas	Malignant melanoma stage I
Melanomas	Malignant melanoma stage II
Melanomas	Malignant melanoma stage III
Melanomas	Malignant melanoma stage IV
Melanomas	Melanoma recurrent
Melanomas	Naevoid melanoma
Melanomas	Nodular melanoma
Melanomas	Superficial spreading melanoma stage I
Melanomas	Superficial spreading melanoma stage II
Melanomas	Superficial spreading melanoma stage III
Melanomas	Superficial spreading melanoma stage IV
Melanomas	Superficial spreading melanoma stage unspecified
Facial paresis	Brow ptosis
Facial paresis	Crocodile tears syndrome
Facial paresis	Facial nerve disorder
Facial paresis	Facial paralysis
Facial paresis	Facial paresis
Facial paresis	Facial spasm
Facial paresis	Hyperacusis
Facial paresis	Melkersson-Rosenthal syndrome
Facial paresis	Oculofacial paralysis
Facial paresis	VIIth nerve injury
Uveitis type events	Autoimmune uveitis
Uveitis type events	Bacterial iritis
Uveitis type events	Blau syndrome
Uveitis type events	Chemical burns of eye
Uveitis type events	Ciliary hyperaemia
Uveitis type events	Cogan's syndrome
Uveitis type events	Cyclitic membrane
Uveitis type events	Cyclitis
Uveitis type events	Diabetic uveitis
Uveitis type events	Heerfordt's syndrome
Uveitis type events	Immune recovery uveitis
Uveitis type events	Infectious iridocyclitis
Uveitis type events	Infective iritis
Uveitis type events	Iridocyclitis

Adverse Event of Special Interest	MedDRA Preferred Term (From MedDRA 26.0)
Uveitis type events	Iritis
Uveitis type events	Sympathetic ophthalmia
Uveitis type events	Traumatic iritis
Uveitis type events	Tubulointerstitial nephritis and uveitis syndrome
Uveitis type events	Uveitis
Uveitis type events	Viral uveitis
Uveitis type events	keratouveitis
QT prolongation	Electrocardiogram QT interval abnormal
QT prolongation	Electrocardiogram QT prolonged
QT prolongation	Long QT syndrome
QT prolongation	Long QT syndrome congenital
QT prolongation	Torsade de pointes
QT prolongation	Ventricular tachycardia
QT prolongation	Cardiac arrest
QT prolongation	Cardiac death
QT prolongation	Cardiac fibrillation
QT prolongation	Cardio-respiratory arrest
QT prolongation	Electrocardiogram repolarisation abnormality
QT prolongation	Electrocardiogram U wave inversion
QT prolongation	Electrocardiogram U wave present
QT prolongation	Electrocardiogram U-wave abnormality
QT prolongation	Loss of consciousness
QT prolongation	Sudden cardiac death
QT prolongation	Sudden death
QT prolongation	Syncope
QT prolongation	Ventricular arrhythmia
QT prolongation	Ventricular fibrillation
QT prolongation	Ventricular flutter
QT prolongation	Ventricular tachyarrhythmia
Non-cutaneous malignancies with RAS mutation	H-RAS gene mutation
Non-cutaneous malignancies with RAS mutation	K-RAS gene mutation
Non-cutaneous malignancies with RAS mutation	N-RAS gene mutation

10.12. Appendix 12: Abbreviations

Abbreviation	Definition
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATP	Adenosine Triphosphate
AUC	Area under the Curve
BCRP	Breast Cancer Resistance Protein
BICR	Blinded (to treatment received) Independent Central Review
BOR	Best Overall Response
BRAF	B-RAF Proto-oncogene, Serine/threonine Kinase
BRAF V600E	B-RAF Proto-oncogene, Serine/threonine Kinase V600E Mutant
BRAF wt	B-RAF Proto-oncogene, Serine/threonine Kinase Wild Type
BSA	Body Surface Area
CCI	[redacted]
[redacted]	[redacted]
CFR	Code of Federal Regulations
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
C_{max}	Maximum Concentration
C_{min}	Minimum Concentration
cORR	Confirmed Overall Response Rate
CR	Complete Response
CRA	Clinical Research Associate
CRC	Colorectal Cancer
CRO	Contract Research Organization
CRP	C-reactive Protein
CSCO	Chinese Society of Clinical Oncology
CT	Computed Tomography
CYP	Cytochrome P450
DDS	Dose-determining Set
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
dMMR	DNA Mismatch Repair
DNA	Deoxyribonucleic Acid
DOR	Duration of Response
ECG	Electrocardiogram

