



Title Page

AN OPEN-LABEL, MULTICENTER, RANDOMIZED PHASE 3 STUDY OF FIRST-LINE ENCORAFENIB PLUS CETUXIMAB WITH OR WITHOUT CHEMOTHERAPY VERSUS STANDARD OF CARE THERAPY WITH A SAFETY LEAD-IN OF ENCORAFENIB AND CETUXIMAB PLUS CHEMOTHERAPY IN PARTICIPANTS WITH METASTATIC BRAF V600E-MUTANT COLORECTAL CANCER

Study Intervention Number:	PF-07263896; LGX818; ONO-7702
Study Intervention Name:	Encorafenib
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ClinicalTrials.gov ID:	NCT04607421
Pediatric Investigational Plan Number:	NA
Protocol Number:	C4221015
Phase:	3
Sponsor Legal Address:	Pfizer Inc. 66 Hudson Boulevard East New York, NY 10001

SHORT TITLE: The BREAKWATER Study (BRAF V600E-mutant colorectal cancer study evaluating EncorAfenib taKen With cetuximAb plus or minus chemoTheRapy)

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Document History

Document	Version Date
Amendment 7	31 May 2024
Amendment 6	13 March 2024
Amendment 5	20 December 2022
Amendment 4	28 February 2022
Amendment 3	24 February 2021
Amendment 2	12 November 2020
Amendment 1	07 August 2020
Original protocol	15 July 2020

The main purpose of Protocol Amendment 7 is to update the randomization ratio for Cohort 3 to be 1:1 (Arm D: Arm E), as implemented in the IRT system prior to the start of enrollment into this cohort. In addition, this amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ethics committees and any protocol administrative change letter(s).

Protocol Amendment Summary of Changes Table

Description of Change	Brief Rationale	Section # and Name
Substantial Modification(s)		
The randomization ratio for Cohort 3 (Arm D: Arm E) was modified from the original 2:1 to 1:1. Resulting from the change in randomization ratio, the number of participants in Cohort 3 was modified from 135 to 136 and the planned sample size of the study was increased from approximately 815 to 816, the ORR analysis power increased from 90% to 93.1%, and the number of PFS events required for the PFS analysis decreased from 82 to 73, and the reference to 14 months of follow-up after the randomization of last participant was removed.	<p>An error in the randomization ratio (1:1 instead of the planned 2:1) for Cohort 3 was discovered after approximately 64% of participants have enrolled. At this point in the study accrual, the randomization will proceed as 1:1.</p> <p>This change will not impact the primary objective of the study as the power for the ORR analysis increased from 90% to 93% and the number of events required for the PFS analysis decreased from 82 to 73.</p>	<p>Section 1.1 Synopsis</p> <p>Section 1.2 Schema</p> <p>Section 4.1 Overall Design</p> <p>Section 6.1.2 Treatment Regimens</p> <p>Section 9.2 Sample Size Determination</p> <p>Section 9.4.1.1 Statistical Testing Strategy</p>
Non-Substantial Modification(s)		
Incorporated additional information about the testing and destruction of biological samples of participants enrolled in China.	This information was added to meet the requirement of China Service Guidance on Human Genetic Resource Approvals and Filing issued on 14 July 2023, and was implemented in a country-specific protocol administrative change letter dated 03 Apr 2024.	Section 10.8.2 Mainland China Specific Procedures

TABLE OF CONTENTS

LIST OF TABLES11

LIST OF FIGURES12

1. PROTOCOL SUMMARY13

 1.1. Synopsis13

 1.2. Schema21

 1.3. Schedule of Activities22

2. INTRODUCTION58

 2.1. Study Rationale58

 2.2. Background58

 2.2.1. *BRAF* V600E-Mutant Metastatic Colorectal Cancer58

 2.2.2. Clinical Overview59

 2.2.2.1. Current Recommendations for Treatment of *BRAF*
 V600E-mutant mCRC59

 2.2.2.2. Encorafenib + Cetuximab for the Treatment of *BRAF*
 V600E-mutant mCRC60

 2.2.2.3. Management of Cancer Patients During COVID-19
 Pandemic62

 2.3. Benefit/Risk Assessment62

 2.3.1. Risk Assessment64

 2.3.2. Benefit Assessment68

 2.3.3. Overall Benefit/Risk Conclusion68

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS68

4. STUDY DESIGN72

 4.1. Overall Design72

 4.2. Scientific Rationale for Study Design73

 4.2.1. Safety Lead-in73

 4.2.2. Assessment of Potential DDI with Encorafenib73

 4.2.3. Investigator’s Choice of Control Regimen74

 4.2.4. Progression-Free Survival and Objective Response Rate as Primary
 Endpoints75

 4.2.5. Biomarkers75

 4.2.6. Use of Contraceptives76

4.3. Justification for Dose	76
4.4. End of Study Definition	77
5. STUDY POPULATION	77
5.1. Inclusion Criteria.....	77
5.1.1. Molecular Prescreening Inclusion Criteria	77
5.1.2. Screening Inclusion Criteria	78
5.2. Exclusion Criteria.....	80
5.2.1. Molecular Prescreening Exclusion Criteria	80
5.2.2. Screening Exclusion Criteria	81
5.3. Lifestyle Considerations.....	84
5.3.1. Contraception.....	85
5.3.2. Meals and Dietary Restrictions.....	85
5.3.3. Photosensitivity.....	85
5.3.4. Screen Failures.....	85
6. STUDY INTERVENTION.....	86
6.1. Study Interventions Administered.....	87
6.1.1. Safety Lead-in.....	89
6.1.1.1. Dose Limiting Toxicity Definition.....	90
6.1.2. Treatment Regimens	91
6.1.3. Administration	95
6.1.3.1. Administration of Encorafenib.....	95
6.1.3.2. Administration of Capecitabine, Cetuximab, 5- Fluorouracil, Irinotecan, Leucovorin, Oxaliplatin and Bevacizumab	96
6.2. Preparation/Handling/Storage/Accountability	97
6.2.1. Preparation and Dispensing	98
6.3. Measures to Minimize Bias: Randomization and Blinding.....	98
6.3.1. Allocation to Study Intervention	98
6.4. Study Intervention Compliance.....	99
6.5. Concomitant Therapy	99
6.5.1. Permitted Concomitant Medications/Therapies	99
6.5.1.1. Surgical Resection.....	100

6.5.1.2. CYP and UGT Substrates and Inhibitors	100
6.5.1.3. Transporter Substrates and Inhibitors	101
6.5.1.4. Drugs with a Conditional or Possible Risk to Prolong the QT Interval and/or Induce Torsade de Pointes.....	101
6.5.2. Prohibited Concomitant Therapy.....	101
6.5.3. Premedication and Concurrent Medication	102
6.5.3.1. Premedication for Cetuximab Administration	102
6.5.3.2. Loperamide.....	103
6.5.3.3. Antibiotics	103
6.5.3.4. Atropine.....	103
6.5.3.5. Hematopoietic Growth Factors	103
6.5.3.6. Antiemetics.....	104
6.6. Dose Modification.....	104
6.6.1. Dose Modifications for Encorafenib	105
6.6.2. Dose Modifications for Cetuximab	109
6.6.3. Dose Modifications for Oxaliplatin, Irinotecan, 5-FU and Capecitabine as Part of mFOLFOX6, FOLFIRI, FOLFOXIRI and CAPOX Regimens	110
6.6.4. Dose Modifications for Bevacizumab	117
6.6.5. Guidance For Administration of Study Intervention in Participants with SARS-CoV-2 Infection.....	120
6.7. Intervention After the End of the Study	120
7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL.....	120
7.1. Discontinuation of Study Intervention	120
7.2. Participant Discontinuation/Withdrawal From the Study	122
7.2.1. Withdrawal of Consent/Assent	123
7.3. Lost to Follow-up	123
8. STUDY ASSESSMENTS AND PROCEDURES.....	123
8.1. Efficacy Assessments	124
8.1.1. Tumor Response Assessments.....	124
8.1.1.1. BICR Evaluation of Imaging Data	126
8.1.2. Patient-reported Outcomes	128

8.1.3. Survival Follow-up	129
8.2. Safety Assessments	129
8.2.1. Participant Demographics and Other Baseline Characteristics	130
8.2.2. Disease Characteristics and Treatment History	130
8.2.3. Physical Examinations.....	130
8.2.4. Body Surface Area.....	130
8.2.5. Dermatological Examinations	131
8.2.6. Vital Signs	131
8.2.7. Electrocardiograms	131
8.2.8. Clinical Safety Laboratory Assessments	132
8.2.9. Pregnancy Testing	133
8.2.10. ECOG Performance Status	133
8.3. Adverse Events and Serious Adverse Events.....	134
8.3.1. Time Period and Frequency for Collecting AE and SAE Information.....	134
8.3.1.1. Reporting SAEs to Pfizer Safety	135
8.3.1.2. Recording Nonserious AEs and SAEs on the CRF	135
8.3.2. Method of Detecting AEs and SAEs	135
8.3.3. Follow-up of AEs and SAEs.....	136
8.3.4. Regulatory Reporting Requirements for SAEs.....	136
8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure	136
8.3.5.1. Exposure During Pregnancy.....	137
8.3.5.2. Exposure During Breastfeeding	138
8.3.5.3. Occupational Exposure	139
8.3.6. Cardiovascular and Death Events.....	139
8.3.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs.....	139
8.3.8. Adverse Events of Special Interest	140
8.3.8.1. Lack of Efficacy	140
8.3.9. Medical Device Deficiencies	140
8.3.10. Medication Errors	140
8.4. Treatment of Overdose.....	141

8.5. Pharmacokinetics	141
8.5.1. Pharmacokinetics for Participants in Mainland China	144
8.6. Pharmacodynamics.....	146
8.7. Genetics	146
8.7.1. Specified Genetics	146
8.7.2. <i>BRAF</i> Testing.....	146
8.7.3. Molecular Prescreening	148
8.7.4. Screening	149
8.7.5. Companion Diagnostic for Eligibility	149
8.7.6. Companion Diagnostic Assay Development	149
8.7.7. Banked Biospecimens for Genetics	150
8.8. Biomarkers	150
8.8.1. CRP and CEA assessments.....	151
8.8.2. Tumor Tissue Assessments.....	151
8.8.3. Circulating Free DNA (cfDNA)	152
8.8.4. Specified Gene Expression (RNA) Research	152
8.8.5. Specified Protein Research	152
8.8.6. Specified Metabolomic Research	153
8.9. Immunogenicity Assessments	153
8.10. Health Economics	153
9. STATISTICAL CONSIDERATIONS	153
9.1. Estimands and Statistical Hypotheses	153
9.1.1. Estimands.....	153
9.1.2. Statistical Hypotheses	156
9.2. Sample Size Determination.....	157
9.3. Analysis Sets	160
9.4. Statistical Analyses	161
9.4.1. General Considerations.....	161
9.4.1.1. Statistical Testing Strategy	161
9.4.1.2. Pooling of Centers	162
9.4.1.3. Stratification Factors	163

9.4.1.4. Definition of Baseline	163
9.4.1.5. Definition of On-treatment Period	163
9.4.2. Primary Endpoints	163
9.4.3. Secondary Endpoints	166
9.4.3.1. PFS Arm A versus Arm C, Arm A versus Arm B, and Cohort 3	166
9.4.3.2. OS	166
9.4.3.3. Objective Response Rate	167
9.4.3.4. Duration of Response	167
9.4.3.5. Time to Response	168
9.4.3.6. PFS (SLI)	168
9.4.3.7. PFS2	168
9.4.3.8. Patient Reported Outcomes	169
9.4.3.9. Pharmacokinetic Analyses	169
9.4.3.10. Exposure-Response of Encorafenib	169
9.4.3.11. Biomarker Analyses	169
9.4.4. Tertiary/Exploratory Endpoints	170
9.4.5. Safety Analyses	170
9.4.5.1. Adverse Events	170
9.4.5.2. Clinical Laboratory Results	170
9.4.5.3. Electrocardiogram Analyses	170
9.4.6. Other Analyses	171
9.4.6.1. Subgroup Analyses	171
9.5. Interim Analyses	171
9.5.1. Interim Efficacy Analysis for OS (Phase 3)	171
9.6. Data Monitoring Committee or Other Independent Oversight Committee	172
10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS	173
10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations	173
10.1.1. Regulatory and Ethical Considerations	173
10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP	173

10.1.2. Financial Disclosure	174
10.1.3. Informed Consent/Assent Process	174
10.1.3.1. Adult Participants	174
10.1.3.2. Pediatric Participants	175
10.1.4. Data Protection	177
10.1.5. Dissemination of Clinical Study Data	178
10.1.6. Data Quality Assurance	179
10.1.7. Source Documents	180
10.1.8. Study and Site Start and Closure	180
10.1.9. Publication Policy	181
10.1.10. Sponsor's Qualified Medical Personnel	182
10.2. Appendix 2: Clinical Laboratory Tests	183
10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	185
10.3.1. Definition of AE	185
10.3.2. Definition of SAE	186
10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs.....	188
10.3.4. Reporting of SAEs	191
10.4. Appendix 4: Contraceptive Guidance	192
10.4.1. Male Participant Reproductive Inclusion Criteria	192
10.4.2. Female Participant Reproductive Inclusion Criteria.....	192
10.4.3. Woman of Childbearing Potential	193
10.4.4. Contraception Methods.....	194
10.5. Appendix 5: Genetics	196
10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments	197
10.7. Appendix 7: ECG Findings of Potential Clinical Concern	199
10.8. Appendix 8: Country-Specific Requirements	201
10.8.1. France Contract Unique	201
10.8.2. Mainland China Specific Procedures.....	201
10.9. Appendix 9: RECIST 1.1	202
10.10. Appendix 10: Patient Global Impression of Severity and Patient Global Impression of Change.....	206

10.11. Appendix 11: Abbreviations207

10.12. Appendix 12: Alternative Measures During Public Emergencies.....213

 10.12.1. Eligibility213

 10.12.2. Telehealth Visits213

 10.12.3. Alternative Facilities for Safety Assessments213

 10.12.3.1. Laboratory Testing213

 10.12.3.2. Imaging.....214

 10.12.3.3. Electrocardiograms.....214

 10.12.4. Study Intervention214

 10.12.5. Home Health Visits.....215

 10.12.6. Adverse Events and Serious Adverse Events215

 10.12.7. Efficacy Assessments215

 10.12.8. Independent Oversight Committees215

10.13. Appendix 13: Protocol Amendment History.....216

REFERENCES236

LIST OF TABLES

Table 1.	Schedule of Activities (Molecular Prescreening and Screening)	22
Table 2.	Schedule of Activities (Safety Lead-in)	25
Table 3.	Schedule of Activities (Phase 3 Arm A and Arm B; Cohort 3 Arm D)	34
Table 4.	Schedule of Activities (Phase 3 Control Arm [Arm C]: mFOLFOX6 or FOLFOXIRI ± Bevacizumab; Cohort 3 Arm E: FOLFIRI ±Bevacizumab)	44
Table 5.	Schedule of Activities (Control Arm [Arm C]: CAPOX ± Bevacizumab)	51
Table 6.	Efficacy of Standard of Care First-Line Therapies in Patients with <i>BRAF</i> -mutant mCRC	59
Table 7.	Study ARRAY-818-302 (EC Arm and Control Arm): Efficacy Results.....	61
Table 8.	Study ARRAY-818-302 (EC Arm and Control Arm): Adverse Events Regardless of Causality Reported in ≥15% of EC Patients	61
Table 9.	DLT Criteria	90
Table 10.	Treatment Regimens (Safety Lead-in).....	92
Table 11.	Treatment Regimen (Phase 3, Arm A)	92
Table 12.	Treatment Regimens (Phase 3, Arm B)	93
Table 13.	Treatment Regimens (Phase 3, Control Arm [Arm C]).....	94
Table 14.	Treatment Regimens: Cohort 3 (Arm D).....	95
Table 15.	Treatment Regimens: Cohort 3 (Arm E)	95
Table 16.	Recommended Encorafenib Dose Reductions.....	105
Table 17.	Recommended Encorafenib Dose Modifications	106
Table 18.	Recommended Cetuximab Dose Reductions.....	109
Table 19.	Recommended Dose Modifications for Cetuximab related Adverse Events	109
Table 20.	Recommended Dose Reductions for Oxaliplatin, Irinotecan and 5-FU as Part of mFOLFOX6 (SLI participants, Phase 3 Arm B and Arm C [Control]), and FOLFIRI (in SLI and Cohort 3 Arm D and Arm E).....	111
Table 21.	Recommended Dose Reductions for Oxaliplatin, Irinotecan and 5-FU as Part of FOLFOXIRI (Phase 3 Arm C [Control Arm])	112

Table 22.	Recommended Dose Reductions for Oxaliplatin and Capecitabine as Part of CAPOX (Phase 3 Control Arm)	112
Table 23.	Recommended Oxaliplatin, Irinotecan and 5-FU Dose Modifications	112
Table 24.	Recommended Capecitabine Dose Modifications	117
Table 25.	Recommended Bevacizumab Dose Modifications	118
Table 26.	Eastern Cooperative Oncology Group (ECOG) Performance Status Scale	134
Table 27.	PK Sampling Schedule for Cohort 1 (EC + FOLFIRI) in SLI	142
Table 28.	PK Sampling Schedule for Cohort 2 (EC + mFOLFOX6) in SLI	143
Table 29.	PK Sampling Schedule for Phase 3 Arm A and Arm B and Cohort 3 Arm D	143
Table 30.	PK Sampling Schedule for the First 16 Participants Enrolled in Phase 3 Arm A in Mainland China	145
Table 31.	PK Sampling Schedule for Participants Enrolled in Phase 3 Arm A and Arm B, and Cohort 3 Arm D (Who Will Not Undergo Intensive PK Sampling) in Mainland China	146
Table 32.	PFS Outcome and Event Dates – Primary Analysis	155
Table 33.	Characteristics of DLT Probability During the DLT Evaluation Period	158
Table 34.	Probability of Observing ≥ 1 Instance of Toxicity at 10% and 15% Incidence Rate	158
Table 35.	Protocol-Required Safety Laboratory Assessments	183
Table 36.	Objective Response Status at Each Assessment for Participants With Measurable Disease at Baseline	205

LIST OF FIGURES

Figure 1.	<i>BRAF</i> Testing	148
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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: An Open-label, Multicenter, Randomized Phase 3 Study of First-line Encorafenib Plus Cetuximab with or without Chemotherapy versus Standard-of-Care Therapy with a Safety Lead-in of Encorafenib and Cetuximab Plus Chemotherapy in Participants with Metastatic *BRAF* V600E-Mutant Colorectal Cancer

Brief Title: The BREAKWATER Study (*BRAF* V600E-mutant colorectal cancer study evaluating Encorafenib with or without cetuximab plus or minus chemotherapy)

Regulatory Agency Identification Number(s):

US IND Number:	115298
EudraCT / EU CT Number:	2020-001288-99 / 2023-509405-77-00
ClinicalTrials.gov ID:	NCT04607421
Pediatric Investigational Plan Number:	NA
Protocol Number:	C4221015
Phase:	3

Rationale

The purpose of the study is to evaluate whether encorafenib plus cetuximab (EC), alone or in combination with chemotherapy, can improve clinical outcomes relative to current standard-of-care (SOC) chemotherapy in participants with previously untreated *BRAF* V600E-mutant metastatic colorectal cancer (mCRC). Since encorafenib has not previously been combined with chemotherapy, the tolerability and pharmacokinetics (PK) of EC in combination with modified fluorouracil/leucovorin/oxaliplatin (mFOLFOX6) and in combination with fluorouracil/leucovorin/irinotecan (FOLFIRI) will be evaluated in separate cohorts in the Safety Lead-in (SLI) portion of the trial in order to identify which chemotherapy combination is to be used in the Phase 3 portion of the study.

After reviewing the totality of the SLI data, the external Data Monitoring Committee (E-DMC) and Steering Committee (SC) determined that there were no new safety signals and recommended that the study can proceed as planned. As a result of the SLI data review, Arm B will consist of EC in combination with mFOLFOX6. In addition, Phase 3 treatment Control Arm (Arm C) will consist of Investigator's choice of mFOLFOX6 ± bevacizumab, fluorouracil/leucovorin/oxaliplatin/irinotecan (FOLFOXIRI) ± bevacizumab or capecitabine/oxaliplatin (CAPOX) ± bevacizumab.

The SLI data continues to show a tolerable safety profile and encouraging antitumor activity of EC + mFOLFOX6 and EC + FOLFIRI in both first-line and second-line participants (Tabernero J et al, Ann Oncol. 2022;33:S808-69). Based on this, an additional primary

endpoint of objective response rate (ORR) (Arm B versus the Control Arm) was included and a cohort with 2 randomized arms was added to the study after the approval of Protocol Amendment 5: EC in combination with FOLFIRI (Arm D) and FOLFIRI with or without bevacizumab (Arm E) in first-line participants (Cohort 3).

In addition, enrollment in Arm A (EC) was discontinued after the approval of Protocol Amendment 5 because 1) antitumor activity, safety and tolerability observed with EC + mFOLFOX6 and EC + FOLFIRI in the SLI portion was encouraging (Tabernero J et al, Ann Oncol. 2022;33:S808-69); 2) the probability to demonstrate superiority for EC versus SOC chemotherapy is relatively low given the data from the ANCHOR-CRC study (NCT03693170), which showed comparable efficacy results of EC + binimetinib in comparison to historical chemotherapy (Van Cutsem E et al. Ann Oncol. 2021;32:S222); and 3) in general, *BRAF* V600E-mutant mCRC patients require a first-line regimen to control the aggressive tumor growth, supporting investigating EC + mFOLFOX6 or EC + FOLFIRI as potentially better treatment options in this patient population.

Objectives, Estimands, and Endpoints

Safety Lead-in	
Objectives	Endpoints
Primary	
<ul style="list-style-type: none"> To determine the safety and tolerability of EC + mFOLFOX6 and EC + FOLFIRI 	<ul style="list-style-type: none"> Incidence of dose-limiting toxicities (DLTs)
Secondary	
<ul style="list-style-type: none"> To assess the overall safety and tolerability of EC + mFOLFOX6 and EC + FOLFIRI 	<ul style="list-style-type: none"> Incidence and severity of adverse events (AEs) graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03 and changes in clinical laboratory parameters, vital signs and electrocardiograms (ECGs) Incidence of dose interruptions, dose modifications and discontinuations due to AEs
<ul style="list-style-type: none"> To estimate the efficacy of EC + mFOLFOX6 and EC + FOLFIRI 	<ul style="list-style-type: none"> ORR by Investigator, defined as the proportion of participants who have achieved a confirmed best overall response (BOR) (complete response [CR] or partial response [PR]) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 Duration of response (DOR) by Investigator, defined as the time from the date of first radiographic evidence of response (CR or PR) to the earliest documented disease progression per RECIST v1.1, or death due to any cause Progression-free survival (PFS) by Investigator, defined as the time from first dose to the earliest documented disease progression per RECIST v1.1, or death due to any cause Time to response (TTR) by Investigator, defined as the time from first dose to first radiographic

	evidence of response (CR or PR) per RECIST v1.1
<ul style="list-style-type: none"> To compare the efficacy of EC + mFOLFOX6 and EC + FOLFIRI 	<ul style="list-style-type: none"> Overall survival (OS) defined as the time from first dose to death due to any cause
<ul style="list-style-type: none"> To characterize the PK of encorafenib, irinotecan, oxaliplatin and relevant metabolites 	<ul style="list-style-type: none"> PK parameters of encorafenib, irinotecan, oxaliplatin and relevant metabolites
<ul style="list-style-type: none"> To assess drug-drug interaction of encorafenib with irinotecan or oxaliplatin 	<ul style="list-style-type: none"> Changes in exposures of irinotecan and its metabolite (SN-38) on Cycle 1 Day 15 compared to Cycle 1 Day 1 in Cohort 1 (EC + FOLFIRI) Changes in exposures of oxaliplatin on Cycle 1 Day 15 compared to Cycle 1 Day 1 in Cohort 2 (EC + mFOLFOX6)
Phase 3	
Objectives	Endpoints
Primary	
<ul style="list-style-type: none"> To compare the efficacy of EC + mFOLFOX6 (Arm B) vs SOC (Control Arm [Arm C]) as measured by PFS and by ORR 	<ul style="list-style-type: none"> PFS by blinded independent central review (BICR), 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 ORR by BICR
Key Secondary	
<ul style="list-style-type: none"> To further compare the efficacy of Arm B vs the Control Arm as measured by OS 	<ul style="list-style-type: none"> OS, defined as the time from the date of randomization to death due to any cause
Secondary (Descriptive Statistics Only)	
<ul style="list-style-type: none"> To further evaluate the efficacy of Arm B vs the Control Arm as measured by ORR, DOR, PFS, progression after next line of therapy (PFS2) and TTR To evaluate the efficacy of EC (Arm A) vs the Control Arm as measured by ORR, DOR, PFS, PFS2, TTR, and OS To evaluate the efficacy of Arm A vs Arm B as measured by OS, PFS, PFS2, ORR, DOR and TTR 	<ul style="list-style-type: none"> ORR by Investigator ORR by BICR (Arm A vs Control Arm, Arm A vs Arm B) DOR by BICR and by Investigator PFS by BICR (Arm A vs Control Arm, Arm A vs Arm B) OS (Arm A vs Control Arm, Arm A vs Arm B) PFS by Investigator TTR (by BICR and by Investigator), defined as the time from the date of randomization to first radiographic evidence of response (CR or PR) per RECIST v1.1 PFS2, defined as the time from the date of randomization to the date of discontinuation of next-line treatment after first objective PD by investigator assessment, the second objective disease progression, or death from any cause, whichever occurs first
<ul style="list-style-type: none"> To determine the safety and tolerability of EC To determine the safety and tolerability of EC + mFOLFOX6 	<ul style="list-style-type: none"> Incidence and severity of AEs graded according to the NCI CTCAE v4.03 and changes in clinical laboratory parameters, vital signs, and ECGs

<ul style="list-style-type: none"> To evaluate quality of life and health states, captured by patient-reported outcome (PRO) measures 	<ul style="list-style-type: none"> PRO scores as measured by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer Patients – 30 Item Core Questionnaire (EORTC QLQ-C30), EuroQol-5D-5L (EQ-5D-5L), and anchoring instruments Patient Global Impression of Severity (PGIS) and Patient Global Impression of Change (PGIC).
<ul style="list-style-type: none"> To evaluate trough concentrations of encorafenib and its metabolite LHY746 in Arm A and Arm B 	<ul style="list-style-type: none"> Trough plasma concentrations of encorafenib and the metabolite LHY746 in Arm A and Arm B
<ul style="list-style-type: none"> To characterize the PK of encorafenib and its metabolite LHY746 in participants randomized in mainland China (Arm A and Arm B) 	<ul style="list-style-type: none"> PK parameters of encorafenib and its metabolite LHY746
<ul style="list-style-type: none"> To confirm the microsatellite instability (MSI) status in tumor tissue 	<ul style="list-style-type: none"> Summarize MSI-status as determined by retrospective central testing of baseline tumor tissue
<ul style="list-style-type: none"> To determine the correlation between circulating tumor DNA (ctDNA) levels, <i>BRAF</i> V600 alterations, and clinical outcome 	<ul style="list-style-type: none"> ctDNA levels and <i>BRAF</i> V600 variant allele fraction (VAF) from ctDNA analysis of plasma samples collected at baseline and on treatment
Cohort 3	
Objectives	Endpoints
Primary	
<ul style="list-style-type: none"> To compare the efficacy of EC + FOLFIRI (Arm D) vs FOLFIRI with or without bevacizumab (Control Arm [Arm E]) as measured by ORR 	<ul style="list-style-type: none"> ORR by BICR
Key Secondary	
<ul style="list-style-type: none"> To further compare the efficacy of Arm D vs Arm E as measured by PFS 	<ul style="list-style-type: none"> PFS by BICR, 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
Secondary (Descriptive Statistics Only)	
<ul style="list-style-type: none"> To further evaluate the efficacy of Arm D vs Arm E as measured by ORR, DOR, PFS, TTR and OS 	<ul style="list-style-type: none"> ORR by Investigator DOR by BICR and by Investigator, defined as the time from the date of first radiographic evidence of response (CR or PR) to the earliest documented disease progression per RECIST v1.1, or death due to any cause PFS by Investigator, 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 OS, defined as the time from the date of randomization to death due to any cause TTR (by BICR and by Investigator), defined as the time from the date of randomization to first

	radiographic evidence of response (CR or PR) per RECIST v1.1
<ul style="list-style-type: none"> To determine the safety and tolerability of EC + FOLFIRI 	<ul style="list-style-type: none"> Incidence and severity of AEs graded according to the NCI CTCAE v4.03 and changes in clinical laboratory parameters, vital signs, and ECGs
<ul style="list-style-type: none"> To evaluate quality of life and health states, captured by PRO measures 	<ul style="list-style-type: none"> PRO scores as measured by the EORTC QLQ-C30, EQ-5D-5L, and anchoring instruments PGIS and PGIC
<ul style="list-style-type: none"> To evaluate trough concentrations of encorafenib and its metabolite LHY746 in Cohort 3 Arm D 	<ul style="list-style-type: none"> Trough plasma concentrations of encorafenib and the metabolite LHY746 in Cohort 3 Arm D
<ul style="list-style-type: none"> To confirm the MSI status in tumor tissue 	<ul style="list-style-type: none"> Summarize MSI-status as determined by retrospective central testing of baseline tumor tissue
<ul style="list-style-type: none"> To determine the correlation between ctDNA levels, <i>BRAF</i> V600 alterations, and clinical outcome 	<ul style="list-style-type: none"> ctDNA levels and <i>BRAF</i> V600 VAF from ctDNA analysis of plasma samples collected at baseline and on treatment

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 will be summarized for Cohort 1 (EC + FOLFIRI) and Cohort 2 (EC + mFOLFOX6), separately.

There are 2 primary estimands in the Phase 3 portion of the study:

- 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 intercurrent events. PFS will be compared between Arm B and the Control Arm (Arm C) using a 1-sided stratified log-rank test.
- The treatment effect of Arm B on objective response (OR) based on BICR assessment per RECIST v1.1 compared to the Control Arm from randomization to the earliest of progression of disease, start of subsequent anticancer therapy, or death due to any cause. Both CR and PR must be confirmed by repeat assessments performed no less than 4 weeks after the criteria for response are first met. ORR comparison between the 2 treatment arms will be assessed using stratified Cochran-Mantel-Haenszel (CMH) test.

The primary estimand in Cohort 3 is the treatment effect of Arm D on OR based on BICR assessment per RECIST v1.1 compared to Arm E from randomization to the earliest of progression of disease, start of subsequent anticancer therapy, or death due to any cause. Both CR and PR must be confirmed by repeat assessments performed no less than 4 weeks after the criteria for response are first met. ORR comparison between the 2 treatment arms will be assessed using stratified CMH test.

Overall Design

This is an open-label, multicenter, randomized Phase 3 study of EC with or without chemotherapy versus SOC chemotherapy in participants with previously untreated *BRAF* V600E-mutant mCRC. Prior to the Phase 3 portion, a SLI will be conducted at a limited number of sites to evaluate the safety/tolerability and PK of EC in combination with either FOLFIRI or mFOLFOX6 (Cohort 1 and Cohort 2, respectively). In addition to the Phase 3 portion, a Cohort 3 with 2 randomized arms will be included: EC in combination with FOLFIRI (Arm D) and FOLFIRI with or without bevacizumab (Arm E) in first-line participants. Cohort 3 will start after the enrollment of the Phase 3 portion is complete and enrollment will only be conducted in countries where authorized.

The primary objective in the Phase 3 portion of the study is to compare the efficacy, as measured by the primary endpoints of PFS by BICR and ORR by BICR, of Arm B versus the Control Arm. The study will be considered positive (ie, demonstrated evidence of effectiveness) if the hypothesis test of either primary endpoint is statistically significant.

The primary objective in the Cohort 3 portion of the study is to compare the efficacy, as measured by the primary endpoint of ORR by BICR of Arm D versus Arm E. The results of Cohort 3 will be considered positive (ie, demonstrated evidence of effectiveness) if the hypothesis test of primary endpoint is statistically significant.

Number of Participants

Approximately 60 participants will be enrolled in the SLI portion (up to 30 per regimen). The results of the SLI will inform which chemotherapy regimen is used in Arm B of the Phase 3 portion of the study. In the Phase 3 portion, approximately 620 participants will be randomized overall, initially at a ratio of 1:1:1 to receive EC (Arm A), EC + chemotherapy (Arm B) or SOC chemotherapy (Control Arm), and then 1:1 to receive EC + chemotherapy (Arm B) or SOC chemotherapy (Control Arm) after the approval of Protocol Amendment 5, with a total of approximately 150 participants for Arm A and 235 participants each for Arm B and the Control Arm (Arm C). Randomization will be stratified based on Eastern Cooperative Oncology Group performance status (ECOG PS) (0 versus 1) and region (United States [US]/Canada versus Europe versus Rest of World). In Cohort 3, 136 participants will be randomized overall, at a ratio of 1:1 to receive EC + FOLFIRI (Arm D, n=68) or FOLFIRI with or without bevacizumab (Arm E, n=68). Randomization will be stratified based on ECOG PS (0 versus 1).

Study Population

The study population is participants with *BRAF* V600E-mutant mCRC who have received ≤ 1 (SLI) or no (Phase 3 and Cohort 3) prior systemic regimen(s) for metastatic disease.

Key inclusion and exclusion criteria are listed below:

Inclusion Criteria

Participants must meet the following key inclusion criteria to be eligible for enrollment into the study:

- Male and female participants age ≥ 18 years (SLI) or ≥ 16 years (Phase 3 and Cohort 3, where permitted locally).
- Histologically or cytologically confirmed Stage IV colorectal adenocarcinoma with presence of a *BRAF* V600E mutation in tumor tissue or blood.
- Have received ≤ 1 (SLI) or no (Phase 3 and Cohort 3) prior systemic regimen(s) for metastatic disease (note: prior adjuvant or neoadjuvant therapy is considered to be metastatic treatment if relapse/metastasis < 6 month from end of adjuvant/neoadjuvant treatment).
- Measurable disease (Phase 3 and Cohort 3) and measurable or non-measurable but evaluable disease per RECIST, v1.1 (SLI), as assessed by Investigator and evidenced by available baseline scans.
- ECOG PS of 0 or 1.
- Adequate bone marrow, hepatic, and renal function.

Exclusion Criteria

Participants with any of the following characteristics/conditions will be excluded:

- Locally confirmed deficient mismatch repair (dMMR) or microsatellite instability-high (MSI-H) colorectal carcinoma or unknown MSI/mismatch repair (MMR) status unless participant is unable to receive immune checkpoint inhibitors due to a pre-existing medical condition.
- Evidence of active and uncontrolled bacterial or viral infection within 2 weeks prior to start of study intervention, with certain noted exceptions for chronic infection with human immunodeficiency virus (HIV), hepatitis B or hepatitis C.
- Symptomatic brain metastases.

Intervention Groups and Duration

SLI: Participants in the SLI will receive either encorafenib (300 mg once daily [QD]) + cetuximab (500 mg/m² every 2 weeks [Q2W]) + mFOLFOX6 or encorafenib (300 mg QD) + cetuximab (500 mg/m² Q2W) + FOLFIRI.

Phase 3: Participants randomized to Arm A of Phase 3 will receive encorafenib (300 mg QD) + cetuximab (500 mg/m² Q2W). Based on the results of the SLI, participants randomized to Arm B of Phase 3 will receive encorafenib (300 mg QD) + cetuximab (500 mg/m² Q2W) + mFOLFOX6. Since mFOLFOX6 is used in Arm B, the Control Arm

will consist of Investigator's choice of mFOLFOX6 ± bevacizumab, FOLFOXIRI ± bevacizumab or CAPOX ± bevacizumab.

Cohort 3: Participants in Cohort 3 will be randomized 1:1 to receive either encorafenib (300 mg QD) + cetuximab (500 mg/m² Q2W) + FOLFIRI (Arm D) or FOLFIRI with or without bevacizumab (Arm E).

Participants will receive study intervention until disease progression (confirmed by BICR in Phase 3 and Cohort 3), withdrawal of consent/assent, lost to follow-up, death or unacceptable toxicity. After discontinuation of study intervention, participants will be followed for survival, until withdrawal of consent/assent, the participant is lost to follow-up, death, or the final OS analyses.

Data Monitoring Committee or Other Independent Oversight Committee

This study will use an E-DMC to review cumulative safety data during the study conduct as well as to review the efficacy at the interim analyses according to the charter. The E-DMC is independent of the study team and includes only external members.

All imaging data acquired in the study for efficacy purposes (eg, computed tomography [CT]/magnetic resonance imaging [MRI] scans) will be transmitted to an imaging vendor for BICR review. These images will be read by readers who are blinded to treatment assignment and to other clinical data as specified in the BICR Charter.

Ethical Considerations

Potential risks of synergistic toxicities of study intervention include QT prolongation, peripheral neuropathy, and gastrointestinal toxicities. Investigators should refer to the approved local label of the products used in this trial (capecitabine, cetuximab, fluorouracil [5-FU], irinotecan, leucovorin, oxaliplatin, and bevacizumab) for the management of participants, especially concerning contraindications, duration of contraception, special warnings and precautions, posology adaptation in case of toxicity, monitoring, as well as medications that are contraindicated or that must be used with caution.

The EC regimen is approved in several countries for the treatment of patients with *BRAF* V600E-mutant mCRC that has progressed after 1 or 2 prior regimens. Based on the activity observed in previously treated patients, there is the potential for the EC regimen to be efficacious in the first-line metastatic setting in patients with *BRAF* V600E-mutant mCRC. Furthermore, based on its demonstrated activity in patients with *BRAF* V600E-mutant mCRC, there is the potential for additional benefits to patients when EC is added to chemotherapy regimens that are the current SOC.

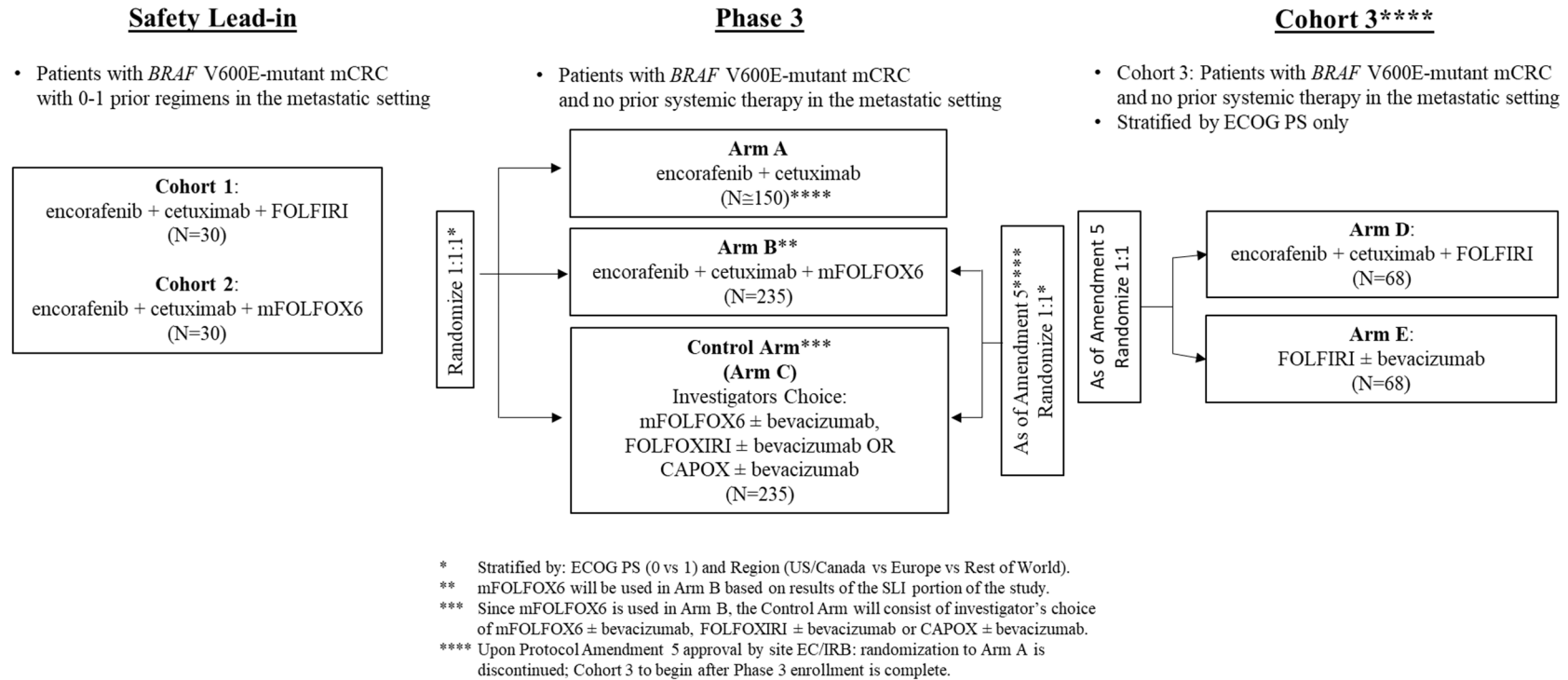
Considering the measures taken to minimize risk to study participants, the potential risks identified in association with the EC regimen with or without mFOLFOX6 or FOLFIRI, as well as the potential risks associated with study procedures and laboratory tests (eg, CT or MRI scans, *BRAF* testing), are justified by the anticipated benefits that may be afforded to participants with *BRAF* V600E-mutant mCRC.

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CT02-GSOP Oncology Clinical Protocol Template (01 May 2024)

Page 20

1.2. Schema



1.3. Schedule of Activities

The SoA table provides an overview of the protocol visits and procedures. Refer to the [STUDY ASSESSMENTS AND PROCEDURES](#) section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant.

Table 1. Schedule of Activities (Molecular Prescreening and Screening)

Evaluation/Window Abbreviations used in this table may be found in Appendix 11 .	Prescreening	Screening	Randomization	Notes/Protocol Section
	Any Time Before Screening	Day -28 to -1		
Administrative Procedures				
Informed consent/assent	X			See Section 10.1.3
Molecular Prescreening inclusion/exclusion criteria	X			See Section 5.1.1 and Section 5.2.1
Contact IRT		X	X	All participants will be registered for the study using the IRT after informed consent/assent is obtained. Phase 3 and Cohort 3 participants will be randomized via IRT upon completion of Screening. Phase 3 and Cohort 3 participants must receive their first dose of study intervention within 5 days of randomization. See Section 6.3.1
Demography	X			See Section 8.2.1
Screening inclusion/exclusion criteria		X		See Section 5.1.2 and Section 5.2.2
Medical history		X		See Section 8.2.1

Table 1. Schedule of Activities (Molecular Prescreening and Screening)

Evaluation/Window Abbreviations used in this table may be found in Appendix 11 .	Prescreening	Screening	Randomization	Notes/Protocol Section
	Any Time Before Screening	Day -28 to -1		
Prior antineoplastic therapy/concomitant medication		X		See Section 6.5
ECOG PS		X		See Section 8.2.10
Verification of eligibility criteria		X		See Section 5
Clinical Procedures/Assessments				
Tumor tissue sample for <i>BRAF</i> V600E mutation testing	X			Central laboratory test for <i>BRAF</i> V600E mutation and other molecular markers. See Section 8.7.2 and Section 8.8.2
Tumor radiographic assessment (CT, MRI)		X		Must be performed prior to enrollment for participants in the SLI and prior to randomization for participants in the Phase 3 portion and Cohort 3. May be performed up to Day -35. See Section 8.1.1
Physical exam		X		See Section 8.2.3
Height/Weight		X		See Section 8.2.3
Vital signs		X		See Section 8.2.6
Triplicate 12-lead ECG		X		See Section 8.2.7
Adverse event assessment		X		See Section 8.3 and Appendix 3
Dermatologic exam		X		See Section 8.2.5
Laboratory Assessments				
Hematology		X		See Section 8.2.8 and Table 35
Chemistry		X		See Section 8.2.8 and Table 35
Coagulation		X		See Section 8.2.8 and Table 35

Table 1. Schedule of Activities (Molecular Prescreening and Screening)

Evaluation/Window Abbreviations used in this table may be found in Appendix 11 .	Prescreening	Screening	Randomization	Notes/Protocol Section
	Any Time Before Screening	Day -28 to -1		
Full Urinalysis		X		See Section 8.2.8 and Table 35
HBV and HCV serology; HIV where mandated		X		See Section 5.2.2 and Table 35
Serum pregnancy test		X		See Section 8.2.9 and Table 35
Discussion of fertility preservation		X		See Section 5.3
FSH		X		See Section 10.4.3 and Table 35
Blood sample for CRP		X		See Section 8.8.1
Blood sample for CEA		X		See Section 8.8.1
Blood sample for <i>BRAF</i> CDx		X		Collect 20 mL of blood optimized for plasma preparation. See Section 8.7.6

Table 2. Schedule of Activities (Safety Lead-in)

Evaluation Abbreviations used in this table may be found in Appendix 11 .	Treatment Period (Each 28 Day Cycle)				Post-Treatment Period			Notes/Protocol Section
	Day 1	Day 3	Day 15	Day 17	End-of- Treatment (EOT) Visit	Follow-up Visit (28 days post last dose)	Long Term Follow-up (Every 3 months)	
Administrative Procedures								
Verify Screening inclusion/exclusion criteria	Cycle 1							Must occur prior to first dose. See Section 5.1.2 and Section 5.2.2
Verify demography; medical history from Screening to Day 1	Cycle 1							See Section 8.2.1 and Section 8.2.2
Contraceptive check	X				X	X	X	Performed monthly during long term follow-up; recommended to be followed for 9 months for females and 6 months for males following the last dose of study intervention. See Section 5.3.1
Concomitant medication/therapies	Assess continuously							See Section 6.5
ECOG PS	Cycle 1							Does not need to be repeated if performed within 72 hours prior to Cycle 1 Day 1 (ie, first day of dosing). See Section 8.2.10

Table 2. Schedule of Activities (Safety Lead-in)

Evaluation Abbreviations used in this table may be found in Appendix 11 .	Treatment Period (Each 28 Day Cycle)				Post-Treatment Period			Notes/Protocol Section
	Day 1	Day 3	Day 15	Day 17	End-of-Treatment (EOT) Visit	Follow-up Visit (28 days post last dose)	Long Term Follow-up (Every 3 months)	
Document survival status						X	X	End of Treatment is defined as when participant permanently discontinues study treatment. With the exception of Cycle 1, all visits during the treatment period, EOT visit, and follow-up visit have a \pm 3-day window. Long Term Follow-up visits have a \pm 7-day window for assessments.
Document subsequent therapies and dates of progression					Assess continuously			See Section 7.1
Dispense encorafenib (with diary)	X							Encorafenib dosing will not begin until Cycle 1 Day 3 for participants receiving FOLFIRI See Section 6.1.3.1
Cetuximab IV infusion	X		X					See Section 6.1.3.2
mFOLFOX6 or FOLFIRI	X		X					See Section 6.1.3.2

Table 2. Schedule of Activities (Safety Lead-in)

Evaluation Abbreviations used in this table may be found in Appendix 11 .	Treatment Period (Each 28 Day Cycle)				Post-Treatment Period			Notes/Protocol Section
	Day 1	Day 3	Day 15	Day 17	End-of-Treatment (EOT) Visit	Follow-up Visit (28 days post last dose)	Long Term Follow-up (Every 3 months)	
Assess study intervention compliance	X				X			End of Treatment is defined as when participant permanently discontinues study treatment. With the exception of Cycle 1, all visits during the treatment period, EOT visit, and follow-up visit have a \pm 3-day window. Long Term Follow-up visits have a \pm 7-day window for assessments.
Clinical Procedures/Assessments								
Physical exam	X				X	X		Does not need to be repeated if performed within 72 hours prior to Cycle 1 Day 1 (ie, first day of dosing). Exam to include visual assessment. See Section 8.2.3
Weight	X		X					Does not need to be repeated if performed within 72 hours prior to Cycle 1 Day 1 (ie, first day of dosing). See Section 8.2.3
BSA	X							Does not need to be repeated if performed within 72 hours prior to Cycle 1 Day 1 (ie, first day of dosing). See Section 8.2.4
Vital signs	X		X		X	X		See Section 8.2.6

Table 2. Schedule of Activities (Safety Lead-in)

Evaluation Abbreviations used in this table may be found in Appendix 11 .	Treatment Period (Each 28 Day Cycle)				Post-Treatment Period			Notes/Protocol Section
	Day 1	Day 3	Day 15	Day 17	End-of-Treatment (EOT) Visit	Follow-up Visit (28 days post last dose)	Long Term Follow-up (Every 3 months)	
Triplicate 12-lead ECG	Cycle 1							Predose only. See Section 8.2.7
Single 12-lead ECG	Cycles 2+				X	X		Predose only. Perform continuous ECGs if QTc abnormality. See Section 8.2.7
Tumor radiographic assessment (CT, MRI)	The first post-baseline scan must be performed 42 to 49 days from the date of first dose then Q6W (\pm 7D) for the first 18 months after the date of first dose then Q8W (\pm 7D) thereafter or until confirmed PD, withdrawal of consent/assent, initiation of subsequent anticancer therapy, participant is lost to follow-up, death, or the final OS analysis.							See Section 8.1.1

Table 2. Schedule of Activities (Safety Lead-in)

Evaluation Abbreviations used in this table may be found in Appendix 11 .	Treatment Period (Each 28 Day Cycle)				Post-Treatment Period			Notes/Protocol Section
	Day 1	Day 3	Day 15	Day 17	End-of-Treatment (EOT) Visit	Follow-up Visit (28 days post last dose)	Long Term Follow-up (Every 3 months)	
Dermatologic exam	X (Cycles 1, 3, 5...)				X	X	X ^a	<p>End of Treatment is defined as when participant permanently discontinues study treatment.</p> <p>With the exception of Cycle 1, all visits during the treatment period, EOT visit, and follow-up visit have a \pm 3-day window.</p> <p>Long Term Follow-up visits have a \pm 7-day window for assessments.</p> <p>Performed every 8 weeks from Cycle 1 Day 1 (ie, on Day 1 of Cycles 3, 5, 7...).</p> <p>a. Following the 28-day follow-up, it is recommended participants be monitored with dermatological examinations for cutaneous secondary malignancies approximately every 2 months for up to 6 months after the last encorafenib dose or until initiation of another antineoplastic therapy. Clinically significant findings that are considered related to study intervention should be reported as SAEs.</p> <p>See Section 8.2.5</p>
Adverse event assessment	Assess continuously							See Section 8.3 and Appendix 3

Table 2. Schedule of Activities (Safety Lead-in)

Evaluation Abbreviations used in this table may be found in Appendix 11 .	Treatment Period (Each 28 Day Cycle)				Post-Treatment Period			Notes/Protocol Section
	Day 1	Day 3	Day 15	Day 17	End-of-Treatment (EOT) Visit	Follow-up Visit (28 days post last dose)	Long Term Follow-up (Every 3 months)	
Laboratory Assessments								
Hematology	X		X		X	X		Does not need to be repeated if performed within 72 hours prior to Cycle 1 Day 1 (ie, first day of dosing). See Section 8.2.8 and Table 35
Chemistry	X		X		X	X		Does not need to be repeated if performed within 72 hours prior to Cycle 1 Day 1 (ie, first day of dosing). See Section 8.2.8 and Table 35
Coagulation	X		X		X	X		Does not need to be repeated if performed within 72 hours prior to Cycle 1 Day 1 (ie, first day of dosing). See Section 8.2.8 and Table 35
Urinalysis	X				X	X		Does not need to be repeated if performed within 72 hours prior to Cycle 1 Day 1 (ie, first day of dosing). Full urinalysis on Cycle 1 Day 1, only urine protein thereafter. See Section 8.2.8 and Table 35

Table 2. Schedule of Activities (Safety Lead-in)

Evaluation Abbreviations used in this table may be found in Appendix 11 .	Treatment Period (Each 28 Day Cycle)				Post-Treatment Period			Notes/Protocol Section
	Day 1	Day 3	Day 15	Day 17	End-of-Treatment (EOT) Visit	Follow-up Visit (28 days post last dose)	Long Term Follow-up (Every 3 months)	
Urine pregnancy test	X				X	X		End of Treatment is defined as when participant permanently discontinues study treatment. With the exception of Cycle 1, all visits during the treatment period, EOT visit, and follow-up visit have a \pm 3-day window. Long Term Follow-up visits have a \pm 7-day window for assessments.
Blood sample for PK	Cycles 1-6	Cycle 1	Cycle 1	Cycle 1				PK sampling must occur on the Day of dosing in the clinic (ie, no 3 day window). Days 1 and 15 of Cycle 1 of Cohort 1 (EC + FOLFIRI): predose, 0.75, 1.5, 2.5, 3.5, 5.5 and 7.5 h post-dosing Days 1 and 15 of Cycle 1 of Cohort 2 (EC + mFOLFOX6): predose, 1, 2, 3, 4, 6 and 8 h post-dosing All other timepoints: Predose only See Section 8.5
Blood sample for CRP	X				X			See Section 8.8.1
Blood sample for CEA	X				X			See Section 8.8.1

Table 2. Schedule of Activities (Safety Lead-in)

Evaluation Abbreviations used in this table may be found in Appendix 11 .	Treatment Period (Each 28 Day Cycle)				Post-Treatment Period			Notes/Protocol Section
	Day 1	Day 3	Day 15	Day 17	End-of-Treatment (EOT) Visit	Follow-up Visit (28 days post last dose)	Long Term Follow-up (Every 3 months)	
Blood sample for cfDNA	Cycles 1,7		Cycles 1, 2		X			End of Treatment is defined as when participant permanently discontinues study treatment. With the exception of Cycle 1, all visits during the treatment period, EOT visit, and follow-up visit have a \pm 3-day window. Long Term Follow-up visits have a \pm 7-day window for assessments.
Blood sample for protein biomarkers	Cycles 1, 2		Cycles 1, 2		X			Collect 20 mL of blood optimized for plasma preparation at indicated visits (all pre-dose). See Section 8.8.3
Blood sample for germline comparator	Cycle 1							Collect 10 mL of whole blood for processing into serum at indicated visits (all pre-dose). See Section 8.8.5
								Collect a 4 mL blood biospecimen prior to first dose of study intervention. See Section 8.8.2

Table 2. Schedule of Activities (Safety Lead-in)

Evaluation Abbreviations used in this table may be found in Appendix 11 .	Treatment Period (Each 28 Day Cycle)				Post-Treatment Period			Notes/Protocol Section
	Day 1	Day 3	Day 15	Day 17	End-of-Treatment (EOT) Visit	Follow-up Visit (28 days post last dose)	Long Term Follow-up (Every 3 months)	
Blood sample for banked biospecimen	Cycle 1							<p>End of Treatment is defined as when participant permanently discontinues study treatment.</p> <p>With the exception of Cycle 1, all visits during the treatment period, EOT visit, and follow-up visit have a \pm 3-day window.</p> <p>Long Term Follow-up visits have a \pm 7-day window for assessments.</p>
FFPE Tumor Tissue					X (optional)			<p>Unless prohibited by local regulations or ethics committee decision, collect a blood sample (4 mL) optimized for genomic analysis before the first dose of study intervention.</p> <p>If not collected on the designated collection day, collect at the next available time point when biospecimens are being collected in conjunction with a participant visit.</p> <p>See Section 8.7.7</p>
								See Section 8.8.2 and Section 8.8.4

Table 3. Schedule of Activities (Phase 3 Arm A and Arm B; Cohort 3 Arm D)

Evaluation Abbreviations used in this table may be found in Appendix 11 .	Treatment Period (Each 28 Day Cycle)		Post-Treatment Period			Notes/Protocol Section
	Day 1	Day 15	End-of-Treatment (EOT) Visit	Follow-up Visit (28 days post last dose)	Long Term Follow-up (Every 3 months)	
						<p>End of Treatment is defined as when participant permanently discontinues all study treatment.</p> <p>Cycle 1 Day 1 assessments, unless otherwise specified, do not need to be repeated if performed within 72 hours prior to initial treatment (ie, first day of dosing).</p> <p>All remaining visits during the treatment period, EOT visit, and follow-up visit have a \pm 3-day window.</p> <p>Long Term-Follow-up visits have \pm7-day window for assessments.</p>
Administrative Procedures						
Verify Screening inclusion/exclusion criteria	Cycle 1					Must occur prior to first dose. See Section 5.1.2 and Section 5.2.2
Verify demography; medical history from Screening to Day 1	Cycle 1					See Section 8.2.1 and Section 8.2.2
Contraceptive check	X		X	X	X	Performed monthly during long term follow-up; recommended to be followed for 9 months for females and 6 months for males following the last dose of study intervention. See Section 5.3.1

Table 3. Schedule of Activities (Phase 3 Arm A and Arm B; Cohort 3 Arm D)

Evaluation Abbreviations used in this table may be found in Appendix 11 .	Treatment Period (Each 28 Day Cycle)		Post-Treatment Period			Notes/Protocol Section
	Day 1	Day 15	End-of-Treatment (EOT) Visit	Follow-up Visit (28 days post last dose)	Long Term Follow-up (Every 3 months)	
						<p>End of Treatment is defined as when participant permanently discontinues all study treatment.</p> <p>Cycle 1 Day 1 assessments, unless otherwise specified, do not need to be repeated if performed within 72 hours prior to initial treatment (ie, first day of dosing).</p> <p>All remaining visits during the treatment period, EOT visit, and follow-up visit have a \pm 3-day window.</p> <p>Long Term-Follow-up visits have \pm7-day window for assessments.</p>
Concomitant medication/therapies	Assess continuously					See Section 6.5
PGIS, PGIC, EORTC QLQ-C30, and EQ-5D-5L	Q6W for the first 18 months after the date of randomization (then Q8W thereafter or until End of Treatment)		X	X		<p>While on treatment, PRO assessments should be done with the same frequency as the tumor radiographic assessments.</p> <p>PGIC will not be performed at baseline.</p> <p>See Section 8.1.2</p>
ECOG PS	Cycle 1					See Section 8.2.10

Table 3. Schedule of Activities (Phase 3 Arm A and Arm B; Cohort 3 Arm D)

Evaluation Abbreviations used in this table may be found in Appendix 11 .	Treatment Period (Each 28 Day Cycle)		Post-Treatment Period			Notes/Protocol Section
	Day 1	Day 15	End-of-Treatment (EOT) Visit	Follow-up Visit (28 days post last dose)	Long Term Follow-up (Every 3 months)	
						<p>End of Treatment is defined as when participant permanently discontinues all study treatment.</p> <p>Cycle 1 Day 1 assessments, unless otherwise specified, do not need to be repeated if performed within 72 hours prior to initial treatment (ie, first day of dosing).</p> <p>All remaining visits during the treatment period, EOT visit, and follow-up visit have a \pm 3-day window.</p> <p>Long Term-Follow-up visits have \pm7-day window for assessments.</p>
Document survival status				X	X	<p>After discontinuation of study intervention, participants will be followed approximately every 3 months, until withdrawal of consent/assent, the participant is lost to follow-up, death, or final OS analysis.</p> <p>See Section 7.1</p>
Document subsequent therapies and dates of progression			Assess continuously			See Section 7.1
Dispense encorafenib (with diary)	X					See Section 6.1.3.1
Cetuximab IV infusion	X	X				See Section 6.1.3.2

Table 3. Schedule of Activities (Phase 3 Arm A and Arm B; Cohort 3 Arm D)

Evaluation Abbreviations used in this table may be found in Appendix 11 .	Treatment Period (Each 28 Day Cycle)		Post-Treatment Period			Notes/Protocol Section
	Day 1	Day 15	End-of-Treatment (EOT) Visit	Follow-up Visit (28 days post last dose)	Long Term Follow-up (Every 3 months)	
						End of Treatment is defined as when participant permanently discontinues all study treatment. Cycle 1 Day 1 assessments, unless otherwise specified, do not need to be repeated if performed within 72 hours prior to initial treatment (ie, first day of dosing). All remaining visits during the treatment period, EOT visit, and follow-up visit have a \pm 3-day window. Long Term-Follow-up visits have \pm 7-day window for assessments.
For Arm B Only: mFOLFOX6	X	X				See Section 6.1.3.2
For Cohort 3 Arm D Only: FOLFIRI	X	X				See Section 6.1.3.2
Assess study intervention compliance	X		X			See Section 6.4
Clinical Procedures/Assessments						
Physical exam	X		X	X		Exam to include visual assessment. See Section 8.2.3
Weight	X	X				See Section 8.2.3
Height	X					Height to be measured in participants <18 years old. See Section 8.2.3

Table 3. Schedule of Activities (Phase 3 Arm A and Arm B; Cohort 3 Arm D)

Evaluation Abbreviations used in this table may be found in Appendix 11 .	Treatment Period (Each 28 Day Cycle)		Post-Treatment Period			Notes/Protocol Section
	Day 1	Day 15	End-of-Treatment (EOT) Visit	Follow-up Visit (28 days post last dose)	Long Term Follow-up (Every 3 months)	
BSA	X					End of Treatment is defined as when participant permanently discontinues all study treatment. Cycle 1 Day 1 assessments, unless otherwise specified, do not need to be repeated if performed within 72 hours prior to initial treatment (ie, first day of dosing). All remaining visits during the treatment period, EOT visit, and follow-up visit have a \pm 3-day window. Long Term-Follow-up visits have \pm 7-day window for assessments.
Vital signs	X	X	X	X		See Section 8.2.4
Triplicate 12-lead ECG	Cycle 1					Must be conducted on Cycle 1 Day 1 (ie, no window). Predose only. See Section 8.2.7
Single 12-lead ECG	Cycles 2+		X	X		Predose only. Perform continuous ECGs if QTc abnormality. See Section 8.2.7
Tumor radiographic assessment (CT, MRI)	The first post-baseline scan must be performed 42 to 49 days from the date of randomization then Q6W (\pm 7D) for the first 18 months after the date of randomization then Q8W (\pm 7D) thereafter or until BICR-confirmed PD (regardless of new anticancer therapy), withdrawal of consent/assent, participant is lost to follow-up, death, or final OS analysis.					See Section 8.1.1

Table 3. Schedule of Activities (Phase 3 Arm A and Arm B; Cohort 3 Arm D)

Evaluation Abbreviations used in this table may be found in Appendix 11 .	Treatment Period (Each 28 Day Cycle)		Post-Treatment Period			Notes/Protocol Section
	Day 1	Day 15	End-of-Treatment (EOT) Visit	Follow-up Visit (28 days post last dose)	Long Term Follow-up (Every 3 months)	
						<p>End of Treatment is defined as when participant permanently discontinues all study treatment.</p> <p>Cycle 1 Day 1 assessments, unless otherwise specified, do not need to be repeated if performed within 72 hours prior to initial treatment (ie, first day of dosing).</p> <p>All remaining visits during the treatment period, EOT visit, and follow-up visit have a \pm 3-day window.</p> <p>Long Term-Follow-up visits have \pm7-day window for assessments.</p>
Dermatologic exam	X (Cycles 1, 3, 5...)		X	X		<p>Performed every 8 weeks from Cycle 1 Day 1 (ie, on Day 1 of Cycles 3, 5, 7...).</p> <p>Following the 28-day follow up, it is recommended participants be monitored with dermatological examinations for cutaneous secondary malignancies approximately every 2 months for up to 6 months after the last encorafenib dose or until initiation of another antineoplastic therapy. Clinically significant findings that are considered related to study intervention should be reported as SAEs.</p> <p>See Section 8.2.5</p>

Table 3. Schedule of Activities (Phase 3 Arm A and Arm B; Cohort 3 Arm D)

Evaluation Abbreviations used in this table may be found in Appendix 11 .	Treatment Period (Each 28 Day Cycle)		Post-Treatment Period			Notes/Protocol Section
	Day 1	Day 15	End-of-Treatment (EOT) Visit	Follow-up Visit (28 days post last dose)	Long Term Follow-up (Every 3 months)	<p>End of Treatment is defined as when participant permanently discontinues all study treatment.</p> <p>Cycle 1 Day 1 assessments, unless otherwise specified, do not need to be repeated if performed within 72 hours prior to initial treatment (ie, first day of dosing).</p> <p>All remaining visits during the treatment period, EOT visit, and follow-up visit have a ± 3-day window.</p> <p>Long Term-Follow-up visits have ±7-day window for assessments.</p>
Adverse event assessment	Assess continuously					See Section 8.3 and Appendix 3
Laboratory Assessments						
Hematology	X	X	X	X		See Section 8.2.8 and Table 35
Chemistry	X	X	X	X		See Section 8.2.8 and Table 35
Coagulation	X	X	X	X		See Section 8.2.8 and Table 35
Urinalysis	X		X	X		Full urinalysis on Cycle 1 Day 1, only urine protein thereafter. See Section 8.2.8 and Table 35
Urine pregnancy test	X		X	X		See Section 8.2.9 and Table 35

Table 3. Schedule of Activities (Phase 3 Arm A and Arm B; Cohort 3 Arm D)

Evaluation Abbreviations used in this table may be found in Appendix 11 .	Treatment Period (Each 28 Day Cycle)		Post-Treatment Period			Notes/Protocol Section
	Day 1	Day 15	End-of-Treatment (EOT) Visit	Follow-up Visit (28 days post last dose)	Long Term Follow-up (Every 3 months)	
						<p>End of Treatment is defined as when participant permanently discontinues all study treatment.</p> <p>Cycle 1 Day 1 assessments, unless otherwise specified, do not need to be repeated if performed within 72 hours prior to initial treatment (ie, first day of dosing).</p> <p>All remaining visits during the treatment period, EOT visit, and follow-up visit have a \pm 3-day window.</p> <p>Long Term-Follow-up visits have \pm7-day window for assessments.</p>
Blood sample for PK	Cycles 1-6					<p>With the exception of Cycle 1 Day 1, which may be performed within 72 hours prior to initial treatment, PK sampling must occur on the Day of dosing encorafenib in the clinic (ie, no 3 day window).</p> <p>Day 1: Predose See Section 8.5</p> <p>For participants in mainland China, see Section 8.5.1</p>
Blood sample for CRP	X		X			See Section 8.8.1
Blood sample for CEA	X		X			See Section 8.8.1

Table 3. Schedule of Activities (Phase 3 Arm A and Arm B; Cohort 3 Arm D)

Evaluation Abbreviations used in this table may be found in Appendix 11 .	Treatment Period (Each 28 Day Cycle)		Post-Treatment Period			Notes/Protocol Section
	Day 1	Day 15	End-of-Treatment (EOT) Visit	Follow-up Visit (28 days post last dose)	Long Term Follow-up (Every 3 months)	
Blood sample for cfDNA	Cycles 1, 7	Cycles 1, 2	X			End of Treatment is defined as when participant permanently discontinues all study treatment. Cycle 1 Day 1 assessments, unless otherwise specified, do not need to be repeated if performed within 72 hours prior to initial treatment (ie, first day of dosing). All remaining visits during the treatment period, EOT visit, and follow-up visit have a \pm 3-day window. Long Term-Follow-up visits have \pm 7-day window for assessments.
Blood sample for protein biomarkers	Cycles 1, 2	Cycles 1, 2	X			Collect 20 mL (or 10 mL for mainland China sites) of blood optimized for plasma preparation at indicated visits (all pre-dose). See Section 8.8.3
Blood sample for germline comparator	Cycle 1					Collect 10 mL (or 1 mL for mainland China sites) of whole blood for processing into serum at indicated visits (all pre-dose). See Section 8.8.5
						Collect a 4 mL blood biospecimen prior to first dose of study intervention. See Section 8.8.2

Table 3. Schedule of Activities (Phase 3 Arm A and Arm B; Cohort 3 Arm D)

Evaluation Abbreviations used in this table may be found in Appendix 11 .	Treatment Period (Each 28 Day Cycle)		Post-Treatment Period			Notes/Protocol Section
	Day 1	Day 15	End-of-Treatment (EOT) Visit	Follow-up Visit (28 days post last dose)	Long Term Follow-up (Every 3 months)	
						<p>End of Treatment is defined as when participant permanently discontinues all study treatment.</p> <p>Cycle 1 Day 1 assessments, unless otherwise specified, do not need to be repeated if performed within 72 hours prior to initial treatment (ie, first day of dosing).</p> <p>All remaining visits during the treatment period, EOT visit, and follow-up visit have a \pm 3-day window.</p> <p>Long Term-Follow-up visits have \pm7-day window for assessments.</p>
Blood sample for banked biospecimen	Cycle 1					<p>Unless prohibited by local regulations or ethics committee decision, collect a blood sample (4 mL) optimized for genomic analysis before the first dose of study intervention.</p> <p>If not collected on the designated collection day, collect at the next available time point when biospecimens are being collected in conjunction with a participant visit.</p> <p>See Section 8.7.7</p>
FFPE Tumor Tissue	X (optional)					<p>On-treatment biopsies, including surgical specimens, should be collected when available but are optional.</p> <p>See Section 8.8.2 and Section 8.8.4</p>

Table 4. Schedule of Activities (Phase 3 Control Arm [Arm C]: mFOLFOX6 or FOLFOXIRI ± Bevacizumab; Cohort 3 Arm E: FOLFIRI ± Bevacizumab)

Evaluation Abbreviations used in this table may be found in Appendix 11 .	Treatment Period (Each 28 Day Cycle)		Post-Treatment Period			Notes/Protocol Section
	Day 1	Day 15	End-of-Treatment (EOT) Visit	Follow-up Visit (28 days post last dose)	Long Term Follow-up (Every 3 months)	
						<p>End of Treatment is defined as when participant permanently discontinues all study treatment.</p> <p>Cycle 1 Day 1 assessments, unless otherwise specified, do not need to be repeated if performed within 72 hours prior to initial treatment (ie, first day of dosing).</p> <p>All remaining visits during the treatment period, EOT visit, and follow-up visit have a ± 3-day window.</p> <p>Long Term-Follow-up visits have a ±7-day window for assessments.</p>
Administrative Procedures						
Verify inclusion/exclusion criteria	Cycle 1					<p>Must occur prior to first dose.</p> <p>See Section 5.1.2 and Section 5.2.2</p>
Verify demography; medical history from Screening to Day 1	Cycle 1					See Section 8.2.1 and Section 8.2.2
Contraceptive check	X		X	X	X	<p>Performed monthly during long term follow-up; recommended to be followed for 9 months for females and 6 months for males following the last dose of study intervention.</p> <p>See Section 5.3.1</p>
Concomitant medication/therapies	Assess continuously					See Section 6.5

Table 4. Schedule of Activities (Phase 3 Control Arm [Arm C]: mFOLFOX6 or FOLFOXIRI ± Bevacizumab; Cohort 3 Arm E: FOLFIRI ± Bevacizumab)

Evaluation Abbreviations used in this table may be found in Appendix 11 .	Treatment Period (Each 28 Day Cycle)		Post-Treatment Period			Notes/Protocol Section
	Day 1	Day 15	End-of-Treatment (EOT) Visit	Follow-up Visit (28 days post last dose)	Long Term Follow-up (Every 3 months)	
PGIS, PGIC, EORTC QLQ-C30, and EQ-5D-5L	Q6W for the first 18 months after the date of randomization then Q8W thereafter or until End of Treatment		X	X		End of Treatment is defined as when participant permanently discontinues all study treatment. Cycle 1 Day 1 assessments, unless otherwise specified, do not need to be repeated if performed within 72 hours prior to initial treatment (ie, first day of dosing). All remaining visits during the treatment period, EOT visit, and follow-up visit have a ± 3-day window. Long Term-Follow-up visits have a ±7-day window for assessments.
ECOG PS	Cycle 1					While on treatment, PRO assessments should be done with the same frequency as the tumor radiographic assessments. PGIC will not be performed at baseline. See Section 8.1.2
Document survival status				X	X	After discontinuation of study intervention, participants will be followed approximately every 3 months until withdrawal of consent/assent, the participant is lost to follow-up, death, or final OS analysis. See Section 7.1
Document subsequent therapies and dates of progression			Assess continuously			See Section 7.1

Table 4. Schedule of Activities (Phase 3 Control Arm [Arm C]: mFOLFOX6 or FOLFOXIRI ± Bevacizumab; Cohort 3 Arm E: FOLFIRI ±Bevacizumab)