Abbreviation	Definition
ECOG	Eastern Co-operative Oncology Group
eCRF	Electronic Case Report From
EGFR	Epidermal Growth Factor Receptor
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer Patients
EQ-5D-5L	EuroQol-5D-5L
ERK	Extracellular Signal-related Kinase
ES	Efficacy Set
ESMO	European Society of Medical Oncology
EU	European Union
FA	Folinic Acid
FACT-C	Functional Assessment of Cancer Therapy-Colon Cancer
FAS	Full Analysis Set
FDG-PET	Fluorodeoxyglucose-positron Emission Tomography
FFPE	Formalin-fixed and Paraffin Embedded
FOLFIRI	5-fluorouracil/Folinic Acid+Irinotecan
FOLFOXIRI	5-fluorouracil/Leucovorin+Irinotecan
5-FU	5-fluorouracil
FSH	Follicle-stimulating Hormone
GCP	Good Clinical Practice
HBV	Hepatitis B Virus
hCG	human Chorionic Gonadotropin
HCV	Hepatitis C Virus
HFSR	Hand-foot Skin Reaction
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HRT	Hormone Replacement Therapy
ICF	Participant Information Sheet and Informed Consent Form
ICH	International Council on Harmonisation
Ig	Immunoglobulin
IEC	Independent Ethics Committee
IRPF	Institut de Recherche Pierre Fabre
IRT	Interactive Response Technology
IV	Intravenous
LC/MS-MS	Liquid Chromatography Tandem Mass Spectrometry
MAPK	Mitogen-activated Protein Kinase
mCRC	Metastatic Colorectal Cancer
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Definition
MEK	Mitogen-activated Protein Kinase Kinase
MRI	Magnetic Resonance Imaging
MSI	Microsatellite Instability
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	Next-generation Sequencing
OAT	Organic Anionic Transporter
OATP	Organic Anion-transporting Peptide
OCT	Organic Cationic Transporter
ORR	Overall Response Rate0
OS	Overall Survival
PCR	Polymerase Chain Reaction
PD	Progressive Disease
PDF	Portable Document Format
PFS	Progression-free Survival
P-gp	P-glycoprotein
PGIC	Patient Global Impression of Change
PK	Pharmacokinetics
PO	Per Oral
PPS	Per-protocol Set
PR	Partial Response
PRO	Patient Reported Outcomes
QD	Once Daily
QoL	Quality of Life
QTcF	QT interval corrected for heart rate using Fridericia's formula
RAF	Proto-oncogene Serine/threonine-Protein Kinase
RAS	Rat Sarcoma Viral Oncogene Homologue
RAS wt	Rat Sarcoma Viral Oncogene Homologue Wild Type
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic Acid
RP2D	Recommended Phase II Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis Software
SD	Stable Disease
SLI	Safety Lead-in
SOC	System Organ Class
SUSAR	Suspected, Unexpected, Serious Adverse Reaction
TEAE	Treatment-emergent Adverse Event

Abbreviation	Definition
TTR	Time to Response
UGT	5'-diphospho-glucuronosyltransferase
ULN	Upper Limit of Normal
US	United States
VAS	Visual Analogue Scale
VEGF	Vascular Endothelial Growth Factor
VRS	Verbal Rating Scale
WHO	World Health Organisation
WOCBP	Women of Childbearing Potential
This may also be referred to as 'objective response rate' in some protocols or publications	

10.13. Appendix 13 : Protocol Amendment History

Document version	Date issue	Type (subs/non subs)	Application area	Country	Description of changes
Protocol V1.0	22OCT20	NA	China	China	"NA - initial protocol";
Protocol V2.0	21APR21	NA	China	China	"The overall rationale for the changes implemented in this protocol version 2.0 is to respond to lead EC comments, then to clarify the OS analysis as per China CDE recommendation reported into the NMPA approval letter dated 25 February 2021, to update the SAE reporting process and to correct some discrepancies between sections".
Protocol V3.0	10JAN2022	Non substantial	China	China	"The overall rationale for the changes is to implement an additional exploratory objective to support a companion diagnostic development in China, then the main other changes are the change of End of Study definition for clarification, the addition of Lipase and Amylase as routine tests, the removal of Bicarbonate as routine test, the change of exclusion criteria related to HBV to be in accordance with the Centers for Disease Control and Prevention (cdc.gov), the change of Visual Acuity measurement according to local practice, the revision of the information related to contraception to be in accordance with local labels for Standard of Care Treatment, the addition of instructions for tumor tissue to be sent for central testing, the addition of prescreening for patients with local BRAF positive testing in case the maximum of indeterminate or discordant central results is reached at site or study level".
Protocol V4.0	22 DEC 2022	Substantial	China	China	"The overall rationale of the changes is to add instructions related to COVID19 restrictions and the impact on study treatment management when temporary interruption is needed, some clarifications to avoid any confusion, to correct some discrepancies between sections and to correct some typo errors".

Protocol V5.0	10JUL2023	Substantial	China	China	The overall rational of the changes is to adjust the cut-off date definition for primary analysis considering that number of events expected to trigger this analysis (n=74) may not be reached due to a high number of censored patients for primary endpoint. The main other changes are related to the update of the encorafenib Investigator Brochure dated may 2023.
Protocol V6.0	16MAY2024	Non Substantial	China	China	The overall rationale of the changes is to change the definition of the End of Study and detail schedule of assessment for participant in Doublet arm that would continue treatment after final analysis cut-off date. Other changes are for clarification or to correct redundancies or typo errors.

10.14.Appendix 14 : Sponsor Personnel

11. References

Aaronson NK, Ahmedzai S, Bergman B et al.
The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology.
J Natl Cancer Inst 1993;85(5):365-376.

Avins AL
Can unequal be more fair? Ethics, subject allocation, and randomised clinical trials.
J Med Ethics. 1998;24(6):401-408. doi:10.1136/jme.24.6.401

Ardekani R, et al.
The Prognostic Value of BRAF Mutation in Colorectal Cancer and Melanoma: A Systematic Review and Meta-Analysis
PLoS One. 2012;7(7):e40506

Barras D, Missiaglia E, Wirapati P et al.
BRAF V600E Mutant Colorectal Cancer Subtypes Based on Gene Expression.
Clin Cancer Res 2017;23(1):104-115.

Bray F, Ferlay J, Soerjomataram I et al.
Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries.
CA Cancer J Clin 2018;68(6):394-424.

Brookmeyer R and Crowley J.
A confidence interval for the median survival time.
Biometrics 1982;38:29-41.

Bylsma LC, Gillezeau C, Garawin T et al.
Prevalence of RAS and BRAF mutations in metastatic colorectal cancer (mCRC) patients by tumour location.
J Clin Oncol 2018;36(4)_suppl:681.

Chapman PB, Hauschild A, Robert C et al.
Improved survival with vemurafenib in melanoma with BRAF V600E mutation.
N Engl J Med 2011;364(26):2507-2516.

Chen J, Guo F, Shi X, et al.
BRAF V600E mutation and KRAS codon 13 mutations predict poor survival in Chinese colorectal cancer patients
BMC Cancer. 2014;14:802.

Clarke S, Yip S, Brown C, et al.
Single-agent irinotecan or 5-fluorouracil and leucovorin (FOLFIRI) as second-line chemotherapy for advanced colorectal cancer; results of a randomised phase II study (DaVINCI) and meta-analysis.
Eur J Cancer 2011;47:1826-36.

Clarke CN, Kopetz ES.
BRAF mutant colorectal cancer as a distinct subset of colorectal cancer: clinical characteristics, clinical behavior, and response to targeted therapies.
J Gastrointest Oncol 2015; 6:660-667.

Clopper CJ, Pearson ES.
The Use of Confidence or Fiducial Limits Illustrated in the Case of the Binomial.
Biometrika 1934;26(4):404-413.

Connolly K, Brungs D, Szeto E, Epstein RJ.
Anticancer activity of combination targeted therapy using cetuximab plus vemurafenib for refractory BRAF (V600E)-mutant metastatic colorectal carcinoma.
Curr Oncol 2014;21(1):e151-154.

Coon CD, Cappelleri JC.
Interpreting change in scores on patient-reported outcome instruments.
Ther Innov Regul Sci 2016;50(1):22-29.