Evaluation Abbreviations used in this table may be found in Appendix 11 .	Treatment Period (Each 28 Day Cycle)		Post-Treatment Period			Notes/Protocol Section
	Day 1	Day 15	End-of-Treatment (EOT) Visit	Follow-up Visit (28 days post last dose)	Long Term Follow-up (Every 3 months)	
mFOLFOX6 (Arm C only), FOLFOXIRI (Arm C only), FOLFIRI (Arm E only)administration	X	X				End of Treatment is defined as when participant permanently discontinues all study treatment. Cycle 1 Day 1 assessments, unless otherwise specified, do not need to be repeated if performed within 72 hours prior to initial treatment (ie, first day of dosing). All remaining visits during the treatment period, EOT visit, and follow-up visit have a ± 3-day window. Long Term-Follow-up visits have a ±7-day window for assessments.
Bevacizumab administration (optional)	X	X				Choice of treatment regimen is at the participant/treating investigator's discretion but must be declared prior to randomization and must not be changed during the course of the participant's treatment. See Section 6.1.3.2
Assess study intervention compliance	X		X			If the investigator decides to administer bevacizumab (Zirabev™ or Avastin®), Zirabev™ must be administered where approved. Where Zirabev™ is not approved, Avastin® may be administered. The decision to use bevacizumab must be made prior to randomization. See Section 6.1.2 and Section 6.1.3.2
Clinical Procedures/Assessments						
Physical exam	X		X	X		Exam to include visual assessment. See Section 8.2.3

Table 4. Schedule of Activities (Phase 3 Control Arm [Arm C]: mFOLFOX6 or FOLFOXIRI ± Bevacizumab; Cohort 3 Arm E: FOLFIRI ± Bevacizumab)

Evaluation Abbreviations used in this table may be found in Appendix 11 .	Treatment Period (Each 28 Day Cycle)		Post-Treatment Period			Notes/Protocol Section
	Day 1	Day 15	End-of-Treatment (EOT) Visit	Follow-up Visit (28 days post last dose)	Long Term Follow-up (Every 3 months)	
						End of Treatment is defined as when participant permanently discontinues all study treatment. Cycle 1 Day 1 assessments, unless otherwise specified, do not need to be repeated if performed within 72 hours prior to initial treatment (ie, first day of dosing). All remaining visits during the treatment period, EOT visit, and follow-up visit have a ± 3-day window. Long Term-Follow-up visits have a ±7-day window for assessments.
Weight	X	X				See Section 8.2.3
Height	X					Height to be measured in participants <18 years old. See Section 8.2.3
BSA	X					See Section 8.2.4
Vital signs	X	X	X	X		See Section 8.2.6
Triplicate 12-lead ECG	Cycle 1					Must be conducted on Cycle 1 Day 1 (ie, no window). Predose only. See Section 8.2.7
Single 12-lead ECG	Cycles 2+		X	X		Predose only. Perform continuous ECGs if QTc abnormality. See Section 8.2.7
Tumor radiographic assessment (CT, MRI)	The first post-baseline scan must be performed 42 to 49 days from the date of randomization then Q6W (± 7D) for the first 18 months after the date of randomization then Q8W (± 7D) thereafter or until BICR-confirmed PD (regardless of new anticancer therapy), withdrawal of consent/assent, participant is lost to follow-up, death, or final OS analysis.					See Section 8.1.1

Table 4. Schedule of Activities (Phase 3 Control Arm [Arm C]: mFOLFOX6 or FOLFOXIRI ± Bevacizumab; Cohort 3 Arm E: FOLFIRI ± Bevacizumab)

Evaluation Abbreviations used in this table may be found in Appendix 11 .	Treatment Period (Each 28 Day Cycle)		Post-Treatment Period			Notes/Protocol Section
	Day 1	Day 15	End-of-Treatment (EOT) Visit	Follow-up Visit (28 days post last dose)	Long Term Follow-up (Every 3 months)	End of Treatment is defined as when participant permanently discontinues all study treatment. Cycle 1 Day 1 assessments, unless otherwise specified, do not need to be repeated if performed within 72 hours prior to initial treatment (ie, first day of dosing). All remaining visits during the treatment period, EOT visit, and follow-up visit have a ± 3-day window. Long Term-Follow-up visits have a ±7-day window for assessments.
Adverse event assessment	Assess continuously					See Section 8.3 and Appendix 3
Laboratory Assessments						
Hematology	X	X	X	X		See Section 8.2.8 and Table 35
Chemistry	X	X	X	X		See Section 8.2.8 and Table 35
Coagulation	X	X	X	X		See Section 8.2.8 and Table 35
Urinalysis	X		X	X		Full urinalysis on Cycle 1 Day 1, only urine protein thereafter. See Section 8.2.8 and Table 35
Urine pregnancy test	X		X	X		See Section 8.2.9 and Table 35
Blood samples for CRP	X		X			See Section 8.8.1
Blood sample for CEA	X		X			See Section 8.8.1

Table 4. Schedule of Activities (Phase 3 Control Arm [Arm C]: mFOLFOX6 or FOLFOXIRI ± Bevacizumab; Cohort 3 Arm E: FOLFIRI ± Bevacizumab)

Evaluation Abbreviations used in this table may be found in Appendix 11 .	Treatment Period (Each 28 Day Cycle)		Post-Treatment Period			Notes/Protocol Section
	Day 1	Day 15	End-of-Treatment (EOT) Visit	Follow-up Visit (28 days post last dose)	Long Term Follow-up (Every 3 months)	
Blood sample for cfDNA	Cycles 1, 7	Cycles 1, 2	X			End of Treatment is defined as when participant permanently discontinues all study treatment. Cycle 1 Day 1 assessments, unless otherwise specified, do not need to be repeated if performed within 72 hours prior to initial treatment (ie, first day of dosing). All remaining visits during the treatment period, EOT visit, and follow-up visit have a ± 3-day window. Long Term-Follow-up visits have a ±7-day window for assessments.
Blood sample for protein biomarkers	Cycles 1, 2	Cycles 1, 2	X			Collect 20 mL (or 10 mL for mainland China sites) of blood optimized for plasma preparation at indicated visits (all pre-dose). See Section 8.8.3
Blood sample for germline comparator	Cycle 1					Collect 10 mL (or 1 mL for mainland China sites) of whole blood for processing into serum at indicated visits (all pre-dose). See Section 8.8.5
Blood sample for banked biospecimen	Cycle 1					Collect a 4 mL blood biospecimen prior to first dose of study intervention. See Section 8.8.2 Unless prohibited by local regulations or ethics committee decision, collect a blood sample (4 mL) optimized for genomic analysis before the first dose of study intervention. If not collected on the designated collection day, collect at the next available time point when biospecimens are being collected in conjunction with a participant visit. See Section 8.7.7

Table 4. Schedule of Activities (Phase 3 Control Arm [Arm C]: mFOLFOX6 or FOLFOXIRI ± Bevacizumab; Cohort 3 Arm E: FOLFIRI ± Bevacizumab)

Evaluation Abbreviations used in this table may be found in Appendix 11 .	Treatment Period (Each 28 Day Cycle)		Post-Treatment Period			Notes/Protocol Section
	Day 1	Day 15	End-of-Treatment (EOT) Visit	Follow-up Visit (28 days post last dose)	Long Term Follow-up (Every 3 months)	
						End of Treatment is defined as when participant permanently discontinues all study treatment. Cycle 1 Day 1 assessments, unless otherwise specified, do not need to be repeated if performed within 72 hours prior to initial treatment (ie, first day of dosing). All remaining visits during the treatment period, EOT visit, and follow-up visit have a ± 3-day window. Long Term-Follow-up visits have a ±7-day window for assessments.
FFPE Tumor Tissue	X (optional)					On-treatment biopsies, including surgical specimens, should be collected when available but are optional. See Section 8.8.2 and Section 8.8.4

Table 5. Schedule of Activities (Control Arm [Arm C]: CAPOX ± Bevacizumab)

Evaluation/Window Abbreviations used in this table may be found in Appendix 11 .	Treatment Period (Each 21 Day Cycle)	Post-Treatment Period			Notes/Protocol Section
	Day 1	End-of- Treatment (EOT) Visit	Follow-up Visit (28 days post last dose)	Long Term Follow-up (Every 3 months)	End of Treatment is defined as when participant permanently discontinues all study treatment. Cycle 1 Day 1 assessments, unless otherwise specified, do not need to be repeated if performed within 72 hours prior to initial treatment (ie, first day of dosing). All remaining visits during the treatment period, EOT visit, and follow-up visit have a ± 3-day window. Long Term Follow-up visits have a ±7-day window for assessments.
Administrative Procedures					
Verify inclusion/ exclusion criteria	Cycle 1				Must occur prior to first dose. See Section 5.1.2 and Section 5.2.2
Verify demography; medical history from Screening to Day 1	Cycle 1				See Section 8.2.1 and Section 8.2.2
Contraceptive check	X	X	X	X	Performed monthly during long term follow-up; recommended to be followed for 9 months for females and 6 months for males following the last dose of study intervention. See Section 5.3.1
Concomitant medication/therapies	Assess continuously				See Section 6.5

Table 5. Schedule of Activities (Control Arm [Arm C]: CAPOX ± Bevacizumab)

Evaluation/Window Abbreviations used in this table may be found in Appendix 11 .	Treatment Period (Each 21 Day Cycle)	Post-Treatment Period			Notes/Protocol Section
	Day 1	End-of- Treatment (EOT) Visit	Follow-up Visit (28 days post last dose)	Long Term Follow-up (Every 3 months)	
					<p>End of Treatment is defined as when participant permanently discontinues all study treatment.</p> <p>Cycle 1 Day 1 assessments, unless otherwise specified, do not need to be repeated if performed within 72 hours prior to initial treatment (ie, first day of dosing).</p> <p>All remaining visits during the treatment period, EOT visit, and follow-up visit have a ± 3-day window.</p> <p>Long Term Follow-up visits have a ±7-day window for assessments.</p>
PGIS, PGIC, EORTC QLQ-C30, and EQ-5D-5L	Q6W for the first 18 months after the date of randomization then Q8W thereafter or until End of Treatment	X	X		<p>While on treatment, PRO assessments should be done with the same frequency as the tumor radiographic assessments.</p> <p>PGIC will not be performed at baseline.</p> <p>See Section 8.1.2</p>
ECOG PS	Cycle 1				See Section 8.2.10
Document survival status			X	X	<p>After discontinuation of study intervention, participants will be followed approximately every 3 months until withdrawal of consent/assent, the participant is lost to follow-up, death, or final OS analysis.</p> <p>See Section 7.1</p>
Document subsequent therapies and dates of progression		Assess continuously			See Section 7.1

Table 5. Schedule of Activities (Control Arm [Arm C]: CAPOX ± Bevacizumab)

Evaluation/Window Abbreviations used in this table may be found in Appendix 11 .	Treatment Period (Each 21 Day Cycle)	Post-Treatment Period			Notes/Protocol Section
	Day 1	End-of- Treatment (EOT) Visit	Follow-up Visit (28 days post last dose)	Long Term Follow-up (Every 3 months)	
					<p>End of Treatment is defined as when participant permanently discontinues all study treatment.</p> <p>Cycle 1 Day 1 assessments, unless otherwise specified, do not need to be repeated if performed within 72 hours prior to initial treatment (ie, first day of dosing).</p> <p>All remaining visits during the treatment period, EOT visit, and follow-up visit have a ± 3-day window.</p> <p>Long Term Follow-up visits have a ±7-day window for assessments.</p>
Dispense capecitabine (with diary)	X				<p>Choice of treatment regimen is at the participant/treating Investigator's discretion but must be declared prior to randomization and must not be changed during the course of the participant's treatment.</p> <p>See Section 6.1.3.2</p>
Oxaliplatin administration	X				<p>See Section 6.1.3.2</p>
Bevacizumab administration (optional)	X				<p>If the investigator decides to administer bevacizumab (Zirabev[™] or Avastin[®]), Zirabev[™] must be administered where approved. Where Zirabev[™] is not approved, Avastin[®] may be administered. The decision to use bevacizumab must be made prior to randomization.</p> <p>See Section 6.1.2 and 6.1.3.2</p>
Assess study intervention compliance	X	X			<p>See Section 6.4</p>

Table 5. Schedule of Activities (Control Arm [Arm C]: CAPOX ± Bevacizumab)

Evaluation/Window Abbreviations used in this table may be found in Appendix 11 .	Treatment Period (Each 21 Day Cycle)	Post-Treatment Period			Notes/Protocol Section
	Day 1	End-of- Treatment (EOT) Visit	Follow-up Visit (28 days post last dose)	Long Term Follow-up (Every 3 months)	End of Treatment is defined as when participant permanently discontinues all study treatment. Cycle 1 Day 1 assessments, unless otherwise specified, do not need to be repeated if performed within 72 hours prior to initial treatment (ie, first day of dosing). All remaining visits during the treatment period, EOT visit, and follow-up visit have a ± 3-day window. Long Term Follow-up visits have a ±7-day window for assessments.
Clinical Procedures/Assessments					
Physical exam	X	X	X		Exam to include visual assessment. See Section 8.2.3
Weight	X				See Section 8.2.3
Height	X				Height to be measured in participants <18 years old. See Section 8.2.3
BSA	X				See Section 8.2.4
Vital signs	X	X	X		See Section 8.2.6
Triplicate 12-lead ECG	Cycle 1				Must be conducted on Cycle 1 Day 1 (ie, no window). Predose only. See Section 8.2.7
Single 12-lead ECG	Cycles 2+	X	X		Predose only. Perform continuous ECGs if QTc abnormality. See Section 8.2.7

Table 5. Schedule of Activities (Control Arm [Arm C]: CAPOX ± Bevacizumab)

Evaluation/Window Abbreviations used in this table may be found in Appendix 11 .	Treatment Period (Each 21 Day Cycle)	Post-Treatment Period			Notes/Protocol Section
	Day 1	End-of-Treatment (EOT) Visit	Follow-up Visit (28 days post last dose)	Long Term Follow-up (Every 3 months)	End of Treatment is defined as when participant permanently discontinues all study treatment. Cycle 1 Day 1 assessments, unless otherwise specified, do not need to be repeated if performed within 72 hours prior to initial treatment (ie, first day of dosing). All remaining visits during the treatment period, EOT visit, and follow-up visit have a ± 3-day window. Long Term Follow-up visits have a ±7-day window for assessments.
Tumor radiographic assessment	The first post-baseline scan must be performed 42 to 49 days from the date of randomization then Q6W (± 7D) for the first 18 months after the date of randomization then Q8W (± 7D) thereafter or until BICR-confirmed PD (regardless of new anticancer therapy), withdrawal of consent/assent, participant is lost to follow-up, death, or final OS analysis.				See Section 8.1.1
Adverse event assessment	Assess continuously				See Section 8.3 and Appendix 3
Laboratory Assessments					
Hematology	X	X	X		See Section 8.2.8 and Table 35
Chemistry	X	X	X		See Section 8.2.8 and Table 35
Coagulation	X	X	X		See Section 8.2.8 and Table 35
Urinalysis	X	X	X		Full urinalysis on Cycle 1 Day 1, only urine protein thereafter. See Section 8.2.8 and Table 35
Urine pregnancy test	X	X	X		See Section 8.2.9 and Table 35
Blood sample for CRP	X	X			See Section 8.8.1

Table 5. Schedule of Activities (Control Arm [Arm C]: CAPOX ± Bevacizumab)

Evaluation/Window Abbreviations used in this table may be found in Appendix 11 .	Treatment Period (Each 21 Day Cycle)	Post-Treatment Period			Notes/Protocol Section
	Day 1	End-of-Treatment (EOT) Visit	Follow-up Visit (28 days post last dose)	Long Term Follow-up (Every 3 months)	
					<p>End of Treatment is defined as when participant permanently discontinues all study treatment.</p> <p>Cycle 1 Day 1 assessments, unless otherwise specified, do not need to be repeated if performed within 72 hours prior to initial treatment (ie, first day of dosing).</p> <p>All remaining visits during the treatment period, EOT visit, and follow-up visit have a \pm 3-day window.</p> <p>Long Term Follow-up visits have a \pm7-day window for assessments.</p>
Blood sample for CEA	X	X			See Section 8.8.1
Blood sample for cfDNA	Cycles 1-3, 9	X			<p>Collect 20 mL (or 10 mL for mainland China sites) of blood optimized for plasma preparation at indicated visits (all pre-dose).</p> <p>See Section 8.8.3</p>
Blood sample for protein biomarkers	Cycles 1-3	X			<p>Collect 10 mL (or 1 mL for mainland China sites) of whole blood for processing into serum at indicated visits (all pre-dose).</p> <p>See Section 8.8.5</p>
Blood sample for germline comparator	Cycle 1				<p>Collect a 4 mL blood biospecimen prior to first dose of study intervention.</p> <p>See Section 8.8.2</p>

Table 5. Schedule of Activities (Control Arm [Arm C]: CAPOX ± Bevacizumab)

Evaluation/Window Abbreviations used in this table may be found in Appendix 11 .	Treatment Period (Each 21 Day Cycle)	Post-Treatment Period			Notes/Protocol Section
	Day 1	End-of- Treatment (EOT) Visit	Follow-up Visit (28 days post last dose)	Long Term Follow-up (Every 3 months)	
					<p>End of Treatment is defined as when participant permanently discontinues all study treatment.</p> <p>Cycle 1 Day 1 assessments, unless otherwise specified, do not need to be repeated if performed within 72 hours prior to initial treatment (ie, first day of dosing).</p> <p>All remaining visits during the treatment period, EOT visit, and follow-up visit have a ± 3-day window.</p> <p>Long Term Follow-up visits have a ±7-day window for assessments.</p>
Blood sample for banked biospecimen	Cycle 1				<p>Unless prohibited by local regulations or ethics committee decision, collect a blood sample (4 mL) optimized for genomic analysis before the first dose of study intervention.</p> <p>If not collected on the designated collection day, collect at the next available time point when biospecimens are being collected in conjunction with a participant visit.</p> <p>See Section 8.7.7</p>
FFPE tumor tissue	X (optional)				<p>On-treatment biopsies, including surgical specimens, should be collected when available but are optional.</p> <p>See Section 8.8.2 and Section 8.8.4</p>

2. INTRODUCTION

Encorafenib (BRAFTOVI®, also known as PF-07263896, LGX818 or ONO-7702) is being investigated in this study in combination with cetuximab with or without mFOLFOX6 or FOLFIRI in participants with previously untreated metastatic *BRAF* V600E-mutant CRC.

2.1. Study Rationale

The purpose of the study is to evaluate whether encorafenib plus cetuximab (EC), alone or in combination with chemotherapy, can improve clinical outcomes relative to current standard-of-care chemotherapy in participants with previously untreated *BRAF* V600E-mutant mCRC. Since encorafenib has not previously been combined with chemotherapy, the tolerability and PK of EC in combination with mFOLFOX6 and in combination with FOLFIRI will be evaluated in separate cohorts in the safety lead-in portion of the trial in order to identify which chemotherapy combination is to be used in the Phase 3 portion of the study.

2.2. Background

2.2.1. *BRAF* V600E-Mutant Metastatic Colorectal Cancer

Metastatic colorectal cancer continues to be a life-threatening condition. Globally, colorectal cancer is the third most commonly diagnosed cancer in males and the second in females, with 1.8 million new cases and almost 861,000 deaths in 2018 according to the WHO.¹ In the US, according to the SEER database, the estimated number of new CRC cases for 2019 was 145,600 resulting in an estimated 51,000 deaths.² In Japan, CRC is the second most common cancer in women with over 150,000 new cases in 2017; there were over 50,000 deaths due to CRC and it was the leading cause of cancer death in women and third most common cause of cancer death in men in 2018.³ In the WHO European Region, CRC is the most common tumor type, with 471,000 new cases each year and a mean mortality rate of 28.2 per 100,000 population.⁴ Approximately 25% of patients present with metastases and 50% of patients eventually develop metastatic disease.⁵

BRAF mutations occur in approximately 10% to 15% of CRC, with a broad range of estimates ranging from as low as 5% to as high as 21%. These mutations primarily (>95%) occur at the V600E codon (consisting of a valine to glutamic acid substitution), are essentially mutually exclusive with *RAS* mutations,⁶⁻¹¹ and lead to constitutive activation of *BRAF* kinase and sustained RAS/RAF/MEK/ERK pathway signaling, resulting in increased cell proliferation and survival.¹²

BRAF mutations are associated with a poor prognosis.¹³⁻¹⁷ Retrospective analyses of Phase 3 studies using standard regimens revealed patients with *BRAF*-mutant mCRC achieved mPFS of approximately 7 months and mOS of approximately 12 months compared to approximately 10 months PFS and 25 months OS in patients with *BRAF*-wt tumors.^{16,18-23}

Previous studies have demonstrated an association between the presence of MSI-H or dMMR and presence of *BRAF* mutations in CRC tumors. Approximately 15-30% of *BRAF*-mutant mCRC tumors were also identified as MSI-H/dMMR.^{14,16,24,25} Immune checkpoint inhibitors

have been shown to be active in patients with previously treated MSI-H/dMMR mCRC^{25,26} and more recently in previously untreated patients with mCRC as well.²⁷

2.2.2. Clinical Overview

2.2.2.1. Current Recommendations for Treatment of *BRAF* V600E-mutant mCRC

Currently, no treatments are indicated specifically for patients with *BRAF* V600E-mutant mCRC in the first-line setting and thus patients receive systemic therapy that is recommended for mCRC in general. The common regimens used in patients with mCRC include mFOLFOX6 (oxaliplatin, leucovorin and fluorouracil [5-FU]), FOLFIRI (irinotecan, leucovorin and 5-FU), FOLFOXIRI (irinotecan, oxaliplatin, leucovorin and 5-FU) and CAPOX (oxaliplatin and capecitabine) each with or without bevacizumab.²⁸ Retrospective subgroup analyses of Phase 2 and 3 studies in previously untreated patients with mCRC patients have shown that all of the standard regimens have similar efficacy in patients with *BRAF*-mutant tumors (Table 6).

Table 6. Efficacy of Standard of Care First-Line Therapies in Patients with *BRAF*-mutant mCRC

Regimen	<i>BRAF</i> -mutant n (%)	Median PFS (Months)	Median OS (Months)
FOLFOX4 ²²	25 (12.5)	3.8	NR
FOLFOX4 + cetuximab ²²	27 (14.0)	2.0	NR
FOLFIRI + bevacizumab ¹⁹	12 (4.7)	5.5	10.7
FOLFOXIRI + bevacizumab ¹⁹	16 (6.3)	7.5	19.0
FOLFIRI or FOLFOX-4 (pooled) ¹⁸	38 (8.5)	3.7	9.9
FOLFIRI or FOLFOX-4 (pooled) + cetuximab ¹⁸	32 (8.0)	7.1	14.1
FOLFIRI + cetuximab ²³	23 (7.7)	6.6	12.3
FOLFIRI + bevacizumab ²³	25 (8.5)	6.6	13.7
<u>CAIRO</u> : capecitabine + irinotecan + oxaliplatin (sequential vs combination) ¹⁶ <u>CAIRO2</u> : capecitabine + oxaliplatin + bevacizumab ± cetuximab ¹⁶ <u>COIN</u> : capecitabine (or 5-FU + leucovorin) + oxaliplatin ± cetuximab ¹⁶ <u>FOCUS</u> : 5-FU + leucovorin + irinotecan vs 5-FU + leucovorin ± irinotecan + oxaliplatin ¹⁶	250 (8.2)	6.2	11.4
CAPOX + bevacizumab in induction + capecitabine + bevacizumab ²¹	30 (5.4)	9.5	15.8

The use of anti-EGFR antibodies such as cetuximab in patients with *BRAF*-mutant mCRC is currently a topic of debate, two meta-analyses of patients with mCRC treated in the 1st-line,

2nd-line, or refractory settings, have shown no benefit for the addition of anti-EGFR antibodies to standard therapy or best supportive care.^{29,30} In previously treated patients data suggest that mutated BRAF is a marker of resistance to anti-EGFR therapy.³¹⁻³³ In the 1st line mCRC setting, unplanned retrospective subset analyses have demonstrated contradictory findings of the effects of adding anti-EGFR antibodies to chemotherapy with some studies showing slight numerical but not statistically significant improvements in OS as discussed above, while others showing either no benefit or even detrimental effects.^{20,34}

ESMO guidelines suggest that there is accumulating data that patients with *BRAF* mutant tumors do not benefit from anti-EGFR antibodies alone or in combination with cytotoxic chemotherapy and the NCCN guidelines state that responses are highly unlikely in patients with *BRAF* V600E-mutant mCRC treated with cetuximab as a single agent or in combination with cytotoxic chemotherapy unless administered concomitantly with a BRAF inhibitor.^{28,35} The addition of anti-EGFR antibodies as part of 1st line therapy is only recommended in patients with *KRAS/NRAS/BRAF* wt and left-sided tumors.^{18,28}

2.2.2.2. Encorafenib + Cetuximab for the Treatment of *BRAF* V600E-mutant mCRC

Encorafenib is a highly selective ATP-competitive small-molecule RAF kinase inhibitor, with the greatest sensitivity observed in melanoma and CRC tumor cell lineages expressing *BRAF* V600E.³⁶ Encorafenib in combination with binimetinib (a potent and selective allosteric, ATP-uncompetitive inhibitor of MEK1/2) has received marketing approval in several jurisdictions for the treatment of patients with unresectable or metastatic melanoma with a *BRAF* V600E or V600K mutation.

Study ARRAY-818-302 (BEACON CRC; NCT02928224) is a Phase 3 trial in patients with *BRAF* V600E-mutant mCRC whose disease had progressed following 1 or 2 prior systemic therapies. Patients in the study were randomized 1:1:1 to receive either EC, EC + binimetinib, or Control (irinotecan + cetuximab or FOLFIRI + cetuximab). The dosage of encorafenib in all patients was 300 mg QD PO. The dosage of cetuximab in all patients was 400 mg/m² IV for the first dose followed by 250 mg/m² IV weekly.

In April 2020, based on the results of the Study ARRAY-818-302, the EC regimen received marketing approval in the US for the treatment of adult patients with mCRC with a *BRAF* V600E mutation, as detected by an FDA-approved test, after prior therapy.³⁷ In June 2020, the EC regimen received approval from the European Commission for the same indication.

Efficacy

A total of 220 patients were randomized to the EC arm and 221 to the Control Arm. The EC regimen demonstrated statistically significant improvement in OS, ORR, and PFS compared to the Control Arm as shown in Table 7. The addition of binimetinib to EC did not improve efficacy (ORR, PFS, or OS) significantly compared with EC.³⁸

Table 7. Study ARRAY-818-302 (EC Arm and Control Arm): Efficacy Results

	EC N = 220	Irinotecan + Cetuximab or FOLFIRI + Cetuximab N = 221
Overall Survival		
Median OS, months (95% CI)	8.4 (7.5, 11.0)	5.4 (4.8, 6.6)
HR (95% CI)	0.60 (0.45, 0.79)	
p-value	<0.001	
Overall Response Rate (per BICR)		
ORR (95% CI)	20% (13%, 29%)	2% (0%, 7%)
CR	5%	0%
PR	15%	2%
Progression Free Survival (per BICR)		
Median PFS, months (95% CI)	4.2 (3.7, 5.4)	1.5 (1.5, 1.7)
HR (95% CI)	0.40 (0.31, 0.52)	
P-value	<0.001	

Safety

In study ARRAY-818-302, the safety of the EC regimen was evaluated in 216 patients. The most common adverse events in the EC treated patients were gastrointestinal-related and skin-related events, including nausea, diarrhea, and acneiform dermatitis (Table 8). Most of these toxicities were generally reversible and manageable by supportive medical care, dose modifications or discontinuations. Other important adverse events occurring in <15% of patients in the EC arm were melanocytic nevi (14%), and myalgia (13%).³⁸

Table 8. Study ARRAY-818-302 (EC Arm and Control Arm): Adverse Events Regardless of Causality Reported in ≥15% of EC Patients

	EC (N = 216)		Irinotecan + Cetuximab or FOLFIRI + Cetuximab (N = 193)	
	Any Grade n (%)	Grade ≥3 n (%)	Any Grade n (%)	Grade ≥3 n (%)
Any adverse event	212 (98)	108 (50)	188 (97)	117 (61)
Nausea	74 (34)	1 (<1)	80 (41)	2 (1)
Diarrhea	72 (33)	4 (2)	93 (48)	19 (10)
Fatigue	65 (30)	9 (4)	53 (27)	8 (4)
Acneiform dermatitis	63 (29)	1 (<1)	76 (39)	5 (3)
Decreased appetite	58 (27)	3 (1)	52 (27)	6 (3)
Abdominal pain	49 (23)	5 (2)	48 (25)	9 (5)

Table 8. Study ARRAY-818-302 (EC Arm and Control Arm): Adverse Events Regardless of Causality Reported in ≥15% of EC Patients

	EC (N = 216)		Irinotecan + Cetuximab or FOLFIRI + Cetuximab (N = 193)	
	Any Grade n (%)	Grade ≥3 n (%)	Any Grade n (%)	Grade ≥3 n (%)
Vomiting	46 (21)	3 (1)	56 (29)	5 (3)
Asthenia	46 (21)	7 (3)	49 (25)	9 (5)
Headache	42 (19)	0 (0)	5 (3)	0 (0)
Arthralgia	41 (19)	2 (1)	1 (1)	0 (0)
Pyrexia	35 (16)	2 (1)	27 (14)	1 (1)
Constipation	33 (15)	0 (0)	35 (18)	2 (1)

The most common laboratory abnormalities (≥2%, Grade ≥3) in patients treated in the EC arm were elevated bilirubin (2%), elevated creatinine (2%), and decreased hemoglobin (4%).³⁸

2.2.2.3. Management of Cancer Patients During COVID-19 Pandemic

Patients with advanced cancers are known to be at higher risk of contracting infections including COVID-19 infection possibly due to underlying immunosuppression and/or increased co-existing medical comorbidities.³⁹ Since advanced cancer is also associated with high risk of morbidity and mortality, the decision to initiate cancer therapies should be a clinical decision based on the patient's condition and access to supportive care. Recently established ESMO guidelines recommend that anti-cancer treatments be initiated within 6 weeks of diagnosis in patients with previously untreated mCRC and especially in those with good clinical condition and for whom the treatment may reduce tumor bulk, or reduce cancer-related symptoms or complications.⁴⁰ Due to the poor prognosis of patients with *BRAF* V600E mCRC, continuation of treatment in the frame of clinical trials is also recommended.⁴⁰ In cancer patients with COVID-19, increased mortality was associated with a variety of factors such as increased age, male sex, smoking, and number of co-morbidities.⁴¹ Recent retrospective analyses have reported no association between all-cause mortality and treatment with cytotoxic chemotherapy within 28-30 days prior to COVID-19 diagnosis.^{42,43}

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of encorafenib may be found in the Investigator's Brochure, which is the SRSD for this study. The SRSDs for capecitabine and cetuximab are the respective EU SmPCs. The SRSDs for 5-FU, irinotecan, leucovorin (or levo-leucovorin which may be supplied), and oxaliplatin are the respective SmPCs (see [Section 6.1](#)). Hereafter leucovorin, folinic acid and calcium folinate are collectively referred to as leucovorin.

In the Control Arm of Phase 3, investigators may choose to administer an anti-VEGF agent. If this decision is made to use an anti-VEGF agent, Zirabev™ must be administered where approved. In regions where Zirabev™ is not approved, participants will receive Avastin®. Hereafter, Zirabev™ and Avastin® are collectively referred to as bevacizumab. The SRSD for these agents is the Avastin® EU SmPC.

Detailed information about the benefits and risks of each study intervention, when administered as a single agent, can be found in the respective SRSDs. Potential risks of synergistic toxicities are outlined in [Section 2.3.1](#). Investigators should refer to the approved local label of the products used in this trial (capecitabine, cetuximab, 5-FU, irinotecan, leucovorin, oxaliplatin, and bevacizumab) for the management of patients, especially concerning contraindications, duration of contraception, special warnings and precautions, posology adaptation in case of toxicity, monitoring, as well as medications that are contraindicated or that must be used with caution.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: Treatment Regimens		
Potential Risks of Synergistic Toxicities		
QT prolongation	<p>In the single-agent encorafenib study CLGX818X2101, an increase of 12.2 milliseconds in QTcF was predicted following 450 mg encorafenib.</p> <p>In the pooled encorafenib single-agent population, the incidence of new QTc prolongation >500 ms or change in QTc >60 ms from baseline (Grade 3/4), was 1.0% (3/301). There was 1 serious Grade 3 event of QT prolongation, which resolved after permanent discontinuation of encorafenib. There were no AEs of Torsades de pointes or ventricular arrhythmias in patients in the encorafenib single-agent pool.</p> <p>In study ARRAY-818-302, 7 (3.2%) patients in the Doublet arm (encorafenib + cetuximab) had a newly occurring QTcF > 500 ms and increases from baseline of >60 ms were observed in 19 (8.8%) patients. There were no AEs of torsades de pointes, ventricular arrhythmias, pre-syncope, syncope, sudden death or cardiac arrest reported contemporaneously with ECG QTcF prolongation > 500 ms.</p> <p>The CredibleMeds® database (https://www.crediblemeds.org/) lists oxaliplatin as having a known risk of TdP cardiac arrhythmia and 5-FU as having a potential risk of TdP. Both are listed as drugs to avoid in patients with congenital LQTS.</p>	<p>Risk for QT prolongation is appropriately described in the encorafenib IB.</p> <p>Administration with medicinal products with a known potential to prolong QT/QTc should be avoided, where possible.</p> <p>Participants at high risk of QT prolongation are excluded from the study as outlined in Section 5.2.2.</p> <p>Monitoring and dose adjustments for QT prolongation are outlined in Table 17.</p>
Peripheral Neuropathy	<p>AEs related to peripheral neuropathies may potentially be more severe and/or more frequent in patients receiving combination treatment regimens with encorafenib and oxaliplatin.</p> <p>In study ARRAY-818-302, 26 (12%) patients in the Doublet arm (encorafenib + cetuximab) had a peripheral neuropathy AE of any Grade and 3 (1.4%) patients had a Grade 3+ event. Most of the 26 AEs were PTs for sensory neuropathies. Almost all patients (95.5%) had received prior oxaliplatin. In the Phase 3 study of binimetinib + encorafenib versus vemurafenib in patients with BRAF-mutant melanoma (study CMEK162B2301), the rates of peripheral neuropathy were 12% and 13%, respectively.</p>	<p>Dose modifications for oxaliplatin in the setting of neurotoxicity are described in Table 23.</p> <p>Nervous system disorders including peripheral neuropathy are described in the IB and considered identified risks for encorafenib. Dose modification for encorafenib in the setting of peripheral neuropathy AEs are described in Table 17.</p>

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	According to the oxaliplatin SmPC, symptoms of dysaesthesia/paraesthesia occur in up to 95% of patients and are most often reversible, although about 3% of patients present with persisting paraesthesias of moderate severity up to 3 years after discontinuation of treatment. Approximately 0.5% of patients have decreased functional activities that are unresolved after discontinuation.	
Gastrointestinal Toxicities	<p>AEs related to GI toxicities may potentially be more severe and/or more frequent in patients receiving combination treatment regimens with encorafenib + cetuximab concomitantly with mFOLFOX6 or FOLFIRI.</p> <p>In ARRAY-818-302, diarrhea, nausea, and vomiting occurred in 21-34% of the patients in the Doublet arm (encorafenib + cetuximab). Seventy-two (33%) patients had diarrhea ADRs (4 patients -Grade 3+), 74 (34%) patients had nausea ADRs (1 patient - Grade 3+), and 46 (21%) had vomiting ADRs (3 Grade 3+).</p> <p>Nausea and vomiting are common ($\geq 40\%$) in patients receiving oxaliplatin. In patients treated with irinotecan in combination with 5-FU on a Q2W regimen, Grade 3-4 diarrhea occurs in approximately 14% of patients. 5-FU is also known to cause severe diarrhea requiring electrolyte replacement and antidiarrheal therapy.</p>	<p>GI toxicities including diarrhea, nausea, and vomiting are known ADRs for encorafenib in combination with cetuximab and described in the encorafenib US and EU product labels.</p> <p>Dose modifications for AEs of GI toxicity are described for the various treatment regimens in Section 6.5.3.</p>
Study Procedures		
CT or MRI procedures for tumor assessments.	<p>CT scans expose the participant to a small dose of radiation. The contrast dye used with the CT scan may cause pain or burning when injected. The dye may worsen kidney function for those with kidney disease or are dehydrated. The dye may cause an allergic reaction.</p> <p>MRI risks include possible reactions to metals due to magnets, loud noises from the machine causing hearing issues, increase in body temperature during long MRIs, and claustrophobia.</p> <p>Participants in this study will be subjected to more frequent (every 6 weeks) CT/MRI scans than is typical for mCRC patients (every 8 weeks) for the first 18 months of the study. Based on this scanning schedule, a patient would receive 3 additional scans in the 18 month period compared with the typical scanning regimen.</p>	Only experienced professionals will conduct the CT or MRI procedures. The participant will be asked about allergies to the contrast dye. Medical history will be reviewed for kidney disease, and information will be provided to minimize dehydration. If possible, an open MRI can be used for those experiencing claustrophobia. The participant may be offered earplugs and/or headphones to minimize the noise.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Other		
<i>BRAF</i> testing	Patients will be eligible for the study based on identification of a <i>BRAF</i> V600E mutation. Inaccurate <i>BRAF</i> testing (ie false positive or false negative) may lead to inappropriate enrollment to or exclusion from this study. A participant with a false negative result may be excluded from receiving potentially beneficial study intervention. Alternatively, a false positive result may lead a participant to receive study intervention, which may be inappropriate given the tumor mutation status.	In cases where there is discordance between the local assay and central laboratory results, or if the central laboratory is not able to confirm presence of a <i>BRAF</i> V600E mutation due to inadequate or poor sample condition within 30 days of initiating study therapy, participants 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. In such instances, participants must be informed that the <i>BRAF</i> mutation status is unconfirmed and must acknowledge on the ICDs that includes this information and describes alternative treatment options.
COVID-19	As discussed in Section 2.2.2.3, cancer patients are at increased risk of infections including COVID-19. In cancer patients who contract COVID-19, increased mortality has been shown to be primarily associated with increased age, male sex, and number of co-morbid medical conditions. Recent retrospective analyses have suggested that cytotoxic chemotherapy is not associated with increased mortality in patients with COVID-19.	<p>Participants with any active infection including COVID-19 are excluded from the study.</p> <p>The following is recommended for the administration of study intervention for participants who have active confirmed (positive by regulatory authority-approved test) or presumed (test pending/clinical suspicion) SARS-CoV-2 infection:</p> <ul style="list-style-type: none"> For symptomatic participants with active SARS-CoV-2 infection, study intervention should be delayed for at least 14 days from the start of symptoms. This delay is intended to allow the resolution of symptoms of SARS-CoV-2 infection.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		<ul style="list-style-type: none"> Prior to restarting treatment, the participant should be afebrile for 72 hours, and SARS-CoV-2-related symptoms should have recovered to ≤ Grade 1 for a minimum of 72 hours. Notify the study team when treatment is restarted. <p>Additional mitigation strategies are provided in Appendix 12.</p>
Adolescent participation	<p>The combination of encorafenib and cetuximab has not previously been evaluated in patients <18. Although rare, when it does occur, young-onset CRC tends to present with distant metastases more often than in older patients, have larger tumor size, and be associated with perineural or lymphovascular invasion and signet cell or mucinous histology. The standard of care treatment for young adult and adolescent patients with Stage IV CRC is the same as in older patients and consists of an oxaliplatin- or irinotecan-containing multiagent regimen combined with a biological agent.⁴⁴ The influence of pubertal changes (changes in body composition, maturation of liver metabolism, and renal function) on drug metabolism have not been shown to result in additional safety risks and the activity and maturation of the enzymes responsible for the metabolism of encorafenib are expected to be comparable to adults.⁴⁵⁻⁴⁹ Thus no relevant changes in exposure due to enzyme differences are expected in adolescents.</p> <p>The inclusion of younger patients is aligned with the recent emphasis on consideration of including adolescent patients in adult clinical trials in indications with the same basic biology and clinical outcomes for whom effective therapeutic options are lacking.^{45,46,50}</p>	<p>Monitor results of ongoing study, C4221011 (A Multicenter, Open-label Phase 1b Study of the Combination of Binimetinib and Encorafenib in Adolescent Patients with Unresectable or Metastatic <i>BRAF</i> V600-mutant Melanoma) [NCT03878719], which is evaluating encorafenib 450 mg QD in combination with binimetinib (approved adult doses for patients with <i>BRAF</i> V600-mutant melanoma) in adolescent patients (aged 12 to <18 years old) with <i>BRAF</i> V600-mutant advanced melanoma.</p>

Note: The pooled encorafenib single-agent population data set was derived from 4 clinical studies (CLGX818X2103 [Phase 1b/2], CMEK162B2301 Part 1 [Phase 3], CMEK162X2102 [Phase 2], CLGX818AUS03 [Phase 2]) with a total of 301 total patients.