Corcoran RB, Ebi H, Turke AB, et al.
EGFR-mediated reactivation of MAPK signaling contributes to insensitivity of BRAF-mutant colorectal cancers to RAF inhibition with vemurafenib.
Cancer Discov 2012;2(3):227-235.

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.

Heads of Medicines Agencies, Clinical Trials Facilitation Group (CTFG).
Recommendations related to contraception and pregnancy testing in clinical trials. Final Version 2014.
http://www.hma.eu/fileadmin/dateien/Human_Medicines/01About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf

Davies H, Bignell GR, Cox C et al.
Mutations of the BRAF gene in human cancer.
Nature 2002;417(6892):949-954.

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(8):753–762.

Downward J.
Targeting RAS signalling pathways in cancer therapy.
Nat Rev Cancer 2003;3(1):11–22.

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 HJ et al.
Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma (COLUMBUS): a multicentre, open-label, randomised phase 3 trial.

Oncol 2018a;19(5):603-615.

Dummer R, Ascierto PA, Gogas HJ et al.
Overall survival in patients with BRAF-mutant melanoma receiving encorafenib plus binimetinib versus vemurafenib or encorafenib (COLUMBUS): a multicentre, open-label, randomised, phase 3 trial.
Lancet Oncol 2018b;19(10):1315-1327.

Eisenhauer EA, Therasse P, Bogaerts J.
New response evaluation criteria in solid tumours: revised RECIST guideline (Version 1.1).
Eur J Cancer 2009; 45(2):228-247.

Flaherty KT, Puzanov I, Kim KB et al.
Inhibition of mutated, activated BRAF in metastatic melanoma.
N Engl J Med 2010;363:809-819.

Flaherty KT, Infante JR, Daud A et al.
Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations.
N Engl J Med 2012;367(18):1694-1703.

Fuchs CS, Marshall J, Mitchell E, et al.
Randomized, controlled trial of irinotecan plus infusional, bolus, or oral fluoropyrimidines in first-line treatment of metastatic colorectal cancer: results from the BICC-C Study.
J Clin Oncol. 2007;25(30):4779-86.

Globocan 2018.
Colorectal Cancer.
WHO International Agency for Research on Cancer.
http://gco.iarc.fr/today/data/factsheets/cancers/10_8_9-Colorectum-fact-sheet.pdf Accessed April 2020.

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.

Grothey A, Tabernero J, Taeb J et al.
ANCHOR CRC: a single-arm, phase 2 study of encorafenib, binimetinib plus cetuximab in previously untreated BRAF V600E mutant metastatic colorectal cancer.
Ann oncol 2020, Vol 31 issue S3.

Hindorf C, Glatting G, Chiesa C et al.
EANM dosimetry committee guidelines for bone marrow and whole-body dosimetry
Eur J Nucl Med Mol Imaging 2010; DOI 10.1007/s00259-010-1422-4.

Holladay JT.
Visual acuity measurements.
J Cataract Refact Surg 2004;30:287-290.

Hong DS, Morris VK, El Osta B et al.
Phase Ib study of vemurafenib in combination with irinotecan and cetuximab in patients with metastatic colorectal cancer with BRAFV600E mutation.
Cancer Discov 2016;6(12):1352-1365.

Hyman DM, Puzanov I, Subbiah V et al.
Vemurafenib in multiple nonmelanoma cancers with BRAF V600 mutations.
N Engl J Med 2015;373(8):726-736.

W00090GE202 Ethnicity Report - Version 1 (Safety section),

W00090GE301 Ethnicity report Version 2 (PK section).

Kalbfleisch JD and Prentice RL.
The statistical analysis of failure time data.
Hoboken: John Wiley& Sons, 2002.

Klein JP and Moeschberger ML.
Survival analysis: Techniques for censored and truncated data.
New York: Springer-Verlag, 1997.

Kopetz S, Desai J, Chan E et al.
Phase II pilot study of vemurafenib in patients with metastatic BRAF-mutated colorectal cancer.
J Clin Oncol 2015;33(34):4032-4038.

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.

Kopetz S, Grothey A, Yaeger, R et al.
Encorafenib, binimetinib, and cetuximab in BRAF V600E–mutated colorectal cancer.
New Engl J Med 2019;381:1632-1643.