2.3.2. Benefit Assessment

The EC regimen is approved in several countries for the treatment of patients with *BRAF* V600E-mutant mCRC that has progressed after 1 or 2 prior regimens (Section 2.2.2). Based on the activity observed in previously treated patients, there is the potential for the EC regimen to be efficacious in the first-line metastatic setting in patients with *BRAF* V600E-mutant mCRC. Furthermore, based on its demonstrated activity in patients with *BRAF* V600E-mutant mCRC, there is the potential for additional benefits to patients when EC is added to chemotherapy regimens that are the current SOC.

2.3.3. Overall Benefit/Risk Conclusion

Considering the measures taken to minimize risk to study participants, the potential risks identified in association with the EC regimen with or without mFOLFOX6 or FOLFIRI are justified by the anticipated benefits that may be afforded to participants with *BRAF* V600E-mutant mCRC.

The potential risks of study intervention in association with COVID-19 infection are justified by the anticipated benefits in participants with *BRAF* V600E mCRC.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

Safety Lead-in	
Objectives	Endpoints
Primary	
<ul style="list-style-type: none"> To determine the safety and tolerability of EC + mFOLFOX6 and EC + FOLFIRI 	<ul style="list-style-type: none"> Incidence of DLTs
Secondary	
<ul style="list-style-type: none"> To assess the overall safety and tolerability of EC + mFOLFOX6 and EC + FOLFIRI 	<ul style="list-style-type: none"> Incidence and severity of AEs graded according to the NCI CTCAE v4.03 and changes in clinical laboratory parameters, vital signs and ECGs Incidence of dose interruptions, dose modifications and discontinuations due to AEs
<ul style="list-style-type: none"> To estimate the efficacy of EC + mFOLFOX6 and EC + FOLFIRI 	<ul style="list-style-type: none"> ORR by Investigator, defined as the proportion of participants who have achieved a confirmed BOR (CR or PR) per RECIST v1.1 DOR by Investigator, defined as the time from the date of first radiographic evidence of response (CR or PR) to the earliest documented disease progression per RECIST v1.1, or death due to any cause PFS by Investigator, defined as the time from the first dose to the earliest documented disease progression per RECIST v1.1, or death due to any cause TTR by Investigator, defined as the time from first dose to first radiographic evidence of response (CR or PR) per RECIST v1.1

<ul style="list-style-type: none"> To estimate the efficacy of EC + mFOLFOX6 and EC + FOLFIRI 	<ul style="list-style-type: none"> OS defined as the time from the first dose to death due to any cause
<ul style="list-style-type: none"> To characterize the PK of encorafenib, irinotecan, oxaliplatin and relevant metabolites 	<ul style="list-style-type: none"> PK parameters of encorafenib, irinotecan, oxaliplatin and relevant metabolites
<ul style="list-style-type: none"> To assess drug-drug interaction of encorafenib with irinotecan or oxaliplatin 	<ul style="list-style-type: none"> Changes in exposures of irinotecan and its metabolite (SN-38) on Cycle 1 Day 15 compared to Cycle 1 Day 1 in Cohort 1 (EC + FOLFIRI) Changes in exposures of oxaliplatin on Cycle 1 Day 15 compared to Cycle 1 Day 1 in Cohort 2 (EC + mFOLFOX6)
Tertiary/Exploratory	
<ul style="list-style-type: none"> To understand the relationship between the therapeutic intervention(s) being studied and the biology of the participant's disease 	<ul style="list-style-type: none"> Measurements of biomarkers, consisting of DNA, RNA, protein or defined cell types, resulting from analyses of peripheral blood and/or tumor tissue biospecimen obtained at baseline, on treatment and/or at end-of-study
Phase 3	
Objectives	Endpoints
Primary	
<ul style="list-style-type: none"> To compare the efficacy of EC + mFOLFOX6 (Arm B) vs SOC (Control Arm [Arm C]) as measured by PFS and by ORR 	<ul style="list-style-type: none"> PFS by BICR, 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 ORR by BICR
Key Secondary	
<ul style="list-style-type: none"> To further compare the efficacy of Arm B vs the Control Arm as measured by OS 	<ul style="list-style-type: none"> OS, defined as the time from the date of randomization to death due to any cause
Secondary (Descriptive Statistics Only)	
<ul style="list-style-type: none"> To further evaluate the efficacy of Arm B vs the Control Arm as measured by ORR, DOR, PFS, PFS2 and TTR To evaluate the efficacy of EC (Arm A) vs the Control Arm as measured by ORR, DOR, PFS, PFS2, TTR, and OS To evaluate the efficacy of Arm A vs Arm B as measured by OS, PFS, PFS2, ORR, DOR and TTR 	<ul style="list-style-type: none"> ORR by Investigator ORR by BICR (Arm A vs Control Arm, Arm A vs Arm B) DOR by BICR and by Investigator PFS by BICR (Arm A vs Control Arm, Arm A vs Arm B) OS (Arm A vs Control Arm, Arm A vs Arm B) PFS by Investigator TTR (by BICR and by Investigator), defined as the time from the date of randomization to first radiographic evidence of response (CR or PR) per RECIST v1.1 PFS2, defined as the time from the date of randomization to the date of discontinuation of next-line treatment after first objective PD by investigator assessment, the second objective disease progression, or death from any cause, whichever occurs first

<ul style="list-style-type: none"> To determine the safety and tolerability of EC To determine the safety and tolerability of EC + mFOLFOX6 	<ul style="list-style-type: none"> Incidence and severity of AEs graded according to the NCI CTCAE v4.03 and changes in clinical laboratory parameters, vital signs, and ECGs
<ul style="list-style-type: none"> To evaluate quality of life and health states, captured by PRO measures 	<ul style="list-style-type: none"> PRO scores as measured by the EORTC QLQ-C30, EQ-5D-5L, and anchoring instruments PGIS and PGIC.
<ul style="list-style-type: none"> To evaluate trough concentrations of encorafenib and its metabolite LHY746 in Arm A and Arm B 	<ul style="list-style-type: none"> Trough plasma concentrations of encorafenib and the metabolite LHY746 in Arm A and Arm B
<ul style="list-style-type: none"> To characterize the PK of encorafenib and its metabolite LHY746 in participants randomized in mainland China (Arm A and Arm B) 	<ul style="list-style-type: none"> PK parameters of encorafenib and its metabolite LHY746
<ul style="list-style-type: none"> To confirm the MSI-status in tumor tissue 	<ul style="list-style-type: none"> Summarize MSI-status as determined by retrospective central testing of baseline tumor tissue
<ul style="list-style-type: none"> To determine the correlation between ctDNA levels, <i>BRAF</i> V600 alterations, and clinical outcome 	<ul style="list-style-type: none"> ctDNA levels and <i>BRAF</i> V600 VAF from ctDNA analysis of plasma samples collected at baseline and on treatment
Tertiary/Exploratory	
<ul style="list-style-type: none"> To understand the relationship between the therapeutic intervention(s) being studied and the biology of the participant's disease 	<ul style="list-style-type: none"> Measurements of biomarkers, consisting of DNA, RNA, protein or defined cell types, resulting from analyses of peripheral blood and/or tumor tissue biospecimen obtained at baseline, on treatment and/or at end-of-study
<ul style="list-style-type: none"> To understand the surgical conversion rate 	<ul style="list-style-type: none"> Surgical conversion rate, defined as the rate of participants who become eligible for surgery and undergo surgery with curative intent as a result of study intervention
Cohort 3	
Objectives	Endpoints
Primary	
<ul style="list-style-type: none"> To compare the efficacy of EC + FOLFIRI (Arm D) vs FOLFIRI with or without bevacizumab (Control Arm [Arm E]) as measured by ORR 	<ul style="list-style-type: none"> ORR by BICR
Key Secondary	
<ul style="list-style-type: none"> To further compare the efficacy of Arm D vs Arm E as measured by PFS 	<ul style="list-style-type: none"> PFS by BICR, 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
Secondary (Descriptive Statistics Only)	
<ul style="list-style-type: none"> To further evaluate the efficacy of Arm D vs Arm E as measured by ORR, DOR, PFS, TTR and OS 	<ul style="list-style-type: none"> ORR by Investigator DOR by BICR and by Investigator, defined as the time from the date of first radiographic evidence of response (CR or PR) to the earliest documented disease progression per RECIST v1.1, or death due to any cause

	<ul style="list-style-type: none"> PFS by Investigator, 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 OS, defined as the time from the date of randomization to death due to any cause TTR (by BICR and by Investigator), defined as the time from the date of randomization to first radiographic evidence of response (CR or PR) per RECIST v1.1
<ul style="list-style-type: none"> To determine the safety and tolerability of EC + FOLFIRI 	<ul style="list-style-type: none"> Incidence and severity of AEs graded according to the NCI CTCAE v4.03 and changes in clinical laboratory parameters, vital signs, and ECGs
<ul style="list-style-type: none"> To evaluate quality of life and health states, captured by PRO measures 	<ul style="list-style-type: none"> PRO scores as measured by the EORTC QLQ-C30, EQ-5D-5L, and anchoring instruments PGIS and PGIC
<ul style="list-style-type: none"> To evaluate trough concentrations of encorafenib and its metabolite LHY746 in Arm D 	<ul style="list-style-type: none"> Trough plasma concentrations of encorafenib and the metabolite LHY746 in Arm D
<ul style="list-style-type: none"> To confirm the MSI status in tumor tissue 	<ul style="list-style-type: none"> Summarize MSI-status as determined by retrospective central testing of baseline tumor tissue
<ul style="list-style-type: none"> To determine the correlation between ctDNA levels, <i>BRAF</i> V600 alterations, and clinical outcome 	<ul style="list-style-type: none"> ctDNA levels and <i>BRAF</i> V600 VAF from ctDNA analysis of plasma samples collected at baseline and on treatment
Tertiary/Exploratory	
<ul style="list-style-type: none"> To understand the relationship between the therapeutic intervention(s) being studied and the biology of the participant's disease 	<ul style="list-style-type: none"> Measurements of biomarkers, consisting of DNA, RNA, protein or defined cell types, resulting from analyses of peripheral blood and/or tumor tissue biospecimen obtained at baseline, on treatment and/or at end-of-study
<ul style="list-style-type: none"> To understand the surgical conversion rate 	<ul style="list-style-type: none"> Surgical conversion rate, defined as the rate of participants who become eligible for surgery and undergo surgery with curative intent as a result of study intervention

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 will be summarized for Cohort 1 (EC + FOLFIRI) and Cohort 2 (EC + mFOLFOX6), separately.

There are 2 primary estimands in the Phase 3 portion of the study:

- The treatment effect in PFS by BICR, as measured by the hazard ratio. PFS is defined as the time from 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 intercurrent events. PFS will be compared between Arm B and the Control Arm using a 1-sided stratified log-rank test.

- The treatment effect of Arm B on OR based on BICR assessment per RECIST v1.1 compared to the Control Arm from randomization to the earliest of progression of disease, start of subsequent anticancer therapy, or death due to any cause. Both CR and PR must be confirmed by repeat assessments performed no less than 4 weeks after the criteria for response are first met. ORR comparison between the 2 treatment arms will be assessed using stratified Cochran-Mantel-Haenszel (CMH) test.

The primary estimand in Cohort 3 is the treatment effect of Arm D on OR based on BICR assessment per RECIST v1.1 compared to the Arm E from randomization to the earliest of progression of disease, start of subsequent anticancer therapy, or death due to any cause. Both CR and PR must be confirmed by repeat assessments performed no less than 4 weeks after the criteria for response are first met. ORR comparison between the 2 treatment arms will be assessed using stratified Cochran-Mantel-Haenszel (CMH) test.

A complete list of estimands is defined in [Section 9.1.1](#).

4. STUDY DESIGN

4.1. Overall Design

This is an open-label, multicenter, randomized Phase 3 study of EC with or without chemotherapy versus standard-of-care chemotherapy in participants with previously untreated *BRAF* V600E-mutant mCRC. Prior to the Phase 3 portion, a SLI will be conducted at a limited number of sites to evaluate the safety/tolerability and PK of EC in combination with either FOLFIRI or mFOLFOX6 (Cohort 1 and Cohort 2, respectively). In addition to the Phase 3 portion, a Cohort 3 with 2 randomized arms will be included: EC in combination with FOLFIRI (Arm D) and FOLFIRI with or without bevacizumab (Arm E) in first-line participants. Cohort 3 will start after the enrollment of the Phase 3 portion is complete and enrollment will only be conducted in countries where authorized.

Approximately 60 participants will be enrolled in the SLI portion (up to 30 per regimen). The results of the SLI will inform which chemotherapy regimen is used in Arm B of the Phase 3 portion of the study. In the Phase 3 portion, approximately 620 participants will be randomized overall, initially at a ratio of 1:1:1 to receive EC (Arm A), EC + chemotherapy (Arm B) or SOC chemotherapy (Control Arm), and then 1:1 to receive EC + chemotherapy (Arm B) or SOC chemotherapy (Control Arm) after the approval of Protocol Amendment 5, with a total of approximately 150 participants for Arm A and 235 participants each for Arm B and the Control Arm (Arm C). Approximately 136 participants will be enrolled in Cohort 3 at a ratio of 1:1 to receive EC + FOLFIRI (Arm D, n=68) or FOLFIRI with or without bevacizumab (Arm E, n=68).

The primary objective in the Phase 3 portion of the study is to compare the efficacy, as measured by the primary endpoints of PFS by BICR and ORR by BICR, of Arm B versus the

Control Arm. The study will be considered positive (ie, demonstrated evidence of effectiveness) if the hypothesis test of either primary endpoint is statistically significant.

The primary objective in the Cohort 3 portion of the study is to compare the efficacy, as measured by the primary endpoint of ORR by BICR of Arm D versus Arm E. The results of Cohort 3 will be considered positive (ie, demonstrated evidence of effectiveness) if the hypothesis test of primary endpoint is statistically significant.

After reviewing the totality of the SLI data, the E-DMC and SC determined that there were no new safety signals and recommended that the study can proceed as planned. As a result of the SLI data review, Arm B will consist of EC in combination with mFOLFOX6. In addition, Phase 3 treatment Control Arm (Arm C) will consist of Investigator's choice of mFOLFOX6 ± bevacizumab, FOLFOXIRI ± bevacizumab or CAPOX ± bevacizumab.

4.2. Scientific Rationale for Study Design

4.2.1. Safety Lead-in

Since the EC regimen has not previously been combined with cytotoxic chemotherapy, a SLI will be conducted prior to the Phase 3 portion of the study to evaluate the safety/tolerability and PK of EC + mFOLFOX6 and EC + FOLFIRI. The results of the SLI will inform which chemotherapy regimen is used in Arm B of the Phase 3 portion of the study (see [Section 6.1.1](#) for detailed description of SLI). The most frequently reported AEs (>25% of patients) among patients treated with EC in the BEACON CRC trial were nausea, diarrhea, fatigue, dermatitis acneiform, and decreased appetite. The potential overlapping toxicities between EC and the chemotherapy regimens are primarily GI toxicities that are managed routinely by treating physicians. Therefore, the safety and tolerability of the combinations will be assessed using the standard doses of all agents.

The SLI will enroll up to 30 participants per cohort to fully assess the safety/tolerability and PK, including the potential for DDI, of EC + mFOLFOX6 and EC + FOLFIRI. For each cohort, the probability of observing at least one instance of a toxicity in 30 participants is >95% when the true toxicity incidence rate is 10%. The decision to initiate Phase 3 will require approval from the study SC and the E-DMC. The E-DMC will also review safety data to confirm the tolerability of the EC + chemotherapy combination after the first 30 participants have been randomized and treated for at least 1 cycle in the Phase 3 portion of the study.

4.2.2. Assessment of Potential DDI with Encorafenib

Irinotecan is metabolized to SN-38, which is 100-1,000 times more potent than the parent. The exposures of both irinotecan and SN-38 have been shown to correlate with the efficacy and toxicity (eg, neutropenia and diarrhea) of irinotecan treatment.⁵¹ SN-38 is conjugated by the enzyme UGT1A1 to form an inactive metabolite, SN-38G, which is readily eliminated.

An alternative pathway of irinotecan metabolism is CYP3A4-mediated oxidation, which produces inactive metabolites. Thus, the PK of irinotecan and SN-38 can be altered when

co-administered with CYP3A4 inducers or inhibitors.⁵² Therefore, strong CYP3A4 inducers or inhibitors should not be co-administered with irinotecan unless there are no therapeutic alternatives.⁵³

In vitro studies indicated that encorafenib is a reversible inhibitor of UGT1A1. Based on recently available data from an ongoing DDI study in patients, single dose encorafenib does not inhibit CYP3A at clinically used doses. However, in patients receiving therapeutic doses, encorafenib plasma exposures at steady-state are lower than expected, indicating net auto-induction following multiple doses. Encorafenib also inhibits multiple transporters that are also involved in disposition and elimination of irinotecan and its metabolites (SN-38 and SN-38G).^{54,55} Therefore, when co-administered with FOLFIRI, encorafenib has the potential to alter the PK of irinotecan or SN-38 via changes in enzyme activities of CYP3A4, UGT1A1 and various transporters. The metabolism of oxaliplatin, 5-FU, and leucovorin is not mediated by CYP450 enzymes, and the risk of CYP450-mediated DDI of encorafenib with these agents is expected to be low.⁵⁶⁻⁵⁸

The potential for a drug-interaction between encorafenib and irinotecan has now been characterized and indicates that encorafenib decreases irinotecan and SN-38 concentrations by approximately 25% at steady state.⁵⁹ Additionally, no increase in the rate of AEs due to higher plasma exposure of irinotecan or SN-38 is anticipated at the initiation of combination treatment (Cycle 1 Day 1). Based on the data from the ongoing DDI study, encorafenib and irinotecan can be co-administered from the initiation of combination treatment.

4.2.3. Investigator's Choice of Control Regimen

Treatment of investigator's choice was chosen as the comparator in the Phase 3 portion of the study because a number of therapeutic options are available as initial therapy for mCRC, allowing selection of the regimen believed to potentially confer the greatest clinical benefit to a given participant. Currently, no treatments are indicated specifically for patients with *BRAF* V600E-mutant mCRC in the first-line setting and there is no single SOC regimen established in this indication (see [Table 6](#)).

Clinical guidelines established by ASCO, ESMO, and JSMO suggest that mFOLFOX6, FOLFIRI, or CAPOX are all acceptable therapeutic options and should be combined with bevacizumab where possible for initial treatment of patients with mCRC irrespective of tumor *BRAF* status.^{28,35,60,61} The more intensive combination of FOLFOXIRI + bevacizumab was also shown to be active based on retrospective analyses of clinical trial data although more recent data from a meta-analysis suggests that the triple combination of 5-FU, oxaliplatin, and irinotecan (with bevacizumab) has similar efficacy as doublet chemotherapy and bevacizumab in patients with *BRAF* V600E-mutant mCRC.⁶² Since the FOLFOXIRI plus bevacizumab regimen is associated with greater toxicity, it is only recommended for patients who are defined as being fit and highly motivated in the ESMO guidelines or those with excellent performance status.

4.2.4. Progression-Free Survival and Objective Response Rate as Primary Endpoints

The primary endpoints will be PFS by BICR and ORR by BICR, and OS will be the key secondary endpoint for the Phase 3 portion. ORR by BICR will be the primary endpoint and PFS by BICR will be the key secondary endpoint for Cohort 3. Given the study design and nature of the disease, it is likely that at the time of the primary endpoint (ie, ORR, PFS) analysis, OS may still be immature, and significance may not have been observed. PFS as a primary endpoint with OS as a key secondary endpoint is commonly used in oncology trials including trials in first-line mCRC.^{19,63}

According to the Dec 2018 FDA guidance on ‘Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics,’ a large improvement in PFS can be used to support traditional approval in select indications.⁶⁴ The EMA CHMP Guideline on the ‘Evaluation of Anticancer Medicinal Products in Man’ states that OS and PFS are acceptable endpoints, and recommends that if PFS is selected as the primary endpoint, OS should be used as a secondary endpoint.⁶⁵

This is an open-label study, therefore the primary endpoints of PFS and ORR in the Phase 3 portion will be determined by BICR to minimize evaluation bias. An E-DMC will review data throughout the trial. An E-DMC Charter that outlines E-DMC membership, the data that will be reviewed and the timing and frequency of the reviews will be established. Because the assessment of PFS for determination of the primary endpoint will be based on a BICR, disease progression will be confirmed by expedited central review to minimize informative censoring.

In addition, because spontaneous remission is rare, ORR provides clear evidence of antitumor activity. ORR could be evaluated earlier than PFS and could be used for an accelerated/conditional approval if clinically meaningful and durable ORR is shown. Thus, the primary endpoint of ORR has been added to the Phase 3 portion of the study and will be the only primary endpoint for Cohort 3, defined as the proportion of participants with confirmed CR or PR according to RECIST v1.1 as assessed by BICR.

4.2.5. Biomarkers

The biomarker analyses applied to pre-treatment, on-treatment (blood only) and end of treatment tumor and/or blood biospecimens are intended to evaluate established and candidate prognostic/predictive biomarkers that may identify participants who preferentially benefit from the study treatments and to evaluate mechanisms of action and/or resistance for each of the combinations being assessed.

BRAF and *KRAS* mutations are associated with poor prognosis in advanced CRC and are almost always mutually exclusive.^{10,66,67} The predominant (>95%) *BRAF* mutation observed in CRC patients is *BRAF* V600E, which leads to constitutive activation of BRAF kinase and sustained RAS/RAF/MEK/ERK pathway signaling, resulting in increased cell proliferation and survival.¹⁶ In mCRC, approximately 5% of patients are MSI-H, compared to 15% in primary CRC.^{16,68} Approximately 15-30% of *BRAF*-mutant mCRC tumors were also identified as MSI-H/dMMR.^{14,16,24,25} The presence of a *BRAF* V600 mutation appears to be a

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CT02-GSOP Oncology Clinical Protocol Template (01 May 2024)

Page 75

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poor prognostic factor independent of MSI status in mCRC,^{14,16} which differs from the MSS-dependent poor prognostic value of *BRAF* V600 in primary CRC.⁶⁹ In this study, MSI status will be confirmed by retrospective central testing in tumor tissue as a secondary endpoint.

Detection of *BRAF* V600E in ctDNA is concordant with tumor tissue in CRC patients.⁷⁰ A decrease in *BRAF* V600E ctDNA levels predicted improved radiographic responses to vemurafenib + cetuximab + irinotecan⁷¹ and was significantly greater in responders compared to non-responders in *BRAF*-mutant CRC patients treated with dabrafenib + panitumumab ± trametinib.⁷² Assessments of ctDNA levels as a surrogate marker for tumor burden and of *BRAF* V600 VAF in ctDNA from plasma samples collected at baseline and on treatment will be secondary endpoints in this study based on recent findings from the ctMoniTR Project and subsequent studies.^{73,74}

Unless prohibited by local regulations or ethics committee decision, additional blood samples will be collected for various exploratory biomarker analyses as described in [Section 8](#). Banked Biospecimens will be collected and stored for further analyses which may, for example, provide greater understanding of the study intervention.

4.2.6. Use of Contraceptives

The study interventions being administered are known to cause risk for severe manifestations of developmental toxicity in humans or suspected on the basis of the intended pharmacology. Therefore, the use of a highly effective method of contraception is required (see [Section 5.3.1](#) and [Appendix 4](#)).

4.3. Justification for Dose

In order to optimize the potential for benefit, while limiting the potential for toxicity, the starting encorafenib dose in the current study is 300 mg QD, corresponding to its single-agent RP2D. This dose of encorafenib was administered in combination with cetuximab in Study ARRAY-818-302 (BEACON CRC) and was shown to be both effective and tolerable in participants with previously treated *BRAF* V600E-mutant mCRC. Based on these results, the approved dose of encorafenib for this indication is 300 mg QD when given in combination with cetuximab.³⁷ Further details are available in the encorafenib SRSD.

The dose regimens selected for capecitabine, 5-FU, irinotecan, leucovorin, oxaliplatin, and bevacizumab are consistent with the respective SRSDs.

The cetuximab regimen approved globally is 400 mg/m² first-dose followed by 250 mg/m² IV weekly. Because many of the cytotoxic doublets used in mCRC are administered biweekly, a biweekly cetuximab regimen has also been tested. In a Phase 1 dose-escalation study in patients with mCRC, doses of cetuximab 400 to 700 mg/m² every 2 weeks were evaluated. The MTD was not identified and 500 mg/m² was identified as the dose for further development based on its PK parameters being most similar to the weekly regimen.⁷⁵ A Phase 2 study in patients with previously treated mCRC treated with biweekly cetuximab 500 mg/m² in combination with irinotecan demonstrated similar efficacy and tolerability as historical data with similar regimens using weekly cetuximab.⁷⁶ The use of the biweekly

regimen is fairly common in current practice and is included as an acceptable regimen in the NCCN guidelines.²⁸ Allowing use of this regimen will provide greater flexibility and perhaps enhance compliance and recruitment within the study in which participants are expected to remain on treatment for approximately 10 months.

4.4. End of Study Definition

The end of study is defined as LPLV. LPLV is defined as the date of the last visit or follow-up contact of the last participant in the study globally.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

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

Pfizer or designee will review select eligibility criteria verified by the investigator or qualified designee to confirm that participants meet study eligibility criteria before they are enrolled into the study. The enrollment approval process will be initiated for a participant after an informed consent/assent document has been signed and the investigator or qualified designee has assessed the participant as eligible. The enrollment approval will be based on review of CRF/system data.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

5.1.1. Molecular Prescreening Inclusion Criteria

Age and Sex:

1. **SLI:** Male or female participants age ≥ 18 years at the time of informed consent.
Phase 3 and Cohort 3: Male or female participants age ≥ 16 years at the time of informed consent/assent in all countries where permitted. In countries or sites where enrollment of adolescents is not permitted (eg, Germany), male or female participants age ≥ 18 years at the time of informed consent.
 - Refer to [Appendix 4](#) for reproductive criteria for male ([Section 10.4.1](#)) and female ([Section 10.4.2](#)) participants.

Weight:

2. Body weight ≥ 40 kg.

Type of Participant and Disease Characteristics:

3. Participants with histologically or cytologically confirmed colorectal adenocarcinoma.
4. Participants with evidence of Stage IV metastatic disease.
Note: Patients with oligometastatic disease previously treated with curative intent are eligible to participate in the study as long as they have baseline measurable disease per RECIST 1.1. Oligometastatic colorectal cancer is characterized by a limited metastatic spread of disease. Oligometastatic disease is defined as the involvement of up to 3 sites with 5 or sometimes more metastases that for their anatomic localization is amenable to local therapies, thus rendering the patient free of disease.⁷⁷
5. Able to provide a sufficient amount of representative tumor specimen for central testing of *BRAF* V600E mutation status (see [Section 8.7.2](#)) and tumor tissue assessment (see [Section 8.8.2](#)).
Note: Tumor sample can be archival or de novo (newly collected fixed biopsy sample) and must be in an FFPE block, or provide a minimum of 15 (a minimum of 10 for mainland China) unstained slides of analyzable tissue. This tissue specimen should be obtained from a biopsy or surgery that was performed within 2 years prior to study enrollment. Participants with fewer than the required number of slides with analyzable tissue may be considered eligible if the Sponsor determines that the slides are sufficient for central testing.

Informed Consent/Assent:

6. Capable of giving signed informed consent/assent as described in [Appendix 1](#), which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.
Note: Participants ≥ 16 years old that are under guardianship may participate with the consent of their legally authorized guardian if permitted by local regulations. When appropriate, adolescent participants will be included in all discussions (see [Section 10.1.3](#)).

5.1.2. Screening Inclusion Criteria

Type of Participant and Disease Characteristics:

7. Participants who have met all Molecular Prescreening inclusion criteria.
8. Participants who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures.
9. Presence of a *BRAF* V600E mutation in tumor tissue or blood (eg, ctDNA genetic testing). The following are acceptable:
 - a. Local laboratory assay (PCR or NGS-based only) performed at any time prior to Screening using either tumor tissue or blood.

- b. Central laboratory assay performed during the Screening period using tumor tissue alone (not blood).

Note: For participants enrolled on the basis of a local *BRAF* mutation assay, tumor samples must be submitted to the central laboratory for *BRAF* testing as soon as possible following signing of the ICD. The *BRAF* status must be confirmed no later than 30 days following first dose of study intervention.

- 10. The Investigator must obtain prior to Cycle 1 Day 1 (SLI) or date of randomization (Phase 3 and Cohort 3) adequate tumor tissue (primary or metastatic, archival or newly obtained) for submission to a central laboratory for confirmation of *BRAF* V600E (see [Section 8.7.2](#)) and tumor tissue assessment (see [Section 8.8.2](#)). Sample must be an FFPE block or minimum of 15 (a minimum of 10 for mainland China) unstained slides containing recently cut, 4-5 µm sections on positively charged slides. This tissue specimen should be obtained from a biopsy or surgery that was performed within 2 years prior to study enrollment. Participants with fewer than the required number of slides with analyzable tissue may be considered eligible if the Sponsor determines that the slides are sufficient for central testing.

Note: Once *BRAF* V600E mutation status is determined by the central laboratory (tumor tissue), the results will be considered definitive for eligibility. No repeat testing will be performed.

Note: 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). See [Section 8.7.2](#) for additional information.

Note: Participants whose sample is determined to be inadequate or who have an indeterminate result on central testing may have additional tumor samples submitted for testing.

- 11. Participants who have received ≤ 1 (SLI) or no (Phase 3 and Cohort 3) prior systemic regimen(s) for metastatic disease.

Note: SLI participants who have received prior oxaliplatin-based regimens in first-line treatment will be enrolled to the FOLFIRI combination cohort (Cohort 1) and participants who have received prior irinotecan in first-line treatment will be enrolled in the mFOLFOX6 combination cohort (Cohort 2).

Note: Participants with early stage disease (eg, Stages I-III) treated with surgery followed by chemotherapy (eg, treatment in the adjuvant setting) or have received prior systemic neoadjuvant therapy with or without radiation who present with new lesions or evidence of disease recurrence during or within 6 months of the last dose of chemotherapy would be considered as having received 1 prior systemic therapy in the metastatic setting.

- 12. ECOG performance status of 0 or 1.

13. Measurable disease in the Phase 3 and Cohort 3 portions of the study and measurable or non-measurable but evaluable disease per RECIST, v1.1 in the SLI, as assessed by Investigator and evidenced by available baseline scans.

Note: Baseline scan is defined as the last scan prior to the date of first dose (SLI) or the date of randomization (Phase 3 and Cohort 3) ([Section 9.4.1](#)).

Note: Baseline scans will be required to be submitted to a central radiology vendor to be assessed by the BICR.

14. Adequate bone marrow function characterized by the following at screening:

- a. ANC $\geq 1.5 \times 10^9/\text{L}$;
- b. Platelets $\geq 100 \times 10^9/\text{L}$;
- c. Hemoglobin ≥ 9.0 g/dL (with or without blood transfusions).

15. Adequate hepatic and renal function characterized by the following at screening:

- a. Serum total bilirubin $\leq 1.5 \times \text{ULN}$ and < 2 mg/dL.

Note: Total bilirubin $> 1.5 \times \text{ULN}$ is allowed if direct (conjugated) $\leq 1.5 \times \text{ULN}$ and indirect (unconjugated) bilirubin is $\leq 4.25 \times \text{ULN}$.

Note: Participants with hyperbilirubinemia due to non-hepatic cause (eg, hemolysis, hematoma) may be enrolled following discussion and agreement with the medical monitor.

- b. ALT and AST $\leq 2.5 \times \text{ULN}$, or $\leq 5 \times \text{ULN}$ in the presence of liver metastases.
- c. Adequate renal function defined by an estimated creatinine clearance ≥ 50 mL/min according to the Cockcroft Gault formula or by 24-hour urine collection for creatinine clearance, or according to local institutional standard method.
- d. Adequate electrolytes, defined as serum potassium and magnesium levels within institutional normal limits.

Note: Replacement treatment to achieve adequate electrolytes will be allowed.

16. Able to swallow, retain, and absorb oral medications.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

5.2.1. Molecular Prescreening Exclusion Criteria

Medical Conditions:

1. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.
2. Presence of acute or chronic pancreatitis.

3. Leptomeningeal disease.
4. History of chronic inflammatory bowel disease requiring medical intervention (immunomodulatory or immunosuppressive medications or surgery) ≤ 12 months prior to randomization.
5. Known DPD deficiency; refer to local fluorouracil or capecitabine label or local clinical guidance, for DPD status recommendation prior to starting treatment.
6. Gilbert's syndrome or known homozygous UGT1A1*28/*28 or UGT1A1*6/*6 genotypes or double heterozygous UGT1A1*6/*28 genotype:
 - a. **SLI:** Participants with documented Gilbert's syndrome or known homozygous UGT1A1*28/*28 or UGT1A1*6/*6 genotypes or double heterozygous UGT1A1*6/*28 genotype will be excluded from Cohort 1 (EC + FOLFIRI) of the SLI.
 - b. **Phase 3:** Participants with documented Gilbert's syndrome or known homozygous UGT1A1*28/*28 or UGT1A1*6/*6 genotypes or double heterozygous UGT1A1*6/*28 genotype may be enrolled, but may not receive FOLFOXIRI if randomized to the Control Arm.
 - c. **Cohort 3:** Participants with documented Gilbert's syndrome or known homozygous UGT1A1*28/*28 or UGT1A1*6/*6 genotypes or double heterozygous UGT1A1*6/*28 genotype will be excluded from Cohort 3 Arm D and Arm E (EC + FOLFIRI and FOLFIRI \pm bevacizumab).

Other Exclusions:

7. Investigator site staff or Pfizer employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.
8. Colorectal adenocarcinoma that is RAS mutant or for which RAS mutation status is unknown.
9. Locally confirmed dMMR or MSI-H colorectal carcinoma or unknown MSI/MMR status. If participant is locally confirmed dMMR or MSI-H and unable to receive immune checkpoint inhibitors due to a pre-existing medical condition, they may be enrolled.

5.2.2. Screening Exclusion Criteria

Medical Conditions:

10. Impaired gastrointestinal function (eg, uncontrolled nausea, vomiting or diarrhea, malabsorption syndrome, small bowel resection) or disease which may significantly alter the absorption of oral study intervention or recent changes in bowel function suggesting current or impending bowel obstruction.

11. Clinically significant cardiovascular diseases, including any of the following:

- a. History of acute myocardial infarction, acute coronary syndromes (including unstable angina, coronary artery bypass graft, coronary angioplasty or stenting) ≤ 6 months prior to randomization;
- b. Congestive heart failure requiring treatment (New York Heart Association Class II and above);
- c. Recent history (within 1 year prior to randomization) or presence of clinically significant cardiac arrhythmias (including uncontrolled atrial fibrillation or uncontrolled paroxysmal supraventricular tachycardia);
- d. History of thromboembolic or cerebrovascular events ≤ 12 weeks prior to randomization. Examples include transient ischemic attacks, cerebrovascular accidents, hemodynamically significant (ie, massive or sub-massive) deep vein thrombosis or pulmonary emboli.
Note: Participants with either deep vein thrombosis or pulmonary emboli that do not result in hemodynamic instability are allowed to enroll as long as they are on a stable dose of anticoagulants for at least 4 weeks.
Note: Participants with thromboembolic events related to indwelling catheters (including PICC lines) or other procedures may be enrolled.
- e. Triplicate average QTcF interval ≥ 480 ms or a history of prolonged QT syndrome.
Note: Participants with bundle-branch block (BBB) or with an implanted cardiac pacemaker, may enroll into the study following consultation with the Sponsor.
- f. Congenital LQTS.

12. Evidence of active noninfectious pneumonitis.

13. Evidence of active and uncontrolled bacterial or viral infection, with certain exceptions, as noted below, for chronic infection with HIV, hepatitis B or hepatitis C (please see below), within 2 weeks prior to start of study intervention.

14. Participants positive for HIV are ineligible unless they meet all of the following:

- a. A stable regimen of highly active anti-retroviral therapy that is not contraindicated (see [Section 6.5](#));
- b. No requirement for concurrent antibiotics or antifungal agents for the prevention of opportunistic infections;
- c. A CD4 count >250 cells/mcL, and an undetectable HIV viral load on standard PCR-based tests.

15. Active hepatitis B or hepatitis C infection

a. Active HBV is defined as any of the following:

- HBsAg(+), HBV DNA >200 IU/mL;
- HBsAg(+), HBV DNA ≤200 IU/mL and persistent or intermittent elevation of ALT/AST (ie, above normal range) and/or liver biopsy showing chronic hepatitis with moderate or severe necroinflammation.

Note: Participants who are HBsAg(-), HBcAb(+) are eligible and should be monitored/treated as per local standard of care.

b. Active HCV is defined as:

- HCV antibody positive; AND
- Presence of HCV RNA.

16. Concurrent or previous other malignancy within 2 years of study entry, except curatively treated basal or squamous cell skin cancer, prostate intraepithelial neoplasm, carcinoma in-situ of the cervix, Bowen's disease or prostate cancer with a Gleason score ≤6. Participants with other curatively treated malignancies with low risk of recurrence not listed may also be considered eligible after review and approval by the medical monitor.

17. Residual CTCAE ≥Grade 2 toxicity from any prior anticancer therapy, with the exception of Grade 2 alopecia or Grade 2 neuropathy.

Note: Participants with ≥ Grade 2 neurotoxicity are excluded from receiving mFOLFOX 6 in the SLI, and entirely from Phase 3.

Prior/Concomitant Therapy:

18. **SLI:** Treatment with any of the following:

- Prior systemic regimen containing both oxaliplatin and irinotecan (eg, FOLFOXIRI).
- Cyclical chemotherapy within a period of time that was shorter than the cycle length used for that treatment (e.g., 6 weeks for nitrosourea, mitomycin-C) prior to starting study treatment.
- 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 ($t_{1/2}$) or ≤ 4 weeks (whichever is shorter) prior to starting study treatment.
- Bevacizumab or aflibercept therapy ≤ 3 weeks prior to starting study treatment.

19. Previous treatment with any selective BRAF inhibitor (eg, encorafenib, dabrafenib, vemurafenib, XL281/BMS-908662) or any EGFR inhibitor (eg, cetuximab, panitumumab) prior to screening.
20. Use of any prohibited medication (including herbal medication), supplement or food that is a moderate or strong inhibitor or inducer of CYP3A4/5 ≤ 1 week prior to the start of study intervention ([Section 6.5.1.2](#)).
21. Major surgery or completion of radiation therapy ≤ 4 weeks prior to enrollment/randomization or radiation therapy that included $>30\%$ of the bone marrow.

Prior/Concurrent Clinical Study Experience:

22. Previous administration with an investigational product (eg, drug or vaccine) within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of study intervention used in this study (whichever is longer).

Other Exclusions:

23. Has met any of the Molecular Prescreening exclusion criteria.
24. Has documented clinical disease progression (eg, worsening of performance status, clinical symptoms, or clinically significant laboratory parameters demonstrating worsening of disease) or radiographic disease progression during the Screening period.
25. Symptomatic brain metastasis.
Note: Participants previously treated or untreated for this condition who are asymptomatic in the absence of corticosteroid and anti-epileptic therapy are allowed. Brain metastases must be stable for ≥ 4 weeks prior to randomization.
26. Known contraindication to receiving cetuximab including hypersensitivity or toxicity that would suggest an inability to tolerate maximum cetuximab dose of 500 mg/m².
27. Known sensitivity or contraindication to any component of study intervention or their excipients at the planned doses.
28. Known contraindication to receive any component of the Control Arm at the planned doses; refer to the most recent local label, as applicable.
29. Pregnant, confirmed by a positive β -hCG laboratory test result, or is breastfeeding (lactating).

5.3. Lifestyle Considerations

The investigator or his or her designee, will discuss with the participant fertility preservation strategies prior to the start of study intervention.

5.3.1. Contraception

Due to the potential of encorafenib to induce CYP3A4 (see [Section 6.5.1.2](#)), hormonal agents (including but not limited to birth control patch, vaginal ring, oral, injectable, or implanted contraceptives) are permissible for participants treated in the SLI, Arm A, Arm B and Cohort 3 Arm D only when combined with other highly effective or acceptable methods. The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant and his or her partner(s) from the permitted list of contraception methods (see [Appendix 4 Section 10.4.4](#)) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the [SoA](#), the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). It is recommended that participants be followed for contraception use for 9 months for females and 6 months for males following the last dose of study intervention. Appropriate tests can also be carried out at home, so that monitoring of successful contraception can be guaranteed even if the participants no longer come to the study site regularly. In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

5.3.2. Meals and Dietary Restrictions

Participants treated in the SLI, Arm A, Arm B and Arm D must avoid consumption of grapefruit, pomegranates, star fruits, Seville oranges or products containing the juice of each during the entire study and preferably 7 days before the first dose of study intervention, due to potential CYP3A4 interaction with encorafenib (see [Section 6.5](#)). Orange juice is allowed.

5.3.3. Photosensitivity

Participants should avoid extended exposure to ultraviolet light and when outdoors, should wear occlusive clothing, sunscreen and sunglasses when receiving 5-FU.

5.3.4. Screen Failures

Screen failures are defined as participants who consent/assent to participate in the clinical study but are not subsequently enrolled in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs. For Molecular Prescreening failures, results of local *BRAF* assay available at Molecular Prescreening or Screening, AEs or SAEs possibly related to a study procedure will be reported.

Tests with results that fail eligibility requirements may be repeated during Screening if the Investigator believes the result to be in error. Additionally, a participant who fails Screening

(screen failure) may repeat the Screening process 1 time if the Investigator believes that there has been a change in eligibility status.

6. STUDY INTERVENTION

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

For the purposes of this protocol, study intervention refers to capecitabine, cetuximab, encorafenib, 5-FU, irinotecan, leucovorin, oxaliplatin, and bevacizumab.

Investigators should refer to the approved local label of the products used in this trial (capecitabine, cetuximab, 5-FU, irinotecan, leucovorin, oxaliplatin, and bevacizumab) for the management of patients, especially concerning contraindications, duration of contraception, special warnings and precautions, posology adaptation in case of toxicity, monitoring, as well as medications that are contraindicated or that must be used with caution.

6.1. Study Interventions Administered

Intervention Name	Encorafenib	Cetuximab	Fluorouracil	Leucovorin ^a	Irinotecan	Oxaliplatin	Capecitabine	Bevacizumab
Treatment Arm	SLI; Phase 3, Arm A and Arm B; Cohort 3 Arm D	SLI; Phase 3, Arm A and Arm B; Cohort 3 Arm D	SLI; Phase 3, Arm B; Phase 3, Control Arm; Cohort 3	SLI; Phase 3, Arm B; Phase 3, Control Arm; Cohort 3	SLI; Phase 3, Control Arm; Cohorts 3	SLI; Phase 3, Arm B ^b ; Phase 3, Control Arm C	Phase 3, Control Arm C	Phase 3, Control Arm C; Cohort 3 Arm E
Type	Drug	Drug	Drug	Drug	Drug	Drug	Drug	Drug
Dose Formulation	Capsule	Injection for intravenous use	Injection for intravenous use	Injection	Solution for intravenous infusion	Concentrate for solution for intravenous use	Tablet	Injection for intravenous use
Unit Dose Strength(s)	75 mg	100 mg/vial, 200 mg/vial, or 500 mg/vial	250 mg/vial, 500 mg/vial, or 1000 mg/vial	50 mg/vial, 100 mg/vial, 200 mg/vial, or 350 mg/vial	40 mg/vial, 100 mg/vial, or 300 mg/vial	50 mg/vial, 100 mg/vial, or 200 mg/vial	150 mg or 500 mg	100 mg/vial or 400 mg/vial
Route of Administration	Oral	Intravenous	Intravenous	Intravenous	Intravenous	Intravenous	Oral	Intravenous
Use	Experimental	Experimental	Experimental (Arms A and B); Comparator (Control Arm)	Experimental (Arms A and B); Comparator (Control Arm)	Experimental (Arms A and B); Comparator (Control Arm)	Experimental (Arms A and B); Comparator (Control Arm)	Comparator	Comparator
IMP or NIMP/AxMP	IMP	IMP or NIMP (USA only)	IMP or NIMP (USA only)	IMP or NIMP (USA only)	IMP or NIMP (USA only)	IMP or NIMP (USA only)	IMP or NIMP (USA only)	IMP or NIMP (USA only)
Sourcing	Provided centrally by the sponsor.	Provided centrally by the sponsor or locally by the trial site.	Provided centrally by the sponsor or locally by the trial site.	Provided centrally by the sponsor or locally by the trial site.	Provided centrally by the sponsor or locally by the trial site.	Provided centrally by the sponsor or locally by the trial site.	Provided centrally by the sponsor or locally by the trial site.	Provided centrally by the sponsor or locally by the trial site.
Packaging and Labeling	Study intervention will be provided in bottles. Each bottle will be open labeled as required per country requirement.	If IMP study intervention will be provided in vials. Each vial will be open labeled as required per country requirement.	If IMP study intervention will be provided in vials. Each vial will be open labeled as required per country requirement.	If IMP study intervention will be provided in vials. Each vial will be open labeled as required per country requirement.	If IMP study intervention will be provided in vials. Each vial will be open labeled as required per country requirement.	If IMP study intervention will be provided in vials. Each vial will be open labeled as required per country requirement.	If IMP study intervention will be provided in bottles. Each bottle will be open labeled as required per country requirement.	If IMP study intervention will be provided in vials. Each vial will be open labeled as required per country requirement.

Encorafenib (BRAFTOVI[®], PF-07263896 also known as LGX818 or ONO-7702)
Protocol C4221015
Final Protocol Amendment 7, 31 May 2024

Intervention Name	Encorafenib	Cetuximab	Fluorouracil	Leucovorin ^a	Irinotecan	Oxaliplatin	Capecitabine	Bevacizumab
SRSD	IB	EU SmPC	UK SmPC	EU/UK SmPC ^c	EU SmPC	EU SmPC	EU SmPC	EU SmPC

a Alternatively, levo-leucovorin or calcium folinate (100 mg/vial, 200 mg/vial, or 300 mg/vial) may be supplied. All three presentations are 10 mg/mL strength.

b Based on the results of the SLI, oxaliplatin will be used in Arm B (see [Section 4.1](#)).

c SRSD for leucovorin (calcium folinate) is the EU SmPC and SRSD for levo-leucovorin is the UK SmPC.

6.1.1. Safety Lead-in

Since the EC regimen has not previously been combined with cytotoxic chemotherapy, the study includes an SLI, to be conducted at a limited number of sites, to evaluate the safety/tolerability and PK of EC + mFOLFOX6 and EC + FOLFIRI in up to 30 participants per cohort. Participants will be enrolled on a rolling basis in an alternating manner to each cohort when possible based on eligibility criteria.

The tolerability assessment will be based on occurrence of DLTs as defined in Section 6.1.1.1. Tolerability will be reviewed by the Sponsor and investigators in approximately weekly telephone conferences during the SLI. If 3 of the first 9 participants are determined to have experienced DLTs in a given cohort, enrollment to that cohort will be put on hold until a discussion with the SC and E-DMC can occur. If the DLTs are confirmed by the SC and the E-DMC and it is determined that the regimen is not tolerable, dosing in that cohort will be suspended.

The SC will review safety data after the 9th evaluable participant in a particular cohort has been followed for at least one 28-day cycle. In either cohort, if the doses are determined to be tolerable by the SC in the first 9 evaluable participants based on an observed rate of DLTs in <33% of participants and evaluation of the overall toxicity profile, the SLI will be expanded for that particular cohort by up to a maximum of approximately 30 participants. Enrollment may continue while the SC reviews safety data from the first 9 participants. The E-DMC will also review data after the 9th participant in a particular cohort has been followed for at least one 28-day cycle to confirm tolerability of the doses.

At the completion of the SLI when all evaluable participants have been followed for a minimum of one 28-day cycle, the SC and the E-DMC will review all accumulated safety data to confirm that the doses are acceptable for use in Arm B (EC + mFOLFOX6 or EC + FOLFIRI) of the randomized Phase 3 portion of the study. The primary criteria in deciding which combination to use in Phase 3 will be based on identifying the combination with the fewest DLTs. If the DLT rate is $\geq 33\%$ in either cohort, that regimen will not be used in Phase 3. If the DLT rate is <33% in both cohorts, additional parameters that may be used to determine the most suitable combination will include dose modifications, AEs of at least Grade 3, AEs leading to treatment discontinuations, SAEs, and PK results including the potential for DDIs (Section 4.2.2). Since only 1 of the combination regimens will be included in the Phase 3 portion of the study, a rigorous selection process will be implemented based on the totality of the data. Finally, although efficacy is not a primary objective, the number of objective responses and DORs may also be taken into consideration in making a final decision.

Although the SLI is planned to enroll up to 30 evaluable participants per cohort, the decision to proceed to Phase 3 may occur earlier if one of the combination regimens is clearly superior based on the collective safety/tolerability and PK. If there are no clearly distinguishing differences between the 2 combinations, the most appropriate regimen to be used in Phase 3 will be determined following a review of the totality of the SLI data. If neither regimen is considered tolerable and/or suitable for evaluation in the randomization portion of the trial,

the decision to proceed as a 2-arm study of EC versus SOC chemotherapy will be made prior to start of randomization in the Phase 3 portion of the study. The decision to initiate Phase 3 will require approval from the study SC and the E-DMC.

6.1.1.1. Dose Limiting Toxicity Definition

For purposes of tolerability decisions, a DLT is defined as any AE or abnormal laboratory value assessed as unrelated to disease, disease progression, intercurrent illness or concomitant medications/therapies occurring during the first 28 days of treatment that meets at least 1 of the criteria listed in Table 9. A participant is classified as DLT-evaluable if he/she experiences a DLT or in the absence of a DLT, receives at least 75 % of the planned dose intensity of each study intervention during the DLT window (see Section 9.3). If a participant does not meet these criteria, he/she may be replaced.

Adverse events that are clinically significant and considered to be related to the study intervention that occur after the DLT observation period will be reviewed in context of all safety data available. That review may result in re-evaluation of the dosing level or regimen.

Severity of AEs will be graded according to CTCAE v4.03. In Cohort 1 (EC + FOLFIRI), any DLT occurring prior to initiation of encorafenib on Day 3 will not be considered for tolerability decisions.

Table 9. DLT Criteria

<ul style="list-style-type: none"> Any AE or laboratory value considered unrelated to underlying disease, disease progression, intercurrent illness or concomitant medications/therapies resulting in the inability to tolerate at least 75% of the planned dose intensity ($[\text{administered dose in mg}/\text{planned dose in mg}] \times 100$) of each study intervention during the 28-day DLT period.
General disorders and administration site conditions <ul style="list-style-type: none"> Fatigue Grade 3 for >14 consecutive days
Respiratory disorders <ul style="list-style-type: none"> Interstitial lung disease/pneumonitis Grade ≥ 2
Skin and subcutaneous tissue disorders^a <ul style="list-style-type: none"> Rash, HFSR, or photosensitivity Grade 3 for >14 consecutive days despite maximal skin toxicity treatment (as per local practice) Rash, HFSR, or photosensitivity Grade 4
Gastrointestinal disorders^a <ul style="list-style-type: none"> 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 Vomiting Grade 4 Mucositis Grade ≥ 3

Table 9. DLT Criteria

Investigations <ul style="list-style-type: none"> • Total bilirubin Grade ≥ 3 • AST or ALT Grade ≥ 3 in conjunction with total bilirubin Grade ≥ 2 of any duration • AST or ALT Grade 3 for >7 consecutive days • AST or ALT Grade 4 • Serum creatinine Grade ≥ 3 • ANC Grade 4 for >7 consecutive days • \geq Grade 3 febrile neutropenia • Grade 3 platelet count decreased with signs of clinically significant bleeding • Platelet count Grade 4 • ECG QTcF prolonged \geq Grade 3^b
Uveitis <ul style="list-style-type: none"> • Grade ≥ 3 for >21 consecutive days • Grade 4 confirmed by ophthalmic examination
Neurotoxicity <ul style="list-style-type: none"> • Paresthesia/dysesthesias Grade ≥ 3
Other hematologic and nonhematologic toxicities^c <ul style="list-style-type: none"> • Any other Grade ≥ 3 AE except: <ul style="list-style-type: none"> ◦ Lymphocyte count decreased (lymphopenia) Grade ≥ 3 unless clinically significant <p>a. Prophylactic treatment for nausea/vomiting or skin AEs should be used at the discretion of the Investigator if the participant experiences nausea/vomiting and/or skin AEs Grade ≥ 1.</p> <p>b. QTcF must be prolonged on two separate ECGs at least 5 minutes apart.</p> <p>c. Isolated laboratory changes (eg 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 medical monitor.</p>

6.1.2. Treatment Regimens

Participants enrolled in the SLI will receive either a regimen of EC + mFOLFOX6 or a regimen of EC + FOLFIRI in 28 day cycles. Recommended regimen administrations for cetuximab, 5-FU, irinotecan, leucovorin and oxaliplatin are described in [Table 10](#); however, all should be administered in accordance with their respective locally approved label or local institutional standards.

Table 10. Treatment Regimens (Safety Lead-in)

Study Treatments	Dose	Frequency
Encorafenib	300 mg (4 × 75 mg) oral capsule	QD
Cetuximab	500 mg/m ² (120-minute IV infusion) ^a	Q2W
mFOLFOX6	Oxaliplatin 85 mg/m ² (120-minute IV infusion) ^a Leucovorin 400 mg/m ² (120-minute IV infusion) ^{a,b,c} 5-FU 400 mg/m ² IV bolus, then 5-FU 2400 mg/m ² continuous IV infusion over 46-48 hours ^a	Q2W
Encorafenib	300 mg (4 × 75 mg) oral capsule ^d	QD
Cetuximab	500 mg/m ² (120-minute IV infusion) ^a	Q2W
FOLFIRI	Irinotecan 180 mg/m ² (90-minute IV infusion) ^a Leucovorin 400 mg/m ² (120-minute IV infusion) ^{a,b,c} 5-FU 400 mg/m ² IV bolus, then 5-FU 2400 mg/m ² continuous IV infusion over 46-48 hours ^a	Q2W

a Approximate infusion times

b Alternatively, 200 mg/m² levo-leucovorin (120-minute IV infusion) may be administered

c Leucovorin may be co-administered with the oxaliplatin or irinotecan infusion

d Encorafenib dosing will not begin until Cycle 1 Day 3 for participants receiving FOLFIRI

Participants randomized to Arm A will receive encorafenib + cetuximab in 28 day cycles. Recommended regimen administrations for cetuximab are described in Table 11; however, cetuximab should be administered in accordance with the locally approved label or local institutional standards.

Table 11. Treatment Regimen (Phase 3, Arm A)

Study Treatments	Dose	Frequency
Encorafenib	300 mg (4 × 75 mg) oral capsule	QD
Cetuximab	500 mg/m ² (120-minute IV infusion) ^a	Q2W

a Approximate infusion times

Note: In the Phase 3 portion of the study, participants must receive their first dose of study intervention within 5 days of randomization.

Participants randomized to Arm B will receive a regimen of EC + mFOLFOX6 in 28-day cycles. Recommended regimen administrations for bolus and infusion treatment are described in Table 12; however, all should be administered in accordance with their respective locally approved label or local institutional standards.

Table 12. Treatment Regimens (Phase 3, Arm B)

Study Treatments	Dose	Frequency
Encorafenib	300 mg (4 × 75 mg) oral capsule	QD
Cetuximab	500 mg/m ² (120-minute IV infusion) ^a	Q2W
mFOLFOX6	Oxaliplatin 85 mg/m ² (120-minute IV infusion) ^a Leucovorin 400 mg/m ² (120-minute IV infusion) ^{a,b,c} 5-FU 400 mg/m ² IV bolus, then 5-FU 2400 mg/m ² continuous IV infusion over 46-48 hours ^a	Q2W

a Approximate infusion times

b Alternatively, 200 mg/m² levo-leucovorin (120-minute IV infusion) may be administered

c Leucovorin may be co-administered with the oxaliplatin

Note: In the Phase 3 portion of the study, participants must receive their first dose of study intervention within 5 days of randomization.

Participants randomized to the Control Arm will receive one of the following per Investigator choice: mFOLFOX6 ± bevacizumab, FOLFOXIRI ± bevacizumab or CAPOX ± bevacizumab. Recommended regimen administrations for 5-FU, irinotecan, leucovorin, oxaliplatin capecitabine and bevacizumab are described in [Table 13](#); however, all should be administered in accordance with their respective locally approved label or local institutional standards.

Table 13. Treatment Regimens (Phase 3, Control Arm [Arm C])

Study Treatments	Dose	Frequency
mFOLFOX6 ± Bevacizumab	Oxaliplatin 85 mg/m ² (120-minute IV infusion) ^a Leucovorin 400 mg/m ² (120-minute IV infusion) ^{a,b,c} 5-FU 400 mg/m ² IV bolus, then 5-FU 2400 mg/m ² continuous IV infusion over 46-48 hours ^a Bevacizumab (optional; given per prescribing instructions)	Q2W 28-day Cycle
FOLFOXIRI ± Bevacizumab	Irinotecan 165 mg/m ² (90-minute IV infusion) ^a Oxaliplatin 85 mg/m ² (120-minute IV infusion) ^a Leucovorin 400 mg/m ² (120-minute IV infusion) ^{a,b,c} 5-FU 2400 or 3200 mg/m ² continuous IV infusion over 46-48 hours (per local standard of care) ^a Bevacizumab (optional; given per prescribing instructions)	Q2W 28-day Cycle
CAPOX ± Bevacizumab	Oxaliplatin 130 mg/m ² (120-minute IV infusion) ^a Capecitabine 1000 mg/m ² oral tablet Bevacizumab (optional; given per prescribing instructions)	Q3W 21-day Cycle BID Days 1-14

a Approximate infusion times

b Alternatively, 200 mg/m² levo-leucovorin (120-minute IV infusion) may be administered

c Leucovorin may be co-administered with the oxaliplatin or irinotecan infusion

Note: The decision of which regimen to use in the Control Arm is at the participant/treating Investigator's discretion but must be declared prior to randomization and the choice of regimen must not be changed during the course of the participant's treatment.

Note: Participants with colonic or rectal stent in place should not receive bevacizumab in any of the Control Arm regimens.

Note: In the Phase 3 portion of the study, participants must receive their first dose of study intervention within 5 days of randomization.

Two randomized (1:1 randomization) treatment arms in Cohort 3 will be included: EC in combination with FOLFIRI in first-line participants (Arm D) (Table 14) and FOLFIRI with or without bevacizumab in first-line participants (Arm E) (Table 15). Cohort 3 will start after the enrollment of the Phase 3 portion is complete and enrollment will only be conducted in countries where authorized.

Table 14. Treatment Regimens: Cohort 3 (Arm D)

Study Treatments	Dose	Frequency
Encorafenib	300 mg (4 × 75 mg) oral capsule ^d	QD
Cetuximab	500 mg/m ² (120-minute IV infusion) ^a	Q2W
FOLFIRI	Irinotecan 180 mg/m ² (90-minute IV infusion) ^a Leucovorin 400 mg/m ² (120-minute IV infusion) ^{a,b,c} 5-FU 400 mg/m ² IV bolus, then 5-FU 2400 mg/m ² continuous IV infusion over 46-48 hours ^a	Q2W

a Approximate infusion times

b Alternatively, 200 mg/m² levo-leucovorin (120-minute IV infusion) may be administered

c Leucovorin may be co-administered with the irinotecan infusion

d Encorafenib dosing will begin on Cycle 1 Day 1

Table 15. Treatment Regimens: Cohort 3 (Arm E)

Study Treatments	Dose	Frequency
FOLFIRI	Irinotecan 180 mg/m ² (90-minute IV infusion) ^a Leucovorin 400 mg/m ² (120-minute IV infusion) ^{a,b,c} 5-FU 400 mg/m ² IV bolus, then 5-FU 2400 mg/m ² continuous IV infusion over 46-48 hours ^a	Q2W
Bevacizumab	Bevacizumab (optional; given per prescribing instructions)	

a Approximate infusion times

b Alternatively, 200 mg/m² levo-leucovorin (120-minute IV infusion) may be administered

c Leucovorin may be co-administered with the irinotecan infusion

6.1.3. Administration

6.1.3.1. Administration of Encorafenib

Encorafenib will be administered on a QD schedule, PO as a flat-fixed dose, and not by body weight or BSA. Encorafenib should be taken without regard to food. Participants will swallow the encorafenib capsules whole, and will not manipulate (eg, open or crush) or chew the encorafenib capsules.

Participants should be instructed to take encorafenib capsules daily with a large glass of water (~250 mL) in the morning at approximately the same time every day. If a participant vomits at any time after dosing, the dose of study intervention should not be re-administered. Doses of encorafenib that are omitted for AEs or any other reason should not be made up during the day (ie, within the 12 hours of the next encorafenib dose), or at the end of the dosing period. Additional information regarding encorafenib administration can be found in

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CT02-GSOP Oncology Clinical Protocol Template (01 May 2024)

Page 95

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the IP Manual. On days when a blood collection is scheduled at the investigational site, participants will take the morning dose of encorafenib at the site under the supervision of the Investigator or designee. On all other days, participants will take encorafenib at home.

Participants must avoid consumption of grapefruit, pomegranates, star fruits, Seville oranges or products containing the juice of each during the entire study and preferably 7 days before the first dose of study intervention, due to potential CYP3A4 interaction with the study interventions. Orange juice is allowed.

When EC is combined with FOLFIRI in the SLI, the first dose of encorafenib will be administered on Cycle 1 Day 3. When encorafenib is combined with FOLFIRI in Cohort 3 Arm D, the first dose of encorafenib will be administered on Cycle 1 Day 1. When encorafenib is administered with irinotecan, encorafenib should be administered immediately prior to the start of the irinotecan infusion. On PK days in particular, it should be ensured that the encorafenib dosing occurs within 5 minutes prior to start of infusion. On all other days, encorafenib will be administered with the start of irinotecan or oxaliplatin infusion.

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

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

The Investigator or responsible site personnel should instruct the participant to take encorafenib as per protocol (promote compliance). The dosage prescribed and dispensed to the participant and all dose changes and all missed doses during the study must be recorded in the eCRF.

6.1.3.2. Administration of Capecitabine, Cetuximab, 5-Fluorouracil, Irinotecan, Leucovorin, Oxaliplatin and Bevacizumab

Capecitabine, cetuximab, 5-FU, irinotecan, leucovorin, oxaliplatin and bevacizumab are to be administered in accordance with their respective locally approved labels or local institutional standards. For detailed dosing information, see Section 6.1.2. Prior to the first cetuximab infusion, participants should receive premedication with an antihistamine and a corticosteroid at least 1 hour prior to administration.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperatures since previously documented for all site storage locations upon return to business.
3. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual.
4. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label.
5. Study interventions should be stored in their original containers.
6. Site staff will instruct participants on the proper storage requirements for take-home study intervention.
7. See the IP manual for storage conditions of the study intervention once reconstituted and/or diluted.
8. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record. All study intervention that is taken home by the participant, both used and unused, must be returned to the investigator by the participant. Returned study intervention must not be redispensed to the participants.
9. Further guidance and information for the final disposition of unused study interventions are provided in the IP manual. All destruction must be adequately

PFIZER CONFIDENTIAL

CT02-GSOP Oncology Clinical Protocol Template (01 May 2024)

Page 97

documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

Upon identification of a product complaint, notify the sponsor within 1 business day of discovery as described in the IP Manual.

6.2.1. Preparation and Dispensing

A qualified staff member will dispense the study intervention using the IRT system via unique container numbers in the bottles or vials provided, in quantities appropriate according to the [SoA](#). A second staff member will verify the dispensing. The participant/caregiver should be instructed to maintain the product in the bottles or vials, provided throughout the course of dosing and return the bottles or vials to the site at the next study visit.

See the IP manual for instructions on how to prepare the study intervention for administration. Study intervention should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance. A second staff member will verify the dispensing.

All vials are single-use.

Only qualified personnel who are familiar with procedures that minimize undue exposure to themselves and to the environment should undertake the preparation, handling, and safe disposal of chemotherapeutic agents.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

This is an open-label study; however, the specific study intervention dispensed to the participant will be assigned using an IRT. For the Phase 3 portion of the study, a randomization list stratified by ECOG (0 versus 1) and region (US/Canada versus Europe versus Rest of World) will be used. For Cohort 3 of the study, a randomization list stratified by ECOG (0 versus 1) will be used.

The site will contact the IRT prior to the start of study intervention administration for each participant. The site will record the study intervention assignment on the applicable CRF, if required. Potential bias will be reduced by central randomization and BICR evaluation of imaging data (Section [8.1.1.1](#)).

The investigator's knowledge of the treatment should not influence the decision to enroll a particular participant or affect the order in which participants are enrolled.

Study intervention will be dispensed at the study visits summarized in the [SoA](#).

Returned study intervention must not be redispensed to the participants.

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

6.4. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

The site will complete the required dosage Preparation Record located in the IP manual. The use of the Preparation Record is preferred, but it does not preclude the use of an existing appropriate clinical site documentation system. The existing clinical site's documentation system should capture all pertinent/required information on the preparation and administration of the dose. This may be used in place of the Preparation Record after approval from the sponsor and/or designee.

When participants self-administer study intervention(s) at home, compliance with study intervention will be assessed at each visit. Participants will receive a diary to document self-administered dosing of study intervention (encorafenib or capecitabine, as applicable) in each cycle to include the dose of study intervention taken, the date of dosing, if any doses were missed and the reason for the missed dose. Compliance will be assessed by direct questioning, counting returned tablets/capsules, and a review of diary entries during the site visits and documented in the source documents and eCRF. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

A record of the number of encorafenib capsules and capecitabine tablets dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions, will also be recorded in the eCRF.

6.5. Concomitant Therapy

The following subsections detail permitted and prohibited concomitant therapies for encorafenib. Guidance on concomitant therapy for all other study interventions can be found in the respective SRSDs.

6.5.1. Permitted Concomitant Medications/Therapies

In general, the use of any concomitant medication/therapies deemed necessary for the care of the participant is permitted, unless otherwise specified. Additional information regarding concomitant medications/therapies is provided in the Investigator's Brochure for encorafenib and the SRSD for all other study interventions.

Participants receiving medications outlined below must be carefully monitored for potentiating of toxicity due to any individual concomitant medication and may require dose

titration of the drug substance. Investigators should use caution when prescribing concomitant medications, as clinical experience with these compounds in participants with cancer is often limited. Investigators should contact the Sponsor when they are unsure whether a drug should be prescribed to a participant in the clinical study. All concomitant medications/therapies, transfusions, procedures and dietary supplements must be documented on the eCRF.

6.5.1.1. Surgical Resection

Participants who undergo complete resection of all metastatic disease may continue study intervention at the discretion of the Investigator and following discussion with the medical monitor.

6.5.1.2. CYP and UGT Substrates and Inhibitors

Encorafenib is a reversible inhibitor of CYP1A2, CYP2B6, CYP2C8/9, CYP2D6, CYP3A4 and UGT1A1 based on in vitro studies. It is also a time-dependent inhibitor of CYP3A4, and induced CYP1A2, CYP2B6, CYP2C9 and CYP3A4 in human hepatocytes. Permitted medications to be used with caution in this study include those that are sensitive substrates of CYP2B6, CYP2C8/9, CYP2D6, CYP3A4 and UGT1A1 or those substrates that have an NTI. Based on recently available data from an ongoing DDI study in patients, single dose encorafenib does not inhibit CYP3A at clinically used doses. Following multiple doses encorafenib plasma exposures at steady-state are lower than expected, indicating net CYP3A auto-induction.

There is a potential for encorafenib to induce CYP3A4, which may reduce the effectiveness of hormonal contraception methods. Therefore, the use of at least 1 form of non-hormonal contraception is required for females of childbearing potential during participation in this study.

Caution should be used 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.

Encorafenib has been identified to be primarily metabolized by CYP3A4 and to a lesser extent by CYP2C19 in vitro. **Concomitant use of moderate CYP3A4 inhibitors should be avoided.** If use of a moderate CYP3A4 inhibitor is unavoidable, short-term use (≤ 30 days) following discussion with the Sponsor may be permitted with an accompanying dose reduction to one-half of the encorafenib dose prior to use of the moderate CYP3A4 inhibitor. After the inhibitor has been discontinued for 3 to 5 elimination half-lives, resume the encorafenib dose that was taken prior to initiating the CYP3A4 inhibitor.

Irinotecan is subject to extensive metabolic conversion by various enzyme systems, including esterases to form the active metabolite SN-38, and UGT1A1 mediating glucuronidation of SN-38 to form the inactive glucuronide metabolite SN-38G. **Concomitant use of strong UGT1A1 inhibitors should be avoided for patients taking irinotecan.**

For tabulated CYP substrates, inhibitors and inducers to be used with caution or avoided, please consult the following open-access websites:

- <https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm>
- <https://drug-interactions.medicine.iu.edu/MainTable.aspx>

Additional information on CYP substrates, inhibitors and inducers can be found on the following subscription-based website:

- <https://www.druginteractionsolutions.org/>

6.5.1.3. Transporter Substrates and Inhibitors

Encorafenib is a BCRP and P-gp inhibitor as well as a potent inhibitor of the renal transporters, OAT1, OAT3 and OCT2, and the hepatic transporters OATP1B1 and OATP1B3.