Kopetz S, Grothey A, Van Cutsem E, et al
Encorafenib plus cetuximab with or without binimetinib for **BRAF** *V600E metastatic colorectal cancer: Updated survival results from a randomized, three-arm, phase III study versus choice of either irinotecan or FOLFIRI plus cetuximab (BEACON CRC).*
Journal of Clinical Oncology 2020 38:15_suppl, 4001-4001

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;19:1079–1095.

Long GV, Stroyakovskiy D, Gogas H et al.
Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: a multicenter, double-blind, phase 3 randomised controlled trial.
Lancet 2015;386:444-451.

Long GV, Flaherty KT, Stroyakovskiy D et al.
Dabrafenib plus trametinib versus dabrafenib monotherapy in patients with metastatic BRAF V600E/K-mutant melanoma: long-term survival and safety analysis of a phase 3 study.
Ann Oncol 2017;28(7):1631-1639.

Loupakis F, Ruzzo A, Cremolini C, et al.

KRAS codon 61, 146 and BRAF mutations predict resistance to cetuximab plus irinotecan in KRAS codon 12 and 13 wild-type metastatic colorectal cancer.
Br J Cancer 2009;101:715-721.

Mehta RS, Song M, Nishihara R, et al.
Dietary patterns and risk of colorectal cancer: analysis by tumor location and molecular subtypes.
Gastroenterology 2017;152:1944–1953.

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;31:1285-1292.

Morris VK, 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 Colorectal Cancer 2014;13(3):164-171

Nardone JR, Hensley JR, Kulik L et al.
The effect of hand and foot skin reaction associated with the multikinase inhibitors sorafenib and sunitinib on health related quality of life.
J Drugs Dermatol 2012;11(11) :e61-e65.

National Cancer Institute Common Terminology Criteria for Adverse Events Version 4 (published 28 May 2009; Version 4.03 14 June 2010).

National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Colon cancer, Version 4.2020.

National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Colon cancer, Version 2.2019.

Osumi H, Shinozaki E, Yamaguchi K et al.
Early change in circulating tumor DNA as a potential predictor of response to chemotherapy in patients with metastatic colorectal cancer.
Sci Rep 917358.

Pathak S, Nunes Q, Daniels I et al.
Is C-reactive protein useful in prognostication for colorectal cancer? A systemic review.
Colorectal Dis 2014;16:769-776.

Peeters M, Oliner KS, Price T, et al.
Updated analysis of KRAS/NRAS and BRAF mutations in study 20050181 of panitumumab (pmab) plus FOLFIRI for second-line treatment (tx) of metastatic colorectal cancer (mCRC).
J Clin Oncol 2014;32:5s, (suppl; abstr 3568).

Planchard D, Kim TM, Mazieres J et al.
Dabrafenib in patients with BRAF(V600E)-positive advanced non-small-cell lung cancer: a single-arm, multicentre, open-label, phase 2 trial.
Lancet Oncol 2016;17(5):642-650.

Prahallad A, Sun C, Huang S, et al.
Unresponsiveness of colon cancer to BRAF(V600E) inhibition through feedback activation of EGFR.
Nature 2012;100:100-104.

Rabin R, de Charro F.
EQ-5D: A measure of health status from the EuroQol Group.
Ann Med 2001;33:337-343.

Saridaki Z, Tzardi M, Sfakianaki M, et al.
BRAFV600E mutation analysis in patients with metastatic colorectal cancer (mCRC) in daily clinical practice: Correlations with clinical characteristics, and its impact on patients' outcome.
PLOS One 2013;8:1-7.

Sorafenib (Nexavar; West Haven, CT: Bayer Pharmaceuticals Corporation; 2007) package insert.

Smith T, Bohlke K, Lyman GH.
Recommendations for the use of WBC growth factors: American Society of Clinical Oncology clinical practice guideline update.
J Clin Oncol. 2015;33:1-16.

Sorbye H, Dragomir A, Sundström M et al.
High BRAF mutation frequency and marked survival differences in subgroups according to KRAS/BRAF mutation status and tumour tissue availability.
PLOS One 2015;10(6):e0131046.

Tabernero J, Chan E, Baselga J et al.
VE-BASKET, a Simon 2-stage adaptive design, phase II,histology-independent study in nonmelanoma solid tumors harboring BRAF V600 mutations (V600m): Activity of vemurafenib (VEM) with or without cetuximab (CTX) in colorectal cancer (CRC).
J Clin Oncol 2014;32:5s(suppl; abstr 3518).