The co-administration of drugs that are known to be sensitive or NTI substrates of BCRP, P-gp, OAT1, OAT3, OCT2, OATP1B1 and OATP1B3 should be used with caution. Dose reductions of drugs that are substrates of OATP1B1, OATP1B3, or BCRP may be required when used concomitantly with encorafenib.

For tabulated transporter substrates, inhibitors and inducers to be used with caution or avoided, please consult with the FDA website:

- <https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm>

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

Investigators should use caution when administering encorafenib or oxaliplatin with concomitant medications with a known, conditional or possible risk to prolong the QT interval and/or induce TdP. Participants receiving such medications must be carefully monitored for potentiating of toxicity due to any individual concomitant medication and may require dose titration of the concomitant medication. See the CredibleMeds® website:

- <https://crediblemeds.org/>

6.5.2. Prohibited Concomitant Therapy

The following therapies are prohibited while participants are receiving study intervention (unless otherwise noted):

- Additional systemic anticancer agents such as cytotoxic chemotherapy, small-molecule targeted agents, biological agents, immune response modifiers or hormonal therapy.

- Investigational drugs, vaccines and devices.
Note: COVID-19 vaccines that are fully approved, approved under an emergency use authorization or are conditionally approved are considered allowed concomitant medications and standard AE collection and reporting processes should be followed. The timing of vaccine dosing relative to the dosing of study medication is at the discretion of the investigator although, should be avoided on the first day of study medication dosing and/or during the DLT observation period, if applicable.

Note: When considering administration of live vaccines within 30 days before the first dose of study intervention, during, and within 90 days after the last dose of study intervention, the investigator should evaluate the benefits and risks for each individual patient, taking into account the administered regimen and the potential risks in immunocompromised patients.

- Radiation therapy (not including palliative radiotherapy at focal sites that covers $\leq 10\%$ of the bone marrow reserve)
Note: The participant must have clear measurable disease outside the radiated field.
Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be considered on a case-by-case basis after consultation with the medical monitor.
Note: Administration of palliative radiation therapy may be considered clinical progression for the purposes of determining PFS if accompanied by radiologic progression.

- Concomitant strong systemic CYP3A4 inhibitors, which could significantly increase the exposure of encorafenib and irinotecan.

For tabulated prohibited CYP substrates, inhibitors and inducers, please consult the following open-access websites:

- <https://www.fda.gov/drugs/developmentapprovalprocess/developmentresource/druginteractionslabeling/ucm093664.htm>
- <https://drug-interactions.medicine.iu.edu/MainTable.aspx>

Additional information on CYP substrates, inhibitors and inducers can be found on the following subscription-based website:

- <https://www.druginteractionsolutions.org/>
- Concomitant moderate or strong systemic CYP3A4 inducers, which could significantly decrease the exposure of encorafenib and irinotecan.

6.5.3. Premedication and Concurrent Medication

6.5.3.1. Premedication for Cetuximab Administration

All participants in the SLI, those in Arm A and Arm B of the Phase 3 portion, and those in Arm D of Cohort 3 must be premedicated in accordance with the cetuximab SRSD prior to the first dose of cetuximab in an effort to prevent an infusion or hypersensitivity reaction. Premedication is recommended prior to subsequent doses, but at the investigator's discretion.

6.5.3.2. Loperamide

For symptoms of diarrhea and/or abdominal cramping, participants should be instructed to begin taking loperamide per the investigator's discretion. It is generally recommended that loperamide be started at the earliest sign of (1) a poorly formed or loose stool or (2) the occurrence of 1 to 2 more bowel movements than usual in 1 day or (3) an increase in stool volume or liquidity.

The loperamide is to be sourced locally and participants should have sufficient supply on hand prior to their initial dose in case antidiarrheal support is required. Additional antidiarrheal measures may be used at the discretion of the treating physician. Participants should be instructed to increase fluid intake to help maintain fluid and electrolyte balance during episodes of diarrhea.

6.5.3.3. Antibiotics

Oral fluoroquinolone treatment should be considered for any of the following:

- Diarrhea persisting for more than 24 hours despite loperamide
- ANC <500 (even in the absence of diarrhea or fever)
- Fever with diarrhea (even in the absence of neutropenia)
- Antibiotic therapy should also be considered in participants who are hospitalized with prolonged diarrhea (even in the absence of neutropenia)

6.5.3.4. Atropine

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, 0.25-1.0 mg IV or SC may be used to treat these symptoms. In participants with troublesome or recurrent symptoms, prophylactic administration of atropine shortly before irinotecan therapy may be considered. Additional antidiarrheal measures may be used at the discretion of the treating physician. Combination anticholinergic medications containing barbiturates or other agents (eg, Donnatal®) should not be used because these may affect irinotecan metabolism. Anticholinergics should be used with caution in participants with potential contraindications (eg, obstructive uropathy, glaucoma, tachycardia, etc).

6.5.3.5. Hematopoietic Growth Factors

Hematopoietic growth factors (e.g., erythropoietin, granulocyte colony-stimulating factor [G-CSF] and granulocyte-macrophage colony stimulating factor [GM-CSF], such as Nivestym and Nyvepria) are not to be administered prior to first dose of study treatment. Use of these drugs after the first dose of study intervention, is permitted at the Investigator's discretion and should be reserved for participants requiring this therapy as per the labeling of these agents or as dictated by local practice (see also the ASCO guidelines).⁷⁸

6.5.3.6. Antiemetics

The following antiemetics are allowed, but should be used with caution when administered with encorafenib as they may affect encorafenib exposure.

- NK1 receptor antagonists rolapitant and fosaprepitant (weak CYP3A4 inhibitors) with no modification to encorafenib dosing
- Aprepitant PO (moderate CYP3A4 inhibitor) is allowed in participants but encorafenib should be reduced for 3-5 half-lives
 - Reduce encorafenib to 150 mg QD (50% reduction) when co-administered with aprepitant PO.
 - Washout period is 2 days after last dose of aprepitant PO (3 half-lives).
 - Encorafenib may be restarted at 300 mg QD on third day after last dose of aprepitant.
- Dexamethasone (weak CYP3A4 inducer) as 2-20 mg with short-term or intermittent use

6.6. Dose Modification

Cycles will consist of 21 days in participants receiving CAPOX (with or without bevacizumab) in the Control Arm and will be 28 days in duration for all other participants. In the SLI, Arm A, Arm B and Cohort 3 Arm D, Day 1 of a cycle is defined by administration of cetuximab and any component of the chemotherapy regimen, and in the Phase 3 Control Arm C and Cohort 3 Arm E by administration of any component of the chemotherapy regimen.

For participants in the SLI, those in Arm B and the Control Arm of the Phase 3 portion, and in Cohort 3, it is recommended that Day 1 of a cycle may not begin until the ANC is $\geq 1500/\text{mm}^3$, the platelet count is $\geq 100,000/\text{mm}^3$, and any treatment-related GI toxicity has resolved to \leq Grade 1 or according to Investigator's clinical judgement. Participants in the SLI, Arm B of the Phase 3 portion and Cohort 3 Arm D may continue daily encorafenib, however dosing with cetuximab should not be administered until Week 1 of the next cycle along with chemotherapy.

Participants will be monitored for AEs on an ongoing basis. If the participant develops a toxicity, the dose may be modified as outlined in the following sections. All dose modifications should be based on the worst preceding toxicity. All dosing interruptions and modifications must be recorded in the eCRF.

If assessment of the toxicity can be clearly attributed to a single study intervention, administration of the offending drug should be modified and the toxicity should be followed until resolution or return to baseline according to the respective dose modification guidelines described in the following sections. Treatment with the other agents in the combination may continue without alterations. In the instance of cetuximab infusion reaction on Cycle 1 Day 1,

administration with the remaining study drugs may begin once toxicity resolves and at the Investigator's discretion.

If attribution of the toxicity cannot be clearly ascribed to a single study intervention, then all agents should be evaluated as to attribution and dose modifications for each individual agent should be assessed according to the tables below. The toxicity should be followed until resolution or return to baseline.

If the toxicity recurs after a dose reduction, the process outlined above should be followed once again to determine attribution to a single study intervention or to all agents.

6.6.1. Dose Modifications for Encorafenib

The recommended dose reductions for encorafenib are presented in Table 16. Dose reductions beyond the second dose reduction are not allowed for encorafenib. Once a dose has been reduced for a given participant, all subsequent doses should be administered at that dose level unless further dose reduction is required or dose is re-escalated. Encorafenib may be re-escalated by a maximum of 1 dose level (and not higher than the starting dose) when the AE that resulted in an encorafenib dose reduction resolves or improves to and remains stable to the participant's baseline for a minimum of 14 days, and provided there are no safety concerns or other concomitant toxicities that would prevent encorafenib re-escalation. There is no limit to the number of times a participant can have their dose of encorafenib reduced or re-escalated; however:

- No dose re-escalation of encorafenib is allowed after a dose reduction due to prolonged QTcF ≥ 500 msec
- No dose re-escalation of encorafenib is allowed after a dose reduction due to retinal toxicity Grade ≥ 2 .

Administration of encorafenib as a single agent is not recommended; if cetuximab is permanently discontinued in Arm A in the Phase 3 portion of the study, permanently discontinue encorafenib.

In the SLI, Phase 3 Arm B portion of the study and Cohort 3 Arm D, if encorafenib is permanently discontinued, cetuximab must also be permanently discontinued; however, therapy with the chemotherapy regimen may continue.

Table 16. Recommended Encorafenib Dose Reductions

Dose Level	Encorafenib Dose
First Dose Reduction	225 mg orally QD
Second Dose Reduction	150 mg orally QD

The recommended dose modifications for encorafenib are presented in Table 17 and are based on the existing dose modification guidelines provided in the current USPI for encorafenib.³⁷

Table 17. Recommended Encorafenib Dose Modifications

Severity of Adverse Reaction ^a	Dose Modification for Encorafenib
<i>New Primary Malignancies</i>	
Cutaneous (SCC, KA and any Other Suspicious Skin Lesion)	Maintain dose of encorafenib (dose interruptions or modifications are not required). Treatment of SCC, KA, and any other suspicious skin lesion (eg, new primary melanoma) should occur based upon institutional practice.
Non-cutaneous <i>RAS</i> mutation-positive malignancies	Permanently discontinue encorafenib.
<i>Uveitis</i>	
Grade 1-3	<p>Grade 1 or 2 uveitis does not respond to specific (eg, topical) ocular therapy, or for Grade 3 uveitis, hold encorafenib for up to 6 weeks and repeat ophthalmic examination within 2 weeks.</p> <ul style="list-style-type: none"> • If Grade 1 uveitis improves to Grade 0, resume at same dose. • If Grade 2 or 3 uveitis improves to Grade 0 or 1, resume at reduced dose. • If not improved, permanently discontinue encorafenib.
Grade 4	Permanently discontinue encorafenib
<i>QTcF Prolongation</i>	
QTcF >500 ms and ≤60 ms increase from baseline	<p>Patients 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 (eg, congestive heart failure, bradyarrhythmias) should be controlled.</p> <ul style="list-style-type: none"> • Hold encorafenib until QTcF ≤500 ms. Resume at reduced dose. • If more than one recurrence, permanently discontinue encorafenib.
QTcF >500 ms and >60 ms increase from baseline	<p>Patients 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.</p> <ul style="list-style-type: none"> • Permanently discontinue encorafenib.

Table 17. Recommended Encorafenib Dose Modifications

Severity of Adverse Reaction ^a	Dose Modification for Encorafenib
Hepatotoxicity	
Grade 2 AST or ALT increased	<p>Maintain encorafenib dose.</p> <ul style="list-style-type: none"> If no improvement within 4 weeks, hold encorafenib until improves to Grade 0-1 or to pre-treatment/baseline levels and then resume at same dose.
Grade 3 or 4 AST or ALT increased	see <i>Other Adverse Reactions</i> .
Rash	
Grade 1	<p>Maintain dose level of encorafenib.</p> <p>Initiate rash treatment per institutional standards; rash should be closely monitored.</p>
Grade 2	<p>1st occurrence:</p> <ul style="list-style-type: none"> Maintain dose level of encorafenib Initiate rash treatment per institutional standards; 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 treatment 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 <p>2nd occurrence:</p> <ul style="list-style-type: none"> Reassess within ≤14 days. If rash worsens or does not improve, interrupt dosing of encorafenib until resolved to Grade ≤1. Then resume treatment at current dose level of encorafenib. For dermatitis acneiform rash, treatment with encorafenib may be maintained if, in the judgment of the investigator, the rash is considered to be unrelated to encorafenib. If treatment with encorafenib was maintained and no improvement within 8 days, interrupt dosing of encorafenib

Table 17. Recommended Encorafenib Dose Modifications

Severity of Adverse Reaction ^a	Dose Modification for Encorafenib
Grade 3	<p>1st occurrence:</p> <ul style="list-style-type: none"> 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. <p>2nd occurrence:</p> <ul style="list-style-type: none"> Interrupt dosing of encorafenib until resolved to Grade ≤1. Then resume treatment at 1 reduced dose level of encorafenib. Resume treatment with encorafenib at the same dose level if, in the judgment of the Investigator, the rash is considered to be unrelated to encorafenib Consider referral to dermatologist and manage rash per dermatologist's recommendation
Grade 4	Permanently discontinue encorafenib.
<i>Nausea/Vomiting</i>	
Grade 1-2	Maintain dose level of encorafenib. Promptly institute antiemetic measure.
Grade 3	<p>Interrupt dosing of encorafenib until resolved to Grade ≤1. Then resume treatment at 1 reduced dose level of encorafenib.</p> <p>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 (as per local practice)</p>
Grade 4	Permanently discontinue encorafenib.
<i>Other Adverse Reactions (including Hemorrhage)</i>	
Recurrent Grade 2 OR First occurrence of any Grade 3	<p>Hold encorafenib for up to 4 weeks.</p> <ul style="list-style-type: none"> If improves to Grade 0-1 or to pretreatment/baseline level, resume at reduced dose. If no improvement, permanently discontinue encorafenib.
First occurrence of any Grade 4	<p>Permanently discontinue encorafenib</p> <p>Hold encorafenib for up to 4 weeks.</p> <ul style="list-style-type: none"> If improved to Grade 0-1 or to pretreatment/baseline level, then resume at reduced dose. If no improvement, permanently discontinue encorafenib.
Recurrent Grade 3	Consider permanently discontinuing encorafenib.
Recurrent Grade 4	Permanently discontinue encorafenib.

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6.6.2. Dose Modifications for Cetuximab

The recommended dose reductions for cetuximab are presented in Table 18.

Cetuximab may be reduced 2 dose levels to a minimum of 300 mg/m² for AEs or laboratory abnormalities ([Appendix 3](#)). Dose reductions beyond the second dose reduction are not allowed for cetuximab. When a dose reduction is required because of an AE, no subsequent dose re-escalation of cetuximab will be permitted for that participant for the duration of study treatment. If after resolution of an AE, treatment is resumed at the same dose, and the same toxicity reoccurs with the same severity, any re-initiation of treatment must be at the next lower dose level irrespective of duration, with some exceptions for skin toxicity. In addition, a participant must permanently discontinue cetuximab if, after treatment is resumed at a lower dose of cetuximab, the same toxicity reoccurs with the same or worse severity.

Administration of cetuximab as a single agent is not recommended; if encorafenib is permanently discontinued in the SLI, Phase 3 Arm A, Phase 3 Arm B, and Cohort 3 Arm D portions of the study, cetuximab must also be permanently discontinued; however, therapy with the chemotherapy regimen may continue.

Table 18. Recommended Cetuximab Dose Reductions

Dose Level	Cetuximab Dose
First Dose Reduction	400 mg/m ² Q2W
Second Dose Reduction	300 mg/m ² Q2W

Recommended dose modifications for cetuximab based on the occurrence of cetuximab treatment-related AEs are summarized in Table 19. Please always refer to the locally approved product label for any adverse reaction not specifically mentioned in the table and for the most updated recommendations.

Table 19. Recommended Dose Modifications for Cetuximab related Adverse Events

Severity of Adverse Event ^a	Dose Modification for Cetuximab During a Cycle of Therapy
Hypomagnesemia	Hypomagnesemia has been seen with cetuximab. Should hypomagnesemia occur, magnesium supplementation should be provided. No dose adjustment is required; however, continue careful monitoring.
Infusion Reaction: <i>If an infusion reaction occurs while cetuximab is being infused, the infusion should be stopped immediately and the participant should be evaluated.</i>	
Grade 1 or 2	Restart and complete the disrupted infusion at the discretion of the Investigator. The infusion must be restarted at a reduced rate. Additional pre-medications such as antihistamines or low-dose systemic corticosteroids may be administered when the infusion is restarted per institutional standards. All subsequent infusions must also be administered at the reduced rate.
Grade 3 or 4	Permanently discontinue cetuximab

Table 19. Recommended Dose Modifications for Cetuximab related Adverse Events

Severity of Adverse Event ^a	Dose Modification for Cetuximab During a Cycle of Therapy
<i>Pulmonary toxicities</i>	
Grade 2 or worsening pulmonary symptoms	Cetuximab therapy should be stopped and symptoms investigated. Cetuximab therapy may resume when symptoms resolve to ≤Grade 1
Grade 3 cough, dyspnea, hypoxia, pneumonitis, or pulmonary infiltrates	Hold cetuximab until interstitial lung disease is ruled out. Permanently discontinue cetuximab if interstitial lung disease is confirmed
<i>Rash</i>	
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	Hold cetuximab until resolved to ≤Grade 2, then: <ul style="list-style-type: none"> • 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	Hold cetuximab until resolved to ≤Grade 2, then: <ul style="list-style-type: none"> • If resolved in ≤7 days (or ≤14 days for acneiform rash), then decrease 1 dose level • If not resolved in ≤7 days despite appropriate skin toxicity therapy (or ≤14 days for acneiform rash), then permanently discontinue cetuximab • Permanently discontinue cetuximab after 3rd recurrence (upon 4th occurrence)
Grade 4, despite skin toxicity therapy	Permanently discontinue cetuximab

^a NCI CTCAE version 4.03

6.6.3. Dose Modifications for Oxaliplatin, Irinotecan, 5-FU and Capecitabine as Part of mFOLFOX6, FOLFIRI, FOLFOXIRI and CAPOX Regimens

The recommended dose reductions for oxaliplatin, irinotecan, 5-FU and capecitabine are presented in, [Table 20](#), [Table 21](#) and [Table 22](#). These recommended dose adjustments for each agent are based on the specific types of toxicities observed and on Investigator judgment of each participant's benefit/risk ratio. Participants who require multiple dose reductions consecutively for Grade 2 toxicity may, at the investigator's discretion, and based on the duration and reversibility of the toxicity, begin the following dose at one dose level higher than the current reduced dose level.

Additional guidance on the recommended dose reductions are as follows:

- Only those agents specified in the table below should be dose reduced.
- Dose reductions beyond the third dose reduction are not allowed for oxaliplatin, irinotecan or 5-FU or beyond the second dose reduction of capecitabine.
- No dose modifications are implemented for leucovorin. If 5-FU is held or omitted, then leucovorin should also be held or omitted, accordingly.
- In the SLI, Arm B in the Phase 3 portion of the study and Arm D of Cohort 3, if oxaliplatin or irinotecan are permanently discontinued, therapy with 5-FU, encorafenib and cetuximab may continue.
- In the SLI, Arm B in the Phase 3 portion of the study and Arm D of Cohort 3, if cetuximab is permanently discontinued, encorafenib may be continued in combination with the chemotherapy regimen.
- In the SLI and Arm B of the Phase 3 portion of the study, if only part of the mFOLFOX6 regimen is permanently discontinued, therapy with the remaining chemotherapy, encorafenib and cetuximab, may continue.
- In the SLI and Arm B of the Phase 3 portion of the study, if the entire regimen of mFOLFOX6 is permanently discontinued, therapy with encorafenib and cetuximab may continue.
- In the SLI and Arm B of the Phase 3 portion of the study, if the entire regimen of mFOLFOX6 and cetuximab are permanently discontinued, encorafenib also needs to be discontinued.
- In the Phase 3 Control Arm C and Cohort 3 Arm E, if only part of the chemotherapy regimen is permanently discontinued, therapy with the remaining chemotherapy regimen may continue.

Table 20. Recommended Dose Reductions for Oxaliplatin, Irinotecan and 5-FU as Part of mFOLFOX6 (SLI participants, Phase 3 Arm B and Arm C [Control]), and FOLFIRI (in SLI and Cohort 3 Arm D and Arm E)

Dose Level	Oxaliplatin	Irinotecan	5-FU Bolus	5-FU Infusion
First Dose Reduction	65 mg/m ²	150 mg/m ²	200 mg/m ²	1920 mg/m ² per 46-48 h
Second Dose Reduction	50 mg/m ²	120 mg/m ²	Omit	1600 mg/m ² per 46-48 h
Third Dose Reduction	40 mg/m ²	100 mg/m ²	Omit	1360 mg/m ² per 46-48 h

Table 21. Recommended Dose Reductions for Oxaliplatin, Irinotecan and 5-FU as Part of FOLFOXIRI (Phase 3 Arm C [Control Arm])

Dose Level	Oxaliplatin	Irinotecan	5-FU Infusion (Starting dose 2400 mg/m ²)	5-FU Infusion (Starting dose 3200 mg/m ²)
First Dose Reduction	65 mg/m ²	130 mg/m ²	1920 mg/m ²	2560 mg/m ²
Second Dose Reduction	50 mg/m ²	100 mg/m ²	1600 mg/m ²	2100 mg/m ²
Third Dose Reduction	40 mg/m ²	80 mg/m ²	1360 mg/m ²	1720 mg/m ²

Table 22. Recommended Dose Reductions for Oxaliplatin and Capecitabine as Part of CAPOX (Phase 3 Control Arm)

Dose Level	Oxaliplatin	Capecitabine
First Dose Reduction	100 mg/m ²	750 mg/m ²
Second Dose Reduction	80 mg/m ²	500 mg/m ²
Third Dose Reduction	65 mg/m ²	Omit

Recommended dose modifications for oxaliplatin, irinotecan, and 5-FU based on the occurrence of mFOLFOX6, FOLFIRI and FOLFOXIRI treatment-related AEs are summarized in Table 23. Please also refer to the locally approved product label for any adverse reaction not specifically mentioned in the table and for the most updated recommendations regarding dose modifications for individual chemotherapeutic agents, which may vary according to individual product labels.

Table 23. Recommended Oxaliplatin, Irinotecan and 5-FU Dose Modifications

Severity of Adverse Reaction ^a	Recommended Dose Modifications
<i>Hematologic toxicities</i>	
Grade 2 neutropenia or thrombocytopenia	<ul style="list-style-type: none"> Reduce 5-FU bolus one dose level with or without reducing 5-FU infusion Consider reducing or discontinuing 5-FU bolus before reducing 5-FU infusion Consider reducing either oxaliplatin or irinotecan one dose level For recurrence: <ul style="list-style-type: none"> Consider discontinuing 5-FU bolus

Table 23. Recommended Oxaliplatin, Irinotecan and 5-FU Dose Modifications

Severity of Adverse Reaction ^a	Recommended Dose Modifications
Grade 3 or 4 neutropenia or thrombocytopenia	<p>Hold 5-FU (bolus and infusion) and either oxaliplatin or irinotecan</p> <ul style="list-style-type: none"> • If counts recover to ANC ≥ 1500 and platelets $\geq 75,000$: <ul style="list-style-type: none"> ○ Permanently discontinue 5-FU bolus ○ Resume 5-FU infusion ○ Resume either oxaliplatin or irinotecan at one lower dose level ○ Administer G-CSF at the investigator's discretion ○ Held doses will not be made up
Febrile neutropenia (defined as ANC < 1000 and $T \geq 38.5^{\circ}\text{C}$)	<ul style="list-style-type: none"> • Hold 5-FU (bolus and infusion) and either oxaliplatin or irinotecan • If fever and neutropenia resolve (ANC ≥ 1500 and platelets $\geq 75,000$): <ul style="list-style-type: none"> ○ Permanently discontinue 5-FU bolus ○ Resume 5-FU infusion and either oxaliplatin or irinotecan at one lower dose level ○ Administer G-CSF at the investigator's discretion ○ Held doses will not be made up
<i>Gastrointestinal toxicities</i>	
<p>For symptoms of diarrhea and/or abdominal cramping, participants should be instructed to begin taking loperamide as described in Section 6.5.3.2. In some instances, treatment with oral fluoroquinolone and/or atropine may be appropriate as described in Section 6.5.3.3 and Section 6.5.3.4, respectively. For severe reactions during the first cycle of treatment, a DPD deficiency may be involved; testing for DPD deficiency may be considered.</p>	
Grade 2 diarrhea following maximal medical intervention	Reduce 5-FU (bolus and/or infusion) and irinotecan one dose level
Grade 3 or 4 diarrhea	<ul style="list-style-type: none"> • Hold 5-FU (bolus and infusion) and either oxaliplatin or irinotecan • If diarrhea resolves to \leq Grade 2, resume 5-FU (bolus and infusion) and either oxaliplatin or irinotecan at one lower dose level • Held doses will not be made up
Grade 2 mucositis	<ul style="list-style-type: none"> • Reduce 5-FU bolus one dose level with or without reducing 5-FU infusion

Table 23. Recommended Oxaliplatin, Irinotecan and 5-FU Dose Modifications

Severity of Adverse Reaction ^a	Recommended Dose Modifications
Grade 3 mucositis	<ul style="list-style-type: none"> Hold 5-FU (bolus and infusion) and either oxaliplatin or irinotecan If mucositis resolves to ≤Grade 2: <ul style="list-style-type: none"> Permanently discontinue 5-FU bolus Resume 5-FU infusion and either oxaliplatin or irinotecan at one lower dose level Held doses will not be made up
Grade 4 mucositis	<ul style="list-style-type: none"> Hold all study treatment If mucositis resolves to ≤Grade 2: <ul style="list-style-type: none"> Permanently discontinue 5-FU bolus Resume 5-FU infusion at two lower dose levels Resume either oxaliplatin or irinotecan at one lower dose level Resume encorafenib, bevacizumab and/or cetuximab at the prior dose Held doses will not be made up
Grade 3 nausea or vomiting	If they persist/occur despite two treatments with adequate (combination) antiemetic therapy, reduce oxaliplatin or irinotecan one dose level for the remainder of study treatment
Grade 4 vomiting	If they persist/occur despite two treatments with adequate (combination) antiemetic therapy, reduce 5-FU (bolus and/or infusion) and either oxaliplatin or irinotecan one dose level for the remainder of study treatment
<i>Pulmonary toxicities</i>	
Grade 3 cough, dyspnea, hypoxia, pneumonitis, or pulmonary infiltrates	<ul style="list-style-type: none"> Hold oxaliplatin and bevacizumab (and cetuximab) until interstitial lung disease is ruled out Continue 5-FU (bolus and infusion) Permanently discontinue all protocol therapy if symptomatic, clinically relevant interstitial lung disease is confirmed
<i>Neurotoxicities</i>	
Grade 2 Paresthesias/dysesthesias	For Grade 2 neurotoxicity <i>persisting</i> between treatments: <ul style="list-style-type: none"> Consider reducing oxaliplatin by one dose level Participants should continue to receive other protocol therapy

Table 23. Recommended Oxaliplatin, Irinotecan and 5-FU Dose Modifications

Severity of Adverse Reaction ^a	Recommended Dose Modifications
Grade 3 Paresthesias/dysesthesias	<p>For Grade 3 neurotoxicity resolving to ≤Grade 2 between treatments:</p> <ul style="list-style-type: none"> Reduce oxaliplatin by one dose level If further dose reduction is required for neurotoxicity beyond the third dose reduction of oxaliplatin, permanently discontinue oxaliplatin Participants should continue to receive other protocol therapy <p>For Grade 3 neurotoxicity <i>persisting</i> between treatments:</p> <ul style="list-style-type: none"> Permanently discontinue oxaliplatin Participants should continue to receive other protocol therapy
Grade 4 Paresthesias/dysesthesias	<ul style="list-style-type: none"> Permanently discontinue oxaliplatin Participants should continue to receive other protocol therapy
Pharyngo-laryngeal dysesthesia	<ul style="list-style-type: none"> Increase the duration of oxaliplatin infusion up to 6 hours for all subsequent treatments Monitor oxygen saturation via a pulse oximeter; if normal, an anxiolytic agent may be given and observe the participant in the clinic until the episode has resolved Once resolved, continue protocol therapy if appropriate
Extravasation	<ul style="list-style-type: none"> Extravasation of oxaliplatin has been associated with necrosis. Stop oxaliplatin infusion and administer at another site Treat extravasation according to institutional guidelines
Cardiovascular toxicities	
Grade 4 or recurrent/worsening venous thromboembolic events (including pulmonary embolism) - OR- Grade 3 cardiac ischemia/infarction - OR- Grade 4 arterial thrombotic event - OR- Grade 4 LV dysfunction	Discontinue all protocol therapy including encorafenib and cetuximab. Re-initiation of any study treatment should be based on Investigator judgement and following discussion with the Sponsor.

Table 23. Recommended Oxaliplatin, Irinotecan and 5-FU Dose Modifications

Severity of Adverse Reaction ^a	Recommended Dose Modifications
QTcF >500 ms	<ul style="list-style-type: none"> Perform regular ECG monitoring (continuous where appropriate) until an adequately trained physician (such as a cardiologist or internist) has reviewed the data Correct electrolyte abnormalities (including magnesium) and control cardiac risk factors for QT prolongation (e.g, congestive heart failure, bradyarrhythmias) Permanently discontinue oxaliplatin
<i>Hypersensitivity reactions</i>	
Grade 1	<ul style="list-style-type: none"> Decrease the infusion rate of the suspect agent by 50% until symptoms resolve, then resume at the initial planned rate
Grade 2	<ul style="list-style-type: none"> Stop infusion of the suspect agent Administer H₁ and/or H₂ blockers, and/or steroids according to institutional policy In case of anaphylactic manifestations, permanently discontinue oxaliplatin and notify the Sponsor Restart other infusions when symptoms resolve and pretreat before all subsequent doses
Grade 3 or 4	<ul style="list-style-type: none"> Stop infusion of the suspect agent Permanently discontinue the suspect agent and notify the Sponsor
<i>Other AEs</i>	
≥Grade 3	<ul style="list-style-type: none"> Hold 5-FU (bolus and infusion) and either oxaliplatin or irinotecan Monitor toxicity at least weekly; if toxicity resolves to ≤Grade 1 within 4 weeks, resume treatment at one lower dose level Consider reducing or discontinuing 5-FU bolus before reducing 5-FU infusion dose

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Recommended dose modifications for capecitabine treatment-related AEs are summarized in [Table 24](#). Please always refer to the locally approved product label for any adverse reaction not specifically mentioned in the table and for the most updated recommendations. In the Phase 3 Control Arm, if capecitabine is discontinued from the CAPOX regimen, treatment with oxaliplatin may continue.

Table 24. Recommended Capecitabine Dose Modifications

Toxicity NCIC Grades	During a Course of Therapy
Grade 1	Maintain dose level
Grade 2	
1 st occurrence	Interrupt until resolved to Grade 0-1; resume treatment at original dose level
2 nd occurrence	Interrupt until resolved to Grade 0-1, resume treatment at one lower dose level
3 rd occurrence	Interrupt until resolved to Grade 0-1, resume treatment at two lower dose levels
4 th occurrence	Discontinue treatment permanently
Grade 3	
1 st occurrence	Interrupt until resolved to Grade 0-1, resume treatment at one lower dose level
2 nd occurrence	Interrupt until resolved to Grade 0-1, resume treatment at two lower dose levels
3 rd occurrence	Discontinue treatment permanently
Grade 4	
1 st occurrence	Discontinue permanently <i>OR</i> If investigator deems it to be in the participant's best interest to continue, interrupt until resolved to Grade 0-1, resume treatment at two lower dose levels
2 nd occurrence	Discontinue permanently

6.6.4. Dose Modifications for Bevacizumab

No dose reductions for bevacizumab are recommended. Participants with colon or rectal stents should not receive bevacizumab due to increased risk of perforation.

For participants for whom elective surgery is contemplated, bevacizumab is to be discontinued for at least 8 weeks prior to surgery. Bevacizumab may be resumed after at least 4 weeks following surgery. These participants should also discontinue aspirin at least 1 week prior to surgery.

For patients for whom non-elective surgery is required, hold bevacizumab as long as possible prior to surgery and for at least 6 weeks following surgery. Other protocol treatment may be given while bevacizumab is held at the discretion of the treating physician.

Recommended dose modifications for bevacizumab based on the occurrence of bevacizumab treatment-related AEs are summarized in [Table 25](#). Please always refer to the locally approved product label for any adverse reaction not specifically mentioned in the table and for the most updated recommendations.

Table 25. Recommended Bevacizumab Dose Modifications

Severity of Adverse Reaction ^a	Dose Modification for Bevacizumab
Infusion Reactions	
If a reaction occurs, the infusion should be discontinued and appropriate medical therapies should be administered. Systemic premedication is not warranted.	
Reversible Posterior Leukoencephalopathy Syndrome (RPLS)	
For signs and symptoms suggestive of RPLS (eg, confusion, headache, seizures, cortical blindness) interrupt bevacizumab. Suspected RPLS should be investigated with MRI. If diagnosis of RPLS is confirmed, bevacizumab should be permanently discontinued.	
Grade 3	If RPLS is ruled out via MRI, the decision on resuming bevacizumab should be based on the nature of the signs/symptoms. For grade 3 events, bevacizumab may be resumed if toxicities completely resolve within 4 weeks.
Grade 4	If RPLS is ruled out via MRI, the decision on resuming bevacizumab should be based on the nature of the signs/symptoms. For grade 4 events with likely relationship to bevacizumab, discontinue bevacizumab.
Hypertension	
Grade 3	Hold bevacizumab if not controlled with medical management; resume once controlled. Consider administering the following antihypertensive therapies in order of preference: calcium antagonists, ACE inhibitors, diuretics, and beta-blockers
Grade 4	Permanently discontinue bevacizumab
Wound Healing Complications	
Wound healing complications requiring medical intervention	Permanently discontinue bevacizumab
Necrotizing fasciitis	Permanently discontinue bevacizumab
Posterior Reversible Encephalopathy Syndrome (PRES)	
Any Grade	Permanently discontinue bevacizumab
Hemorrhage	
Grade ≥2 pulmonary or CNS	Permanently discontinue bevacizumab
Grade 3 or 4 non-pulmonary and non-CNS	Permanently discontinue bevacizumab

Table 25. Recommended Bevacizumab Dose Modifications

Severity of Adverse Reaction ^a	Dose Modification for Bevacizumab
<i>Venous thrombosis</i>	
Grade 3 or 4	Permanently discontinue bevacizumab
<i>Arterial thromboembolic event</i>	
Any Grade	Permanently discontinue bevacizumab
<i>Congestive heart failure</i>	
Symptomatic or NYHA Class ≥2 heart failure	Permanently discontinue bevacizumab
<i>Renal Injury and Proteinuria</i>	
Nephrotic syndrome	Permanently discontinue bevacizumab
<i>GI perforation</i>	
Any Grade	Permanently discontinue bevacizumab
<i>Bowel obstruction</i>	
Grade 1	Participants who experience partial obstruction not requiring medical intervention may continue on bevacizumab
Grade 2	Hold bevacizumab in participants who experience partial obstruction requiring medical intervention. Resume upon complete resolution
Grade 3/4	Permanently discontinue bevacizumab
Wound dehiscence	Permanently discontinue bevacizumab
<i>Pulmonary toxicities</i>	
Grade 3 cough, dyspnea, hypoxia, pneumonitis, or pulmonary infiltrates	Hold bevacizumab until interstitial lung disease is ruled out. Permanently discontinue bevacizumab if interstitial lung disease is confirmed
<i>Other unspecified bevacizumab-related adverse events</i>	
Grade 3	Hold bevacizumab until recovery to ≤Grade 1
Grade 4	Permanently discontinue bevacizumab

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6.6.5. Guidance For Administration of Study Intervention in Participants with SARS-CoV-2 Infection

Each individual participants case is unique and decisions surrounding study intervention should be based on the investigator's clinical judgement and in accordance with local and regional recommendations. The following modifications are general suggestions for participants with active SARS-CoV-2 infection including those that are confirmed positive based on a locally approved test or presumed positive based on clinical suspicion:

- In participants with active infection and symptoms, consider delaying study intervention for at least 14 days from start of symptoms.
- Consider restarting treatment when SARS-CoV-2-associated symptoms have recovered to \leq Grade 1 for ≥ 72 hours and participant has been afebrile for ≥ 72 hours

Additional guidance is provided in [Appendix 12](#).

6.7. Intervention After the End of the Study

At the end of the study, any participants who are still deriving clinical benefit from study intervention, Sponsor will work with investigator to explore options for continued study intervention (eg, continuation study), in accordance with local regulations and requirements.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue study intervention (definitive discontinuation). Reasons for definitive discontinuation of study intervention include the following:

- Withdrawal of consent/assent. Participants may choose to withdraw from the study at any time without penalty of jeopardizing their healthcare or loss of benefits to which the participant is otherwise entitled. Participants will have the option of withdrawing consent/assent for study treatment but continue in the follow-up period of the study for safety/efficacy assessments. See Section [7.2.1](#).
- Unacceptable AEs or failure to tolerate study intervention defined as:
 - Grade 4 or life-threatening AE as outlined in [Appendix 3](#), (except with approval from the medical monitor);
 - Toxicity requiring more than the allowed number of dose reductions for any study intervention as described in Section [6.6](#);

- Occurrence of an AE that is related to study treatment and in the judgment of the Investigator compromises the participant's ability to continue study-specific procedures, or is considered to not be in the participant's best interest.
- Dose interruption due to an AE or clinically significant laboratory abnormality, unless judged by the Investigator and medical monitor or designee to be in the best interest of the participant to continue treatment, as follows:
 - Encorafenib: Dose interruption >28 consecutive days;
 - Cetuximab: >2 missed consecutive doses of cetuximab;
 - mFOLFOX6/FOLFIRI/FOLFOXIRI: If the initiation of a new cycle or therapy during a cycle is delayed for ≥ 4 weeks;
 - CAPOX: If the initiation of a new cycle or therapy during a cycle is delayed for ≥ 3 weeks.
- Progressive disease (defined by RECIST, v1.1; see Section 8.1.1).

Note: For the SLI, disease progression will be determined by Investigator. For the Phase 3 portion and Cohort 3, disease progression will be identified by the investigator and confirmed by BICR.

Note: In Phase 3 and Cohort 3, if disease progression is identified by Investigator (based on clinical or radiographic evidence), every effort should be made to continue study intervention until confirmed by BICR (see Section 8.1.1.2).

Note: Participants with disease progression who are continuing to derive clinical benefit from the study intervention per the Investigator will be eligible to continue, provided the risk/benefit for doing so is favorable and after discussion with the Sponsor.
- Participant becomes pregnant or begins breastfeeding.
- Significant protocol deviation that, in the opinion of the Investigator and/or Sponsor, renders the participant unsuitable for further study intervention administration.
- Participant is noncompliant with study procedures or study treatment that in the judgment of the Investigator or Sponsor renders the participant unsuitable for further study participation.
- Lost to follow-up.
- Death.
- Termination of the study by the Sponsor.

At the time of study treatment discontinuation, an end of treatment visit should be conducted. Note that discontinuation of study intervention does not represent withdrawal from the study. If study intervention is definitively discontinued, the participant will remain in the study to

be evaluated for safety, disease assessments, subsequent anticancer therapies, and survival. See the [SoA](#) for data to be collected and for any further evaluations that need to be completed at the EOT visit, 28-day follow-up visit and long-term follow-up.

In the event of discontinuation of study intervention, it must be documented on the appropriate CRF/in the medical records whether the participant is discontinuing further receipt of study intervention or also from study procedures, posttreatment study follow-up, and/or future collection of additional information.

In the event of study termination, the sponsor may work with sites to explore options for alternative source of post-study treatment for remaining participants.

After participants have discontinued treatment for any reason, they will be contacted approximately every 3 months in long-term follow-up until withdrawal of consent/assent, the participant is lost to follow-up, death, or the final OS analysis. If participants withdraw consent/assent for study intervention they will continue to be contacted for survival status unless they specifically request that they not be contacted. 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.

When a participant discontinues treatment for “disease progression” without BICR confirmation, it will not be counted as a PFS event and disease assessments will continue to be performed until PD is determined by BICR (see Section [8.1.1](#)).

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request. Reasons for discontinuation from the study include the following:

- Refused further follow-up (ie, withdrawal of consent/assent);
- Lost to follow-up;
- Death;
- Study terminated by sponsor;
- Termination of the study by the local health authority, IRB or IEC.

If a participant withdraws from the study, he/she may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent/assent (see Section [7.2.1](#)) for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent/assent.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

7.2.1. Withdrawal of Consent/Assent

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent/assent for any further contact with him or her or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent/assent from future follow-up, whenever possible. The withdrawal of consent/assent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

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:

- The site 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 designee must make every effort to regain contact with the participant (where possible, 3 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

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures.

Study procedures and their timing are summarized in the [SoA](#). Protocol waivers or exemptions are not allowed.

Safety issues should be discussed with the sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue study intervention (see Section 10.1.1.1).

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. 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 (eg, blood count) and obtained before signing of the ICD may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

8.1. Efficacy Assessments

8.1.1. Tumor Response Assessments

Tumor responses will be evaluated according to RECIST, v1.1 (Appendix 9). Measurable disease will be based on local Investigator assessment of baseline scans. Baseline scans should be sent to the BICR within 30 days of randomization. For the SLI portion of the study, tumor responses will be evaluated locally by the Investigator and may be transmitted to an imaging vendor for BICR review. For the Phase 3 and Cohort 3 portions of the study, tumor responses will be evaluated locally by the Investigator and centrally by BICR.

All potential sites of tumor lesions will be assessed at the time points specified in Table 1 (Screening), Table 2 (SLI), Table 3 (Phase 3 Arm A, Arm B and Cohort 3 Arm D), Table 4 (Phase 3 Arm C and Cohort 3 Arm E), and Table 5 (Phase 3 Arm C, CAPOX with or without bevacizumab):

At screening (prior to randomization for participants in the Phase 3 portion and Cohort 3), the following should be performed:

- A CT scan with IV contrast of chest, abdomen and pelvis is the preferred technique. If there is concern about radiation exposure, an MRI may be used instead of a CT.
- In participants with a history of asymptomatic brain metastases, a brain MRI or CT scan
- If clinically indicated, a whole body bone scan (ie, if bone metastases are suspected or known at baseline). Sites may use a whole body bone imaging method per their local standard of care (eg, Tc99m bone scan, FDG-PET, NaF PET scan or whole-body bone MRI). Skeletal lesions identified on a whole body bone scan at baseline, which are not visible on the chest, abdomen, or pelvis CT (or MRI) scan should be imaged at baseline using localized CT, MRI, or X-ray. Skeletal target lesions identified at baseline should continue to be imaged at subsequent scheduled visits using localized CT, MRI, or X-ray.

Every effort must be made to assess each lesion that is identified at screening by the same method throughout the study so that the comparison is consistent.

The first post-baseline scan must be performed 42 to 49 days from the date of first dose or from randomization for Phase 3. All post-screening assessments should be performed every 6 weeks from the date of randomization (or from the first dose for SLI) for the first 18 months of treatment, then every 8 weeks thereafter until BICR-confirmed disease progression (regardless of new anticancer therapy for Phase 3 and Cohort 3; for SLI confirmation by BICR is not required), withdrawal of consent/assent, participant is lost to follow-up, death, or the final OS analysis.

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

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

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

All CT scans should be performed with IV contrast. If a 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, with IV contrast, if possible, may be performed if MRI is contra-indicated.

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

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

While FDG-PET scans are not required for this study, sites may perform combined PET/CT scans per their local standard of care, provided the CT is of similar diagnostic quality as CT 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 PD in accordance with RECIST.

Preferably, each center should preferably have a designated radiologist responsible for the interpretation of scans and response evaluations for study participants. At a minimum, a single radiologist will perform all evaluations for an individual participant.

8.1.1.1. BICR Evaluation of Imaging Data

All imaging data acquired in the study for efficacy purposes (eg, CT/MRI scans) will be transmitted to an imaging vendor for BICR review. These images will be read by readers who are blinded to treatment assignment and to other clinical data as specified in the BICR Charter. Image transmission to the imaging vendor should be performed according to the Imaging Vendor Manual.

8.1.1.1.1. Time Points without Locally Determined Progression

Tumor measurements and/or assessments for time points with no locally determined progression received by the BICR will be read on an ongoing basis (rolling reads) in Phase 3 and Cohort 3 as detailed in the Imaging Manual. BICR interpretation of these data will not be communicated to the site, even if progression is assessed by the BICR (please see below).

8.1.1.1.2. Time Points with Locally Determined Progression

All participants in Phase 3 and Cohort 3 who have PD determined by the local Investigator require an expedited tumor response review by the BICR, and sites must send the radiological data to the BICR immediately (within 2 business days) upon acquisition. The Investigator seeking an expedited review must indicate this request on the radiology

transmittal form. The imaging vendor will ensure that the central reviewers involved in the BICR are blinded to the expedited status of the reading.

The BICR will perform the review of radiological data and the results of the reading will be communicated to the site within 5 business days from BICR confirmation on acceptable image receipt.

While the Investigator is waiting for the results from the BICR, every effort should be made to continue administration of study intervention. However, during this time, the Investigator should do whatever is medically necessary for the participant.

If the BICR determines PD, the study site will be informed and the participant will discontinue study intervention, cease tumor assessments and begin follow-up assessments as outlined in the [SoA](#). If according to the Investigator's clinical judgment, a participant with evidence of PD is still experiencing clinical benefit, the participant may be eligible for continued treatment after discussion between the Investigator and the Sponsor.

If the BICR does not conclude PD, the study site will be informed and the participant should continue receiving study intervention unless clinically indicated (eg, rapid clinical deterioration) for an immediate change in therapy. Participants will continue to have tumor assessments performed every 6 weeks from randomization for the first 18 months, then every 8 weeks for the remainder of the study, irrespective of the days of study intervention administration, until the BICR declares PD, withdrawal of consent/assent, lost to follow-up or death.

In summary, for expedited time points (time points assessed as PD locally by the Investigator):

- Sites must send the radiological and/or pathological data to the BICR immediately (within 2 business days) upon acquisition. While the Investigator is waiting for the results from the BICR, it is preferable that the participant continue treatment with study intervention.
- If the BICR determines PD, the study site will be informed. This participant will then discontinue study intervention, cease tumor assessments and begin follow-up assessments. If according to the Investigator's clinical judgment, a participant with evidence of PD is still experiencing clinical benefit, the participant may be eligible for continued treatment after discussion between the Investigator and the Sponsor.
- If the BICR does not conclude PD, the study site will be informed. As long as it is clinically acceptable, every effort should be made to continue the participant on study intervention until the BICR declares PD.

8.1.2. Patient-reported Outcomes

Cancer-specific global health status and quality of life, functioning, and symptoms data will be collected using the EORTC QLQ-C30 questionnaire and general health status will be assessed using the EQ-5D-5L health questionnaire. PGIS and PGIC will also be collected (See [Appendix 10](#)) according to FDA guidance⁷⁹ to enable the implementation of anchor-based methods to establish meaningful change in PROs.

These questionnaires will be administered at the time points specified in [Table 3](#) (Arm A, Arm B and Cohort 3 Arm D), and [Table 4](#) (Phase 3 Arm C and Cohort 3 Arm E) and [Table 5](#) (Phase 3 Arm C, CAPOX with or without bevacizumab). These questionnaires will be used to explore PRO measures of health-related QoL, functioning, cancer symptoms, and treatment-related side effects.

The EORTC QLQ-C30 is a reliable and valid self-administered questionnaire used in oncology trials.⁸⁰ The questionnaire is easily understood by most participants and is quick to complete (mean time 11 minutes).

It contains 30 items and is composed of both multi-item scales and single-item measures. These include five functional scales (physical, role, emotional, cognitive and social functioning), three symptom scales (fatigue, nausea/vomiting, and pain), six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea and financial impact) and a global health status/QoL scale. All the scales and single-item measures range in score from 0 to 100.

Higher scores on the functional scales represent higher levels of functioning. Higher scores on the global health status/quality of life scale represent higher health status/quality of life. Higher scores on symptom scales/items represent a greater presence of symptoms.

The EQ-5D-5L is a standardized measure of health utility that provides a single index value for the participant's health status. It is frequently used for economic evaluations of health care and has been shown to be a valid and reliable instrument, and comprises a short descriptive system questionnaire and a visual analogue scale (EQ VAS) that are cognitively undemanding, taking about 2 minutes to complete.

The EQ-5D-5L contains one item for each of five dimensions of health (ie, mobility, self-care, usual activities, pain or discomfort, and anxiety or depression). Response options for each item vary from having no problems (eg, "...no problems walking about"), moderate problems (e.g., "...some problems walking about"), or extreme problems (eg, "...unable to walk about"). Participant responses to the five dimensions reflect a specific health state that corresponds to a population preference weight for that state on a continuous scale of 0 (death) to 1 (perfect health).

The visual analog scale (ranging from 0 to 100) is included to capture participant's rating of their overall health status. Higher scores of the EQ-5D-5L represent better health states. All scoring and handling of data will follow the User's Guide defined by the EuroQoL Group.

The PGIS is a single-item questionnaire designed to assess participant's overall impression of disease severity at a given point in time. The PGIC is a single-item questionnaire designed to assess the participant's overall sense of whether there has been a change in symptoms or QoL since starting treatment. The PGIS and PGIC can be employed as anchors in responder analyses of other PRO instruments, to help interpret clinically meaningful changes in scores.

The questionnaires should be administered to participants in their preferred language at the beginning of the study visit prior to receiving any study treatment, prior to any other study assessment or consultation with the Investigator, and prior to being informed of their current disease status. Participants should be given sufficient space and time to complete the study questionnaires.

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

8.1.3. Survival Follow-up

Participants who have discontinued all study intervention (for any reason) will be contacted (eg, telephone, email, site visits, family member contact) approximately every 3 months for survival status and initiation of subsequent anticancer therapies/dates of progression, until death, withdrawal of consent, lost to follow-up, or the final OS analysis, whichever occurs first. If participants withdraw consent for study intervention, they will continue to be contacted for survival status unless they specifically request that they are not to be contacted. 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.

Upon the final OS analysis in each portion of the study (SLI, Phase 3 and Cohort 3), as specified in Section 9.4.3.2, no further contact for survival status will occur for participants enrolled in the specific study portion in the long-term survival follow-up stage. In addition, for participants remaining on study intervention, the sponsor will work with sites to explore options for alternative sources of post-study study intervention (see Section 6.7) until all patients are discontinued from study intervention.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the [SoA](#). Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

Medical history, physical examination, and neurological examination information, as applicable, collected during the course of the study will be considered source data only and will not be required to be reported on the case report form, unless otherwise noted. However, any untoward findings identified on physical and/or neurological examinations conducted during the active collection period will be captured as AEs, if those findings meet the definition of an AE. Data collected at screening that are used for inclusion/exclusion criteria,

such as laboratory data, ECGs, and vital signs, as well as demographic data collected at screening will be reported.

8.2.1. Participant Demographics and Other Baseline Characteristics

Demographic data will be collected at Prescreening and general medical history will be collected at Screening by the Investigator or qualified designee and will include relevant medical and surgical history within the last 10 years and current illnesses.

8.2.2. Disease Characteristics and Treatment History

A disease-targeted medical and treatment history will be collected at Screening. Details regarding the participant's malignancy under study, including date and stage at initial diagnosis, date and extent of metastatic disease at study entry, tumor histology, relevant disease characteristics and prior treatments, including systemic, radiation and surgical procedures, will be recorded.

8.2.3. Physical Examinations

At Screening, the physical examination should be comprehensive and include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. Participants should be assessed at each visit for symptoms of new or worsening visual disturbance. If symptoms of new or worsening visual disturbances including diminished central vision, blurred vision or loss of vision are identified, these should be recorded as adverse events and a prompt ophthalmologic examination is recommended. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast and pelvic examinations will be performed. Body weight will be measured as part of the physical examination on Day 1 of each cycle and on Day 15 during 28-day cycle regimens. For participants ≥ 18 years old, height will be measured only at Screening. For participants < 18 years old, height will be measured at Screening and Day 1 of each cycle.

For subsequent visits, the physical examinations should be targeted as clinically indicated. Investigators should pay special attention to clinical signs related to previous serious illnesses.

All physical examinations occurring on dosing days must be performed prior to study intervention administration. Any treatment-emergent abnormal findings will be recorded as AEs.

8.2.4. Body Surface Area

BSA will be calculated at the start of each cycle. The most recent participant weight available should be used to calculate BSA in order to determine the appropriate dose for that cycle. If the participant's weight at the beginning of each cycle varies by $> 10\%$ from the previous cycle, the dose must be recalculated.

In calculating the BSA, actual height and weight should be used. In participants with BSA $> 2.2 \text{ m}^2$, either actual BSA or 2.2 m^2 may be used. As per ASCO guidelines, any of the

established formulas may be used to calculate BSA.⁸¹ A single formula should be used consistently throughout the study for a given participant.

8.2.5. Dermatological Examinations

Dermatologic evaluations will be performed at the site by the Investigator to monitor for the possible development of keratoacanthoma and/or squamous cell carcinoma, as these have been reported to occur with selective BRAF inhibitor treatment.⁸²⁻⁸⁴ This assessment may be performed predose or postdose at the time points specified in the [SoA](#). Following the 28-day follow-up, dermatologic examinations for skin malignancies are recommended every 2 months until 6 months after the last dose of encorafenib or until initiation of another antineoplastic therapy. Participants should be referred to a dermatologist for any abnormalities identified on the Investigator's dermatologic examination.

8.2.6. Vital Signs

Temperature, pulse rate, respiratory rate, and blood pressure will be assessed per institutional standards prior to blood collection for laboratory tests (when timing is feasible).

All vital sign measurements occurring on dosing days must be performed prior to study intervention administration. Abnormal vital sign results identified after the first dose of study treatment constitute an AE if they are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy or require changes in study intervention/treatment.

8.2.7. Electrocardiograms

Standard 12 lead ECGs utilizing limb leads (with a 10 second rhythm strip) should be collected at times specified in the [SoA](#) using an ECG machine that automatically calculates the heart rate and measures PR, QT, and QTcF intervals and QRS complex. For ECG machines that do not report QTcF, calculation of QTcF from QT and heart rate, for example using online tools, is required. Alternative lead placement methodology using torso leads (eg, Mason-Likar) should not be used given the potential risk of discrepancies with ECGs acquired using standard limb lead placement. All scheduled ECGs should be performed after the participant has rested quietly for at least 5 minutes in a supine position.

A triplicate ECG (3 serial ECGs conducted within approximately 5 to 10 minutes total time) will be performed at screening to determine eligibility and predose on Cycle 1 Day 1 before administration of any study intervention to serve as baseline. A single ECG will be performed at all remaining time points specified in the [SoA](#). The oxaliplatin SmPc notes that the QT interval should be monitored on a regular basis before and after administration of oxaliplatin. If single ECG reveals QTc abnormality, continuous ECG should be performed as noted below. All scheduled ECGs should be performed after the participant has rested quietly for at least 5 minutes in a supine position. When an ECG is to be performed at the same time point as a blood collection, the ECG is to be performed first.

A study participant should undergo continuous ECG monitoring until an adequately trained physician (ie, cardiologist or internist) has reviewed the data if:

- a. a postdose QTcF interval remains ≥ 60 msec from the baseline **and** is > 450 msec; or
- b. an absolute QTcF value is ≥ 500 msec for any scheduled ECG for greater than 4 hours (or sooner, at the discretion of the investigator); or
- c. QTcF intervals get progressively longer by 30 ms increments.

Caution should be exercised in patients with a history or a predisposition for prolongation of QT, those who are taking medicinal products known to prolong QT interval, and those with electrolyte disturbances such as hypokalaemia, hypocalcaemia, or hypomagnesaemia. In case of QT prolongation, oxaliplatin treatment should be discontinued.

Consider consulting a cardiologist if QTcF intervals do not return to less than the criteria listed above after 8 hours of monitoring (or sooner, at the discretion of the investigator). New or worsened clinically significant findings occurring after the informed consent/assent must be recorded as an AE in the eCRF. ECG tracings should be made available if requested by the Sponsor.

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads be placed in the same positions each time in order to achieve precise ECG recordings. If a machine-read QTcF value is prolonged, as defined above, repeat measurements may not be necessary if a qualified medical provider's interpretation determines that the QTcF values are in the acceptable range.

ECG values of potential clinical concern are listed in [Appendix 7](#).

8.2.8. Clinical Safety Laboratory Assessments

See [Appendix 2](#) for the list of clinical safety laboratory tests to be performed and the [SoA](#) for the timing and frequency. All protocol-required laboratory assessments, as defined in [Appendix 2](#), must be conducted in accordance with the laboratory manual and the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. 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.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days after the last dose of study intervention 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.

See [Appendix 6](#) for suggested actions and follow-up assessments in the event of potential drug-induced liver injury.

At Screening, laboratory results from the central laboratory should be used by the Investigator to determine the participant's eligibility for the study. If a particular central laboratory result is not available, a local laboratory test result for that particular analyte may be utilized to determine a participant's eligibility to participate in the study. Local laboratory test results may also be used at baseline and when results are time-sensitive (eg, for participant safety or adjustment of study intervention dose or schedule). Part of the sample obtained for local laboratory analysis should be sent to the central laboratory for analysis. Local laboratory results obtained during the study will not be captured in the eCRF unless they are needed to clarify why a treatment decision was made or an AE was recorded.

Additional unscheduled clinical laboratory tests may be obtained at any time during the study at the Investigator's discretion. In addition to local testing, these samples should also be sent to the central laboratory for analysis when feasible.

8.2.9. Pregnancy Testing

Pregnancy tests may be urine or serum tests (serum required at Screening), but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the [SoA](#). Following a negative pregnancy test result at screening, appropriate contraception must be commenced and a second negative pregnancy test result will be required at the baseline visit prior the participant's receiving the study intervention. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected). Pregnancy tests may also be repeated if requested by IRBs/ethics committees or if required by local regulations. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be permanently discontinued from all study intervention if the serum pregnancy result is positive.

8.2.10. ECOG Performance Status

Assessment of ECOG PS ([Table 26](#)) will be assessed at the time points specified in [Table 1](#) (Screening), [Table 2](#) (SLI), [Table 3](#) (Arm A, Arm B and Cohort 3 Arm D), [Table 4](#) (Phase 3 Arm C and Cohort 3 Arm E) and [Table 5](#) (Phase 3 Arm C, CAPOX with or without bevacizumab).

ECOG PS should be obtained on the scheduled day, even if study treatment is being held.

Table 26. Eastern Cooperative Oncology Group (ECOG) Performance Status Scale

0	Fully active, able to carry on all predisease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, 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

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE and an SAE can be found in [Appendix 3](#).

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention (see [Section 7.1](#)).

Each participant will be questioned about the occurrence of AEs in a nonleading manner.

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent/assent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including a minimum of 28 calendar days, except as indicated below, after the last administration of the study intervention. Beyond 28 days after the last dose of study treatment, only SAEs considered related to study treatment should be collected.

Follow-up by the investigator continues throughout and after the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

If the participant withdraws from the study and also withdraws consent/assent for the collection of future information, the active collection period ends when consent/assent is withdrawn.

If a participant definitively discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the CT SAE Report Form.

Investigators are not obligated to actively seek AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and he/she considers the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the CT SAE Report Form.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are reported to Pfizer Safety on the CT SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

If a participant begins a new anticancer therapy, SAEs occurring during the above-indicated active collection period must still be reported to Pfizer Safety irrespective of any intervening treatment. Note that a switch to a commercially available version of the study intervention is considered as a new anticancer therapy for the purposes of SAE reporting.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.3.1 will be recorded in the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant.

If a participant begins a new anticancer therapy, the recording period for nonserious AEs ends at the time the new treatment is started; however, SAEs must continue to be recorded on the CRF during the above-indicated active collection period. Note that a switch to a commercially available version of the study intervention is considered as a new anticancer therapy for the purposes of SAE reporting.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in [Section 7.3](#)).

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is given in [Appendix 3](#).

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an 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 both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ethics committees, and investigators.

Investigator 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 SUSARs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the SRSD(s) for the study and will notify the IRB/ethics committee, if appropriate according to local requirements.

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the study intervention under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention exposes a female partner prior to or around the time of conception.
- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental exposure during pregnancy:
 - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by inhalation or skin contact.
 - A male family member or healthcare provider who has been exposed to the study intervention by inhalation or skin contact then exposes his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 6 months after the last dose.
- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP Supplemental Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless

preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study intervention.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.
- A female is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental exposure during breastfeeding is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by inhalation or skin contact.

The investigator must report exposure during breastfeeding to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the CT SAE Report Form. When exposure during breastfeeding occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study, so the information is not recorded on a CRF. However, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the exposure during breastfeeding.

8.3.5.3. Occupational Exposure

An occupational exposure occurs when a person receives unplanned direct contact with the study intervention, which may or may not lead to the occurrence of an AE. Such persons may include healthcare providers, family members, and other roles that are involved in the trial participant's care.

The investigator must report occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness, regardless of whether there is an associated SAE. The information must be reported using the CT SAE Report Form. Since the information does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

8.3.6. Cardiovascular and Death Events

Not applicable.

8.3.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

The following DREs are common in participants with advanced CRC and can be serious/life threatening:

- Progression of Disease.
Progression of malignancy, if documented by use of appropriate method (for example, as per RECIST criteria for solid tumors) will be designated as progression of disease in the eCRF. If the malignancy has a fatal outcome during the study or within the active collection period, then the event leading to death must be recorded as an AE on the CRF, and as an SAE with CTCAE Grade 5.
- Elective hospitalization for treatment of disease under study.

Because these events are typically associated with the disease under study, they will not be reported according to the standard process for expedited reporting of SAEs even though the event may meet the definition of an SAE. These events will be recorded on the corresponding CRF page in the participant's CRF within the appropriate time frame. These DREs will be monitored by a safety review team on a routine basis.

NOTE: However, if either of the following conditions applies, then the event must be recorded and reported as an SAE (instead of a DRE):

- The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant.

OR

- The investigator considers that there is a reasonable possibility that the event was related to study intervention.

8.3.8. Adverse Events of Special Interest

Not applicable.

8.3.8.1. Lack of Efficacy

Lack of efficacy is reportable to Pfizer Safety only if associated with an SAE.

8.3.9. Medical Device Deficiencies

Not applicable.

8.3.10. Medication Errors

Medication errors may result from the administration or consumption of the study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Exposures to the study intervention under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant exposure to the study intervention;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified within 24 hours.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and nonserious, are recorded on the AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE**.

8.4. Treatment of Overdose

For this study, any dose of study intervention greater than the protocol-specified dose and schedule (see Section 6.1.2) will be considered an overdose.

The Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities until study intervention can no longer be detected systemically (at least 100 days for an overdose of bevacizumab; at least 28 days for all other study interventions).
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Safety **only when associated with an SAE**.

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.

8.5. Pharmacokinetics

Blood samples of up to approximately ~7 mL will be collected from all participants in the SLI for measurement of plasma concentrations of encorafenib and LHY746 and irinotecan and SN-38 or oxaliplatin (total platinum and platinum in plasma ultrafiltrate) as specified in Table 27 and Table 28. Pre-dose blood samples (~2 mL) prior to encorafenib administration will be collected on Day 1 of Cycle 1 through 6 from all participants in Phase 3 Arm A and Arm B, and Cohort 3 Arm D for plasma concentrations of encorafenib and LHY746 (Table 29). On days of PK blood sample collection, participants will take the morning dose of encorafenib at the investigational site under the supervision of the Investigator or designee. PK sampling must occur on the day of dosing in the clinic (ie, no 3-day window). Samples must not be drawn from the same arm in which IV study intervention is being administered. Instructions for the collection and handling of PK samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

Table 27. PK Sampling Schedule for Cohort 1 (EC + FOLFIRI) in SLI

Visit	Sampling Time	Irinotecan PK Sample (3 mL Blood)	Encorafenib PK Sample (2 mL Blood)
Cycle 1 Day 1	0 h (predose ^b)	X	
	0.75 h	X	
	1.5 h	X ^c	
	2.5 h	X	
	3.5 h	X	
	5.5 h	X	
	7.5 h	X	
Cycle 1 Day 3	0 h (predose ^d)	X	
Cycle 1 Day 15 ^a	0 h (predose ^d)	X	X
	0.75 h	X	X
	1.5 h	X ^c	X
	2.5 h	X	X
	3.5 h	X	X
	5.5 h	X	X
	7.5 h	X	X
Cycle 1 Day 17 ^a	0 h (predose ^d)	X	X
Day 1 of Cycle 2 – 6 ^a	0 h (Predose ^d)	X	X

a Encorafenib will be administered within 5 minutes before the start of irinotecan infusion

b Predose is within 30 minutes prior to irinotecan infusion

c Immediately before irinotecan infusion ends

d Predose is within 30 minutes prior to encorafenib

Note: the time points are related to the start time of administration of respective drugs. Collection of samples up to and including 8 hours after dose administration should be obtained within ~ 10% of the nominal time relative to dosing (eg, within 6 minutes of a 1-hour sample)

Table 28. PK Sampling Schedule for Cohort 2 (EC + mFOLFOX6) in SLI

Visit	Sampling Time	Oxaliplatin PK Sample (5 mL Blood)	Encorafenib PK Sample (2 mL Blood)
Cycle 1 Day 1 ^a	0 h (predose ^b)	X	X
	1 h	X	X
	2 h	X ^c	X
	3 h	X	X
	4 h	X	X
	6 h	X	X
	8 h	X	X
Cycle 1 Day 3	0 h (Predose ^b)	X	X
Cycle 1 Day 15 ^a	0 h (predose ^b)	X	X
	1 h	X	X
	2 h	X ^c	X
	3 h	X	X
	4 h	X	X
	6 h	X	X
	8 h	X	X
Cycle 1 Day 17 ^a	0 h (predose ^b)	X	X
Day 1 of Cycle 2 – 6 ^a	0 h (predose ^b)	X	X

a Encorafenib will be administered within 5 minutes before the start of oxaliplatin infusion

b Predose is within 30 minutes prior to encorafenib dosing

c Immediately before oxaliplatin infusion ends

Note: the time points are related to the start time of administration of respective drugs. Collection of samples up to and including 8 hours after dose administration should be obtained within ~ 10% of the nominal time relative to dosing (eg, within 6 minutes of a 1 hour sample)

Table 29. PK Sampling Schedule for Phase 3 Arm A and Arm B and Cohort 3 Arm D

Visit	Sampling Time	Encorafenib PK Sample (2 mL Blood)
Day 1 of Cycle 1 – 6	0 h (predose)	X

Note: With the exception of Cycle 1 Day 1, which may be performed within 72 hours prior to initial treatment, predose is within 30 minutes prior to encorafenib dosing

The actual times may vary but the number of samples will remain the same. All efforts should be made to obtain the samples at the exact nominal time relative to dosing. Collection of samples up to and including 8 hours after dose administration that are obtained within 10% of the nominal time relative to dosing (eg, within 6 minutes of a 60-minute sample) will

not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the eCRF.

Samples collected for analyses of study intervention plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study, for metabolite identification and/or evaluation of the bioanalytical method, or for other internal exploratory purposes.

Genetic analyses will not be performed on these plasma samples.

Samples collected for measurement of plasma concentrations of encorafenib and a metabolite LHY746, irinotecan and a metabolite SN-38, or oxaliplatin will be analyzed using validated analytical methods in compliance with applicable SOPs. Exploratory metabolite identification or quantitation may be performed using either validated or exploratory methods.

The PK samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PK sample handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised.

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but will not constitute a protocol amendment. The IRB/ethics committee will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICD.

8.5.1. Pharmacokinetics for Participants in Mainland China

Up to the first 16 participants ≥ 18 years old randomized to Arm A in mainland China (to obtain approximately 12 PK evaluable participants) will undergo a more intensive PK sampling (Table 30), including serial whole blood samples (2 mL) collected on Day 1 and Day 15 of Cycle 1 at pre-dose and at 0.5, 1, 2, 3, 4, 5, 6, 8 and 24 hours post-dose to assess plasma concentration of encorafenib and its metabolite LHY746. If a dose interruption occurs prior to Cycle 1 Day 15, the intensive PK sampling on Cycle 1 Day 15 is suggested to be changed to Day 1 or Day 15 of Cycle 2. Participants may be skipped if they are determined by the investigator to be ineligible for intensive PK sampling. Pre-dose blood samples prior to encorafenib administration will be collected on Day 1 of Cycle 2 through 6. Intensive PK sampling may be taken in Arm B participants in mainland China if 16 participants are not fully enrolled in Arm A.

For the other participants randomized to Arm A and Arm B or randomized in Cohort 3 Arm D who will not undergo intensive PK sampling in mainland China, pre-dose blood samples

(~2 mL) prior to encorafenib administration will be collected on Day 1 of Cycle 1 through 6 for plasma concentrations of encorafenib and LHY746 (Table 31).

Table 30. PK Sampling Schedule for the First 16 Participants Enrolled in Phase 3 Arm A in Mainland China

<i>Note: PK Sampling may be taken in Arm B if 16 participants are not fully enrolled in Arm A.</i>		
Visit	Sampling Time	Encorafenib PK Sample (2 mL Blood)
Cycle 1 Day 1 ^a	0 h (predose ^b)	X
	0.5 h	X
	1 h	X
	2 h	X
	3 h	X
	4 h	X
	5 h	X
	6 h	X
	8 h	X
Cycle 1 Day 2	24 h (predose ^b)	X
Cycle 1 Day 15 ^a	0 h (predose ^b)	X
	0.5 h	X
	1 h	X
	2 h	X
	3 h	X
	4 h	X
	5 h	X
	6 h	X
	8 h	X
Cycle 1 Day 16	24 h (predose ^b)	X
Day 1 of Cycle 2 – 6 ^a	0 h (predose ^b)	X

a Encorafenib will be administered within 5 minutes before the start of oxaliplatin infusion

b Predose is within 30 minutes prior to encorafenib dosing

Note: the time points are related to the start time of administration of respective drugs. Collection of samples up to and including 8 hours after dose administration should be obtained within ~ 10% of the nominal time relative to dosing (eg, within 6 minutes of a 1-hour sample)

Table 31. PK Sampling Schedule for Participants Enrolled in Phase 3 Arm A and Arm B, and Cohort 3 Arm D (Who Will Not Undergo Intensive PK Sampling) in Mainland China

Visit	Sampling Time	Encorafenib PK Sample (2 mL Blood)
Day 1 of Cycle 1 – 6	0 h (predose)	X

Note: With the exception of Cycle 1 Day 1, which may be performed within 72 hours prior to initial treatment, predose is within 30 minutes prior to encorafenib dosing.

8.6. Pharmacodynamics

Biomarker samples may be used for exploratory PD analyses (see Section 8.8).

Pre-dose blood samples will be collected to enable measurements which may include but are not limited to: cfDNA, proteomic profiles, or epigenetics at the timepoints specified in the SoA.

As part of understanding the PD of the investigational product, samples may be used for evaluation of the bioanalytical method, as well as for other internal exploratory purposes. These data may not be included in the CSR.

Some samples may be analyzed using a validated analytical method in compliance with applicable SOPs while others may be analyzed using a non-characterized assay (non-validated).

The pharmacodynamic samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the pharmacodynamic sample handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised.

8.7. Genetics

8.7.1. Specified Genetics

Molecular profiling will be performed as described in Section 8.8. There is no intent to perform specific free-standing germline genomic analyses, but will be used as controls to assist in identifying and profiling somatic tumor mutations (see Section 8.8.2 for further details). No additional specified genetics will be evaluated in this study.