Tabernero J, Yoshino T, Cohn A, et al.
Ramucirumab versus placebo in combination with second-line FOLFIRI in patients with metastatic colorectal carcinoma that progressed during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (RAISE): a randomised, double-blind, multicenter, phase 3 study.
Lancet Oncol. 2015;16:499-508.

Tabernero J, van Geel R, Guren TK et al.
Phase 2 results: Encorafenib (ENCO) and cetuximab (CETUX) with or without alpelisib (ALP) in patients with advanced BRAF-mutant colorectal cancer (BRAF mCRC).
J Clin Oncol 2016;34:5s(suppl; abstr 3544).

Tampellini M, Ottone A, Alabiso I et al.
The prognostic role of baseline CEA and CA 19-9 values and their time-dependent variations in advanced colorectal cancer patients submitted to first-line therapy.
Tumour Biol 2015;36:1519-1527.

Thomsen M, Kersten C, Sorbye H et al.
Interleukin-6 and C-reactive protein as prognosticbiomarkers in metastatic colorectal cancer.
Oncotarget 2016;15:75013-75022.

Thomsen M, Skovlund E, Sorbye H.
Prognostic role of carcinoembryonic antigen and carbohydrate antigen 19-9 in metastatic colorectal cancer: a BRAF-mutant subset with high CA 19-9 level and poor outcome.
Brit J Cancer 2018; 118:1609–1616.

Tran B, Kopetz S, Tie J, et al.
Impact of BRAF mutation and microsatellite instability on the pattern of metastatic spread and prognosis in metastatic colorectal cancer.
Cancer 2011;117:4623–4632.

Ulivi P, Capelli L, Valgiusti M et al.
Predictive role of multiple gene alterations in response to cetuximab in metastatic colorectal cancer: A single center study.
J Transl Med 2012;10:87.

Ursem C, Atreya CE Van Loon, K.
Emerging treatment options for BRAF-mutant colorectal cancer.
Gastrointestinal cancer: targets and therapy 2018;8:13-23.

Van Cutsem E, Köhne CH, Láng I, 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):2011–2019.

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 et al.
ESMO consensus guidelines for the management of patients with metastatic colorectal cancer.
Ann Oncol 2016;27(8):1386-1422.

van Geel RMJM, Tabernero J, Elez E et al.
A Phase Ib dose-escalation study of encorafenib and cetuximab with or without alpelisib in metastatic BRAF-mutant colorectal cancer.
Cancer Discov 2017;7(6):610-619.

Van Moos R, Thuerlimann JK, Aopro M et al.
Pegylated liposomal doxorubicin-associated hand–foot syndrome: Recommendations of an international panel of experts.
Eur J Cancer 2008;44(6):781-790.

Ward WL, Hahn EA, Mo F, et al.

Reliability and validity of the Functional Assessment of Cancer Therapy-Colorectal (FACT-C) quality of life instrument.
Qual Life Res 1999; May;8(3):181-195.

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(3):779-789.

Yang Y, Wang D, Jin L, et al.
Prognostic value of the combination of microsatellite instability and BRAF mutation in colorectal cancer.
Cancer Manag Res 2018;10:3911–3929.

Yokota T, Ura T, Shibata N et al.
BRAF mutation is a powerful prognostic factor in advanced and recurrent colorectal cancer.
Brit J Cancer 2011;104 856-862.

Yoshino T, Arnold D, Taniguchi H, et al.
Pan-Asian adapted ESMO consensus guidelines for the management of patients with metastatic colorectal cancer: a JSMO–ESMO initiative endorsed by CSCO, KACO, MOS, SSO and TOS.
Ann Oncol 2018;29:44–70.

Yuan Y, Wang X, Chen G et al.
Updates in version 2019 of CSCO guidelines for colorectal cancer from version 2018
Chin J Cancer Res 2019; Jun; 31(3):423–425.

Zhang Y, Chen Z, Li J.
The current status of treatment for colorectal cancer in China.
Medicine (Baltimore) 2017 96(40):e8242.

Zhang L, Cao F, Zhang G, et al.
Trends in and Predictions of Colorectal Cancer Incidence and Mortality in China From 1990 to 2025.
Front Oncol. 2019;9:98.