8.7.2. BRAF Testing

Participants will be eligible for the study based on identification of a *BRAF* V600E mutation in the tumor as determined by the central laboratory as part of Molecular Prescreening for the trial or by a local assay result from either blood or tumor tissue biopsy obtained any time prior to Screening (see Figure 1). Only PCR and NGS-based local assays results will be acceptable. If the participant is enrolled based on local assay results (using either tumor

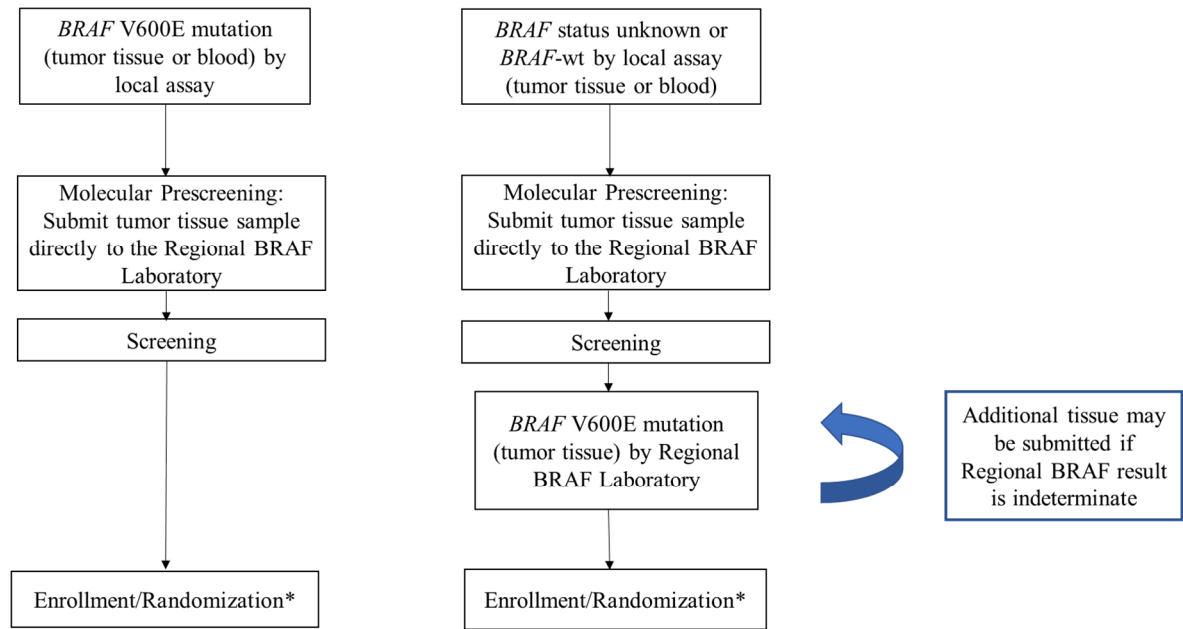
tissue or blood), the *BRAF* mutation status must be confirmed by the central laboratory (using tumor tissue only) no later than 30 days from first dose of study treatment. Either archival tumor tissue or newly collected fixed biopsy sample is required for the assessment of *BRAF* V600E mutation by the Sponsor designated central laboratory(ies). This tissue specimen should be obtained from a biopsy or surgery that was performed within 2 years prior to study enrollment. The *therascreen*® *BRAF* V600E RGQ PCR Kit is partially CE-marked for analytical performance according to 98/79/EC Annex VIII and is an approved medical device by the US FDA.

In cases where there is discordance between the local assay and central laboratory results, or if the central laboratory is not able to confirm presence of a *BRAF* V600E mutation due to inadequate or poor sample condition within 30 days of initiating study therapy, participants 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. In such instances, participants must be informed that the *BRAF* mutation status is unconfirmed and must acknowledge on the ICD that includes this information and describes alternative treatment options.

Central laboratory *BRAF* mutation tests with a definitive result (positive or negative) cannot be repeated to resolve a discordant result. Participants whose sample is determined to be inadequate or who have an indeterminate result on central testing may have samples resubmitted 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 in a total of 6% of the total planned enrollment of the Phase 3 portion or Cohort 3 of the trial or discordance between the local assay and the central laboratory in 3% of the total planned enrollment of Phase 3 or Cohort 3, all subsequent participants of Phase 3 or Cohort 3 will be required to have *BRAF* V600E determined by the central laboratory for enrollment (ie, local *BRAF* testing will no longer be accepted for trial eligibility).

As the central laboratory's diagnostic test may be more sensitive and specific than local testing, tumor samples previously determined to be *BRAF*-wt by local assessment may 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,⁸⁵ should be considered for testing by central laboratory regardless of the results of prior local *BRAF* mutation testing.

Figure 1. BRAF Testing



*Confirmation of *BRAF* V600E by Regional BRAF Laboratory required within 30 days of starting study intervention

8.7.3. Molecular Prescreening

Molecular Prescreening can be performed at any time prior to Screening. An informed consent/assent must be signed prior to any Molecular Prescreening procedure for confirmation of *BRAF* V600E status. A FFPE tumor tissue block or minimum of 15 slides (a minimum of 10 slides for mainland China) from the most recent tumor resection or biopsy must be provided for all participants enrolled in the study and submitted to the designated central laboratory(ies). This tissue specimen should be obtained from a biopsy or surgery that was performed within 2 years prior to study enrollment. If an archival tumor sample is not available, a fresh tumor biopsy must be obtained. In participants with documented *BRAF* V600E status determined by local assay prior to the study, when possible, the same tissue source should be submitted to the central laboratory in order to minimize the potential for discordance.

Slide sections must be freshly cut (ie, cut no more than 7 weeks prior to shipment to the central laboratory), 4-5 µm thick and mounted on positively-charged microscope slides. A minimum of 15 slides should be provided for *BRAF* mutation test and tumor tissue assessment (Section 8.8.2). Participants with fewer than 15 slides of analyzable tissue may be considered eligible if the Sponsor determines that the slides are sufficient for central testing of *BRAF* V600E mutation status and tumor tissue assessment. Tumor tissue from cytologic sampling (eg, fine needle aspiration, including FFPE cell pellet material) is not adequate and should not be submitted.

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

8.7.4. Screening

Participants with documented *BRAF* V600E status determined by the central laboratory during Molecular Prescreening or by local assay prior to this study must sign an ICD before additional screening procedures to determine eligibility for participation in the study are performed. A copy of the ICD will be given to the participant or their legal representative. The date that informed consent/assent was obtained must be documented in source documents. Participants will be registered for the study using the IRT after the informed consent/assent is obtained. Refer and comply with detailed guidelines in the IRT manual.

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.

8.7.5. Companion Diagnostic for Eligibility

Participants are required to have their disease assessed for a *BRAF* V600E mutation based on testing de novo or archival tumor tissue using the QIAGEN *therascreen*® *BRAF* V600E RGQ PCR Kit (FDA approved [USA]; partially CE marked for use in Europe) performed by a study-sponsored CAP/CLIA-certified central clinical laboratory. Testing may be performed during Molecular Prescreening or Screening.

Details on processes for collection and shipment of these samples can be found in the laboratory manual.

Although it is anticipated that most samples will be consumed by planned analyses during the course of the study, any unused samples may be stored at a facility selected by the sponsor for a maximum of 10 years (or according to local regulations) following the last participant's last visit for the study unless prohibited by local regulations or ethics committee decision.

8.7.6. Companion Diagnostic Assay Development

An in vitro diagnostic assay may be developed in accordance with FDA's Quality System Regulations and Design Control requirements. Any tumor samples remaining after testing for *BRAF* V600E and/or a blood sample collected during Screening ("Blood sample for *BRAF* CDx" – 20 mL of blood optimized for plasma preparation) may be used for companion diagnostic development and Health Authority registration, and to assess the concordance between the results for *BRAF* V600E status obtained using the central laboratory assay to determine eligibility for the study and the companion diagnostic assay which will be submitted for premarket approval.

Details on processes for collection and shipment of these samples can be found in the laboratory manual.

Although it is anticipated that most samples will be consumed by planned analyses during the course of the study, any unused samples may be stored at a facility selected by the sponsor for a maximum of 10 years (or according to local regulations) following the last participant's last visit for the study unless prohibited by local regulations or ethics committee decision.

Note: For participants in mainland China, sample collection and testing for *BRAF* V600E will not be performed until approval by HGRAC.

8.7.7. Banked Biospecimens for Genetics

A 4 mL blood sample optimized for DNA isolation [Prep D1] will be collected at the time specified in the [SoA](#) as local regulations and IRBs/ethics committees allow.

Banked Biospecimens may be used for research related to the study intervention(s) and cancer. Genes and other analytes (eg, proteins, RNA, nondrug metabolites) may be studied using the banked samples.

See [Appendix 5](#) for information regarding genetic research. Details on processes for collection and shipment of these samples can be found in the lab manual.

Note: Banked biospecimens are not applicable for participants in mainland China.

8.8. Biomarkers

Unless prohibited by local regulations or ethics committee decision, the following samples for biomarker research are required and will be collected from all participants in this study within the SLI and Phase 3 portions as specified in the SoA:

- Approximately 2 mL blood sample at designated time points to measure levels of CRP and CEA.
- Pre-treatment tumor tissue samples to enable retrospective genomic profiling (eg *RAS* mutations, MSI status) and expression analyses (eg gene, protein).
- Approximately 20 mL blood samples (or 10 mL for mainland China sites) at designated time points to be processed to plasma for assessment of cfDNA.
- Approximately 10 mL blood samples (or 1 mL for mainland China sites) at designated time points to be processed to serum for proteomic profiling.
- Approximately 4 mL whole blood samples at baseline for filtering of somatic mutation data.
- **Optional:** Tumor tissue samples at progression/EOT for assessment of tumoral changes which may occur over the course of therapy, including potential acquired resistance mechanisms.

Note: For participants in mainland China, sample collection and biomarker testing will not be performed until approval by HGRAC.

8.8.1. CRP and CEA assessments

Blood samples (2 mL) will be collected to measure levels of CRP and CEA using routine clinical laboratory testing. These analyses will be used to explore relationships between levels of CRP and CEA and clinical outcome.

8.8.2. Tumor Tissue Assessments

Tumor biospecimens representing FFPE tissue samples from tumor resection or biopsy will be used to analyze candidate DNA, RNA, or protein markers, or relevant signature of markers for their ability to identify those participants who are most likely to benefit from treatment with the study intervention.

Tumor tissue requirements are included in Section 8.7.2 and further details are provided in the Laboratory Manual for mandatory pre-screening/screening tumor samples. Optional on-treatment de novo tumor biopsies obtained during surgical resection or upon disease progression/EOT are requested except in instances where the procedure poses unacceptable risks per Investigator documentation. The EOT tumor biopsy should be performed before initiation of subsequent anti-cancer therapy and preferably no later than 7 days after the EOT visit. These tumor samples may be used to investigate acquired mechanisms of resistance and changes in the tumor and TME (eg, PD-L1 expression, presence of regulatory T-cells, myeloid-derived suppressors). Additional information on tissue collection procedures can be found in the Laboratory/Study Manual.

Targeted and/or whole exome/genome sequencing and/or transcriptome and/or epigenetic analyses will be performed using the remainder of the de novo or archival tumor tissue samples submitted at prescreening or screening for eligibility assessment to evaluate the genomic landscape (eg, *RAS* mutations, MSI status, etc) within the participant population. Additionally, these samples and tumor tissue collected at progression/EOT (when available) will be used to gain insight into the mechanisms that confirm sensitivity/resistance to study treatment. The results of these analyses may be combined with the results from targeted genomic analyses performed for enrollment eligibility assessment to further explore correlations of molecular profiling with response to study treatment. In addition, these samples may be used to help support development of a potential tumor tissue diagnostic test for encorafenib.

Unless prohibited by local regulations or ethics committee decision, whole blood samples (4 mL) will be collected from all participants on Day 1 before the first dose of study treatment (Cycle 1 Day 1) for exploratory targeted and/or whole exome/genome sequencing. These samples will be used to characterize the germline status of genetic variants (eg, DDR genes, MMR genes, etc). They will not otherwise be used to generate free-standing germline sequencing results, but rather as controls to assist in identifying and profiling somatic tumor DNA mutations. These samples are required for all enrolled participants where tumor tissue for genomic screening was collected from same participant.

8.8.3. Circulating Free DNA (cfDNA)

Blood samples (20 mL or 10 mL for mainland China sites) for cfDNA analyses will be collected from all participants at timepoints specified in the SoA and may also include remnant sample from “Blood sample for *BRAF* CDx”. cfDNA extracted from these samples will be used to assess epigenetic (eg, methylation) and genetic changes (eg, *BRAF*, *KRAS*, *NRAS*, etc) in ctDNA to (a) estimate the relationship between tumor burden (as assessed by VAF and/or methylation) and response to study treatment, (b) explore correlations with tumor molecular profiling, and (c) understand potential mechanisms of acquired resistance to study treatment. A targeted sequencing panel may be used for these analyses, which may include DDR genes and MSI status. Exploratory whole exome/genome sequencing and/or epigenetic analyses may be performed. In addition, these samples may be used to help support development of a potential blood-based test for encorafenib.

Although it is anticipated that most samples will be consumed by planned analyses during the course of the study, any unused samples may be stored at a facility selected by the sponsor for a maximum of 10 years (or according to local regulations) following the last participant’s last visit for the study.

8.8.4. Specified Gene Expression (RNA) Research

An FFPE tissue sample for RNA isolation will be collected as noted in Section 8.8.2. The samples will be analyzed by targeted and/or transcriptomic profiling to evaluate gene expression levels and may be used to identify signatures associated with response, resistance and adverse events in response to treatment.

Details on processes for collection and shipment of these samples can be found in the laboratory manual.

Although it is anticipated that most samples will be consumed by planned analyses during the course of the study, any unused samples may be stored at a facility selected by the sponsor for a maximum of 10 years (or according to local regulations) following the last participant’s last visit for the study.

8.8.5. Specified Protein Research

Approximately 10 mL blood sample or 1 mL for mainland China sites (processed for approximately 5 mL of serum or 0.5 mL for mainland China sites) for protein analyses will be collected from all participants at the timepoints specified in the SoA. The sample(s) may be analyzed for proteomic signatures associated with response or resistance to therapy in pretreatment and on-treatment samples. This sample may also be used for additional research based on emerging knowledge of CRC biology.

Details on processes for collection and shipment of these sample(s) can be found in the laboratory manual.

Although it is anticipated that most samples will be consumed by planned analyses during the course of the study, any unused samples may be stored at a facility selected by the sponsor

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CT02-GSOP Oncology Clinical Protocol Template (01 May 2024)

for a maximum of 10 years (or according to local regulations) following the last participant's last visit for the study.

8.8.6. Specified Metabolomic Research

Specified metabolomic research is not included in this study.

8.9. Immunogenicity Assessments

Immunogenicity assessments are not included in this study.

8.10. Health Economics

Health economic parameters may be captured as part of the trial to understand overall and differential healthcare resource utilization associated with each treatment and the Control Arm, by using the data entered in the clinical database. Such parameters may include, but will not be limited to, AEs and SAE data, concomitant medications, and surgical and non-surgical procedures. All information will be kept confidential.

9. STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a SAP, which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Estimands and Statistical Hypotheses

9.1.1. Estimands

Estimands are defined below for the primary endpoint of incidence of DLTs in the SLI, for the primary and key secondary endpoints in the Phase 3 portion of the study, and for the primary and key secondary endpoints in Cohort 3.

Safety Lead-in

Primary Estimand (DLT):

- Population: all participants with local or central laboratory confirmed *BRAF* V600E-mCRC, as defined by the screening inclusion/exclusion criteria in [Section 5.1.2](#) and [Section 5.2.2](#) to reflect the targeted population of the SLI portion of the study.
- Variable: DLT rate 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 6.1.1.1](#).
- 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.

Phase 3, Two Primary Estimands

PFS for Arm B vs Control Arm:

- Population: all participants who are randomized in the Phase 3 portion of the study. This analysis population will be based on FAS defined in Section 9.3.
- Variable: PFS by BICR, 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.
- Intercurrent events: hypothetical strategy will be applied for the intercurrent events. Details of the intercurrent events and censoring rules for the primary analysis are summarized in Table 32.
- Population-level summary measure: hazard ratio for PFS and corresponding 2-sided CI based on Cox proportional hazard model stratified by ECOG performance status at randomization and region. PFS will be compared between the two treatment arms using a 1-sided stratified log-rank test.

OR for Arm B vs Control Arm:

- Population: the first 110 participants who are randomized in the Phase 3 portion of the study into each of Arm B and Arm C (Full Analysis Set, ORR Subset defined in Section 9.3).
- Variable: Objective response defined as complete response (CR), or partial response (PR) according to RECIST v1.1 based on BICR assessment, from the date of randomization until the date of the first documentation of progression of disease (PD). Both CR and PR must be confirmed by repeat assessments performed no less than 4 weeks after the criteria for response are first met. Only tumor assessments performed on or before the start date of subsequent anticancer therapies will be considered in the assessment.
- Intercurrent events: All data collected after an intercurrent event of subsequent anticancer therapy or first PD will be excluded.
- Population-level summary measure: stratified (by the randomization strata) odds ratio in terms of OR defined as the odds of OR with Arm B divided by the odds of OR with Arm C, with its 2-sided 95% CI. ORR treatment effect will be compared using Cochran-Mantel-Haenszel test stratified by the randomization strata.

Key Secondary Estimand (OS for Arm B vs Control Arm):

- Population: all participants who are randomized in the Phase 3 portion of the study. This analysis population will be based on FAS defined in Section 9.3.
- Variable: OS, defined as the time from the date of randomization to death due to any cause.
- Intercurrent events: hypothetical strategy will be applied for the intercurrent events of lost to follow-up or withdrawal of consent/assent. Participants not known to have died are censored at the date of last contact.
- Population-level summary measure: hazard ratio for OS and corresponding 2-sided CI based on Cox proportional hazard model stratified by ECOG performance status at randomization and region. OS will be compared between the two treatment arms using a 1-sided stratified log-rank test.

Table 32. PFS Outcome and Event Dates – Primary Analysis

Situation	Date of Progression/Censoring	Outcome
No adequate baseline assessment, including no disease at baseline	Date of randomization ^a	Censored ^a
PD or death ≤ 12 (or 16) ^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 16) ^b weeks after the last adequate tumor assessment ^c	Date of last adequate tumor assessment ^c documenting no PD prior to new anti-cancer therapy, or missed assessments	Censored
No PD		
New anti-cancer therapy given ^d		

^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 2 times the length of the tumor assessment interval, which is 12 weeks for the first 18 months after randomization, and 16 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.

^d New anticancer therapy includes systemic therapy, radiation or surgery.

Cohort 3

Primary Estimand (OR):

- Population: all participants who are randomized in Cohort 3. This analysis population will be based on FAS defined in Section 9.3.
- Variable: Objective response defined as CR, or PR according to RECIST v1.1 based on BICR assessment, from the date of randomization until the date of the first documentation of PD, death or start of new anticancer therapy. Both CR and PR must

PFIZER CONFIDENTIAL

CT02-GSOP Oncology Clinical Protocol Template (01 May 2024)

Page 155

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be confirmed by repeat assessments performed no less than 4 weeks after the criteria for response are first met. Only tumor assessments performed on or before the start date of subsequent anticancer therapies will be considered in the assessment.

- Intercurrent events: All data collected after an intercurrent event of subsequent anticancer therapy or first PD will be excluded.
- Population-level summary measure: stratified (by the randomization strata) odds ratio in terms of OR defined as the odds of OR with Arm D divided by the odds of OR with Arm E, with its 2-sided 95% CI. ORR treatment effect will be compared using Cochran-Mantel-Haenszel test stratified by the randomization strata. Participants who do not have a post-baseline tumor assessment due to early progression of disease, who receive anti-cancer therapies other than the study treatments prior to reaching a CR or PR, or who die, have PD, or stop tumor assessments for any reason prior to reaching a CR or PR will be counted as non-responders in the assessment of OR. Each participant will have an objective response status (0: no OR; 1: OR).

Key Secondary Estimand (PFS):

- Population: all participants who are randomized in the Cohort 3. This analysis population will be based on FAS defined in Section 9.3.
- Variable: PFS by BICR, 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.
- Intercurrent events: hypothetical strategy will be applied for the intercurrent events. Details of the intercurrent events and censoring rules are summarized in Table 32.
- Population-level summary measure: hazard ratio for PFS and corresponding 2-sided CI based on Cox proportional hazard model stratified by the randomization strata. PFS will be compared between the two treatment arms using a 1-sided stratified log-rank test.

9.1.2. Statistical Hypotheses

There is no statistical hypothesis for the SLI portion of the study.

Phase 3

For Phase 3 portion of the study, the primary objective is to compare the efficacy, as measured by the primary endpoints of PFS by BICR and ORR by BICR, of Arm B versus the Control Arm. The following statistical hypotheses will be tested to address the primary objective:

$$H_{01}: HR_{PFS(B \text{ versus Control})} \geq 1 \text{ versus } H_{11}: HR_{PFS(B \text{ versus Control})} < 1$$

$$H_{02}: OR_{OR(B \text{ versus Control})} \leq 1 \text{ versus } H_{12}: OR_{OR(B \text{ versus Control})} > 1$$

where $HR_{PFS(B \text{ versus Control})}$ is the hazard ratio for PFS of Arm B versus the Control Arm and $OR_{OR(B \text{ versus Control})}$ is the odds ratio for objective response of Arm B versus the Control Arm.

The key secondary objective is to compare the efficacy, as measured by the key secondary endpoint of OS, of Arm B versus Control. The following statistical hypothesis will be tested to address the key secondary objective:

$$H_{03}: HR_{OS} (B \text{ versus Control}) \geq 1 \text{ versus } H_{13}: HR_{OS} (B \text{ versus Control}) < 1$$

where $HR_{OS} (B \text{ versus Control})$ is the hazard ratio for OS of Arm B versus the Control Arm.

Overall 1-sided alpha of 0.025 for the study will be preserved using 1-sided alpha of 0.001 for the comparison of ORR by BICR of Arm B vs Control Arm, 1-sided alpha of 0.023 for the comparison of PFS by BICR of Arm B vs Control Arm. A hierarchical testing procedure will be used to control the family-wise type I error rate. In addition, 1-sided alpha of 0.001 will be reserved for the comparison of PFS by BICR of Arm A vs Arm C, even if there is no plan for formal testing. Details of this strategy are described in [Section 9.4.1.1](#). The study will be considered positive (ie, demonstrated evidence of effectiveness) if the hypothesis test of either primary endpoint is statistically significant.

Cohort 3

The primary objective is to compare the efficacy, as measured by ORR by BICR, of Arm D versus Arm E. The following statistical hypothesis will be tested:

$$H_{01}: OR_{OR(D \text{ versus E})} \leq 1 \text{ versus } H_{11}: OR_{OR(D \text{ versus E})} > 1$$

where $OR_{OR(D \text{ versus E})}$ is the odds ratio for objective response of Arm D versus Arm E.

The key secondary objective is to compare the efficacy, as measured by the key secondary endpoint of PFS by BICR, of Arm D versus Arm E. The following statistical hypothesis will be tested to address the key secondary objective:

$$H_{02}: HR_{PFS} (D \text{ versus E}) \geq 1 \text{ versus } H_{12}: HR_{PFS} (D \text{ versus E}) < 1$$

where $HR_{PFS} (D \text{ versus E})$ is the hazard ratio for PFS of Arm D versus Arm E

9.2. Sample Size Determination

The planned sample size of the study is approximately 816 participants including approximately 60 participants in the SLI, approximately 470 participants in the Phase 3 portion of the study (Arm B and Arm C), and approximately 136 participants in Cohort 3. In addition, up to the time of Protocol Amendment 5 approval, approximately 150 participants are estimated to be randomized in Arm A of the Phase 3 portion of the study.

Safety Lead-in

The primary endpoint of the SLI of the study is incidence of DLTs. Up to 60 evaluable participants will be enrolled on a rolling basis in an alternating manner to receive either EC + mFOLFOX6 or EC + FOLFIRI (up to 30 participants per cohort). The safety data will be evaluated by the SC after the first 9 evaluable participants in each cohort have been followed

for a minimum of 28 days with EC + mFOLFOX6 or EC + FOLFIRI. The target DLT rate in the first 28 days is <33% (ie, <3 out of 9 evaluable participants with DLTs).

Table 33 provides a comparison of the characteristics of this DLT evaluation rule and the traditional 3 + 3 rules based on 9 participants.

Table 33. Characteristics of DLT Probability During the DLT Evaluation Period

True DLT Rate During DLT Evaluation Period	Probability of Dose Declared Toxic Using 3 + 3 Rules	Probability of Observed DLT Rate $\geq 33\%$ in 9 Participants During DLT Evaluation Period
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

The DLT evaluation period is the first 28 days after the first dose of study intervention in the SLI, and the DLT-evaluable is defined in Section 6.1.1.1.

If the doses are determined to be tolerable in the first 9 evaluable participants in either or both regimens based on the observed DLT rate (<33%) and evaluation of the overall toxicity profile, the SLI will be expanded for a total of up to 30 evaluable participants in each cohort. If the DLT rate is $\geq 33\%$ in either cohort, that combination regimen will not be evaluated further in the SLI and will not be used in Phase 3.

Table 34 summarizes the probability of observing at least one instance of a toxicity that has a true incidence rate of 10% and 15% for the given number of participants.

Table 34. Probability of Observing ≥ 1 Instance of Toxicity at 10% and 15% Incidence Rate

True Toxicity Incidence Rate	Number of Participants	Probability of Observing ≥ 1 Instance of Toxicity
10%	15	0.79
	20	0.88
	30	0.96
15%	15	0.91
	20	0.96
	30	0.99

If any participant is deemed non-evaluable for DLT, additional participants may be enrolled to ensure there are a sufficient number of evaluable participants in the SLI.

Phase 3

Approximately 620 participants will be randomized overall, initially at a ratio of 1:1:1 to receive EC (Arm A), EC + chemotherapy (Arm B) or SOC chemotherapy (Arm C), and then

1:1 to receive EC + chemotherapy (Arm B) or SOC chemotherapy (Arm C) after the approval of Protocol Amendment 5, with a total of approximately 150 participants for Arm A and 235 participants each for Arm B and Arm C. Randomization is stratified by ECOG performance status (0 versus 1) and region (US/Canada versus Europe versus Rest of World).

Primary Endpoints

Approximately 230 PFS by BICR events will be required to have at least 85% power to detect a hazard ratio of 0.67 between Arm B and Arm C using a 1-sided stratified log-rank test at a significance level of 0.023.

The sample size of 235 participants per arm was determined based on the assumptions of a hazard ratio of 0.67 under the exponential model assumptions, and median PFS of 7 months on the Arm C. The sample size further assumes a dropout hazard rate of 0.07 within each treatment arm, non-uniform participants accrual over 26 months (for 2 arms: 6 participants per month for the first 5 months, 11 participants a month for months 6 through 7, 16 participants a month for months 8 through 11, 23 participants a month for months 12 through 16, and 24 participants per month thereafter).

The sample size of 220 participants (110 per arm) will provide 90% power for test of odds ratio of 2 proportions between the Arm B and Arm C using a 1-sided chi-square test at a significance level of 0.001 assuming an ORR by BICR of 35% and 65% for Arm C and Arm B, respectively.

Key Secondary Endpoint

For the comparison of Arm B versus Arm C OS, 297 OS events in Arm B + Arm C will achieve 85% power to detect an OS HR of 0.70 using a 1-sided stratified log-rank test at a significance level of 0.023, and a 2-look group-sequential design with a Lan-DeMets (O'Brien-Fleming) spending function to determine the efficacy boundaries. An exponential distribution for OS was assumed, that corresponds to an improvement in the median OS of 6.4 months (21.4 months in Arm B versus 15 months in Arm C). The sample size further assumes a dropout hazard rate of 0.011 within each treatment arm, interim analysis after 80% of OS events, and follow-up after the last participant is randomized of about 24 months.

Cohort 3

Primary Endpoint

The sample size calculation is based on the primary endpoint of ORR as determined by BICR per RECIST v1.1. The hypothesis to be tested is described in Section 9.1.2. The sample size of 136 participants (68 in Arm D and 68 in Arm E) will provide 93.1% power for test of odds ratio of 2 proportions between the Arm D and Arm E using a 1-sided chi-square test at a significance level of 0.025 assuming an ORR by BICR of 35% and 65% for Arm E and Arm D, respectively.

Key Secondary Endpoint

For the comparison of Arm D versus Arm E PFS by BICR, 136 participants and 73 PFS events in Arm D + Arm E will achieve 80% power to detect a PFS HR of 0.519 using a 1-sided stratified log-rank test at a significance level of 0.025. An exponential distribution for PFS was assumed, that corresponds to an improvement in the median PFS of 6.5 months (13.5 months in Arm D versus 7 months in Arm E). The sample size further assumes a dropout hazard rate of 0.015 within each treatment arm, and uniform participants accrual of 20 participants a month.

9.3. Analysis Sets

For purposes of analysis, the following analysis sets are defined:

Participant Analysis Set	Description
Enrolled	All participants who sign the Screening ICD.
DLT-Evaluable Analysis Set	All participants who receive at least 1 dose of study intervention in the SLI and either experience DLT during the DLT evaluation period or complete the DLT evaluation period without DLT. Participants without DLTs who do not receive at least 75% of the planned dose of each study intervention during the DLT evaluation period for reasons other than treatment-related toxicity (eg, protocol violation) are not evaluable for DLT. The DLT evaluation period is the first 28 days after the first dose of study intervention.
Full Analysis Set (FAS)	For participants in the SLI the FAS includes all participants who receive at least 1 dose of study intervention. For participants in the Phase 3 portion and Cohort 3, the FAS includes all participants who are randomized in the Phase 3 portion and Cohort 3 of the study, respectively. Participants will be analyzed according to the study treatment assigned at randomization.
Full Analysis Set, ORR Subset	For the primary analysis of ORR/DOR/TTR in the Phase 3 portion of the study, “Full Analysis Set, ORR Subset” comprises the first 110 participants randomized in each Arm B and Arm C.
Centrally Assessed <i>BRAF</i> V600E Positive Analysis Set	All participants who are randomized in the Phase 3 portion of the study with a confirmed central laboratory result of <i>BRAF</i> V600E mutation. Participants will be analyzed according to the study treatment assigned at randomization.
Safety Analysis Set	All participants who receive at least 1 dose of study intervention. For the Phase 3 portion and Cohort 3 of the study, participants will be analyzed according to the study treatment assigned at randomization unless the incorrect treatment(s) was/were received throughout the dosing period in which case participants will be analyzed according to the actual study treatment received in the first cycle.

Participant Analysis Set	Description
PK Analysis Set	<p>The PK concentration set is defined as all enrolled participants who are treated and have at least 1 analyte concentration.</p> <p>The PK parameter analysis set is defined as all enrolled participants treated who have sufficient information to estimate at least 1 of the PK parameters of interest and have no major protocol deviations affecting PK assessment.</p>
Biomarker Analysis Set	All participants who are in the safety analysis set and who had at least 1 of the pharmacodynamic parameters or biomarkers evaluated at pre and/or post dose.

9.4. Statistical Analyses

The SAP will be developed and finalized before any analyses are performed and will describe the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1. General Considerations

All analyses will be performed by treatment arm for the SLI, Phase 3 portion, and Cohort 3 of the study separately. All efficacy analyses will be performed using the FAS, and all safety analyses will be performed using the safety analysis set.

In general, descriptive summaries will be presented for the efficacy and safety variables collected. Continuous variables will be summarized using mean, standard deviation, minimum, median, and maximum. Categorical variables will be summarized using frequency counts and percentages.

Unless otherwise specified, the calculation of proportions will be based on the sample size of the population of interest. Counts of missing observations will be included in the denominator and presented as a separate category if not otherwise specified in the SAP.

Statistical analyses will be performed using SAS® version 9.4 or higher.

9.4.1.1. Statistical Testing Strategy

For the Phase 3 portion of the study a hierarchical testing procedure will be used to control the family-wise type I error rate.

Eight months after randomization of the first 110 participants each in Arm B and in Arm C, or after the completion of enrollment of the Phase 3 portion of the study, whichever occurs later, the ORR by BICR will be compared for Arm B versus Arm C, on these first 220 participants, using a 1-sided alpha of 0.001.

Once at least 230 PFS events by BICR will be observed for Arm B + Arm C and at least 12 months after the completion of enrollment of the Phase 3 portion of the study, the

PFS analysis for the primary comparison of PFS by BICR for Arm B versus the Arm C will be tested using a 1-sided alpha of 0.023.

At the time of ORR and PFS analysis if at least one of them will be significant an interim analysis for OS will be conducted and hierarchical procedure for control of alpha for ORR/PFS and OS will be applied.

If the results of the interim analysis of OS are not statistically significant, a final OS analysis will be performed once 297 events are observed for Arm B + Arm C. Details of the OS interim efficacy analysis are described in Section 9.5.1 and will be included in the SAP.

The overall significance level for Phase 3 portion of the study is 0.025 (1-sided) and will be used as follows:

- 1-sided alpha of 0.001 for the comparison of ORR by BICR of Arm B vs Arm C;
- 1-sided alpha of 0.023 for the comparison of PFS by BICR of Arm B vs Arm C;
- alpha for the comparison of OS of Arm B vs Arm C will depend on the outcome of ORR and PFS;
- 1-sided alpha of 0.001 for the comparison of PFS by BICR of Arm A vs Arm C, even if there is no plan for formal testing;

In Cohort 3, the analysis of ORR by BICR comparing Arm D versus Arm E will be performed at least 8 months after the randomization of the last participant using 1-sided alpha of 0.025. A hierarchical testing procedure will be used to control the family-wise type I error rate at 0.025 (1-sided) level for ORR and PFS. PFS by BICR will be tested when at least 73 events will be observed, only if the analysis for ORR is statistically significant. If ORR results are not statistically significant, PFS will be analyzed descriptively.

No formal statistical testing will be performed on the secondary and exploratory endpoints (with the exception for key endpoint described above), sensitivity analyses and subgroup analyses. These results will be reported with descriptive statistics only.

Confidence intervals will be 2-sided with a confidence level of 95%, if not otherwise specified.

9.4.1.2. Pooling of Centers

In order to provide overall estimates of treatment effects, data will be pooled across trial 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.

9.4.1.3. Stratification Factors

For Phase 3 portion the stratification factors used for stratified statistical analyses are those used at randomization via the IRT: ECOG performance status (0 versus 1) and region (US/Canada versus Europe versus Rest of World).

For Cohort 3 the only stratification factor used for stratified statistical analyses and at randomization via the IRT is ECOG performance status (0 versus 1).

9.4.1.4. Definition of Baseline

For all endpoints assessments in the SLI, and all safety assessments in the Phase 3 portion of the study and in Cohort 3, baseline is defined as the last completed assessment prior to date of first dose in the SLI, Cohort 3, and Phase 3, 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 baseline assessment.

For efficacy assessments in the Phase 3 portion of the study and in Cohort 3, baseline is defined as the last assessment prior to randomization. If the assessment that is planned to be performed before randomization per 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 baseline assessment. If no tumor assessment was performed prior to randomization, any tumor assessment conducted between randomization and prior to or on the first study intervention dose date will be considered as baseline tumor assessment.

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

9.4.1.5. Definition of On-treatment Period

The on-treatment period is defined as the time from the first dose of study treatment through minimum of (last dose of study treatment + 28 days, start day of subsequent anticancer therapy - 1 day) unless otherwise described in the SAP.

9.4.2. Primary Endpoints

Safety Lead-in

The primary endpoint in the SLI of the study is incidence of DLTs. The number and proportion of participants experiencing DLTs during the DLT-evaluation period will be summarized and listed by treatment cohort. Analyses of DLT will be performed on DLT-Evaluable Set.

Phase 3

The primary objective is to compare the efficacy, as measured by the primary endpoints of PFS by BICR and ORR by BICR, of Arm B versus Arm C.

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. PFS will be calculated in months as follows:

$$\text{PFS (months)} = (\text{date of event or censoring} - \text{randomization date} + 1) / 30.4375$$

Participants without an event or with an event more than 12 weeks (for the first 18 months after randomization) or 16 weeks (after the first 18 months of randomization) after the last adequate tumor assessment will be censored on the date of the last adequate tumor assessment that documented no progression. In addition, if a new anti-cancer therapy 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 anti-cancer therapy. Anticancer therapy includes systemic anticancer therapy, radiation, and surgery.

An adequate post-baseline assessment is defined as an assessment where a response of CR, PR, SD, non-CR/non-PD, or PD can be determined. Time points where the response is NE 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 post-baseline 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 32](#).

The primary analysis will be performed to compare PFS between Arm B versus Arm C using a 1-sided stratified log-rank test at the 0.023 significance level.

The treatment effect will be estimated using a Cox's proportional hazards model stratified by randomization strata to calculate the hazard ratio for PFS of Arm B versus Arm C.

The 95% CIs for the hazard ratios will be reported. PFS time will be estimated using the Kaplan-Meier method and displayed graphically by treatment arm. The median PFS and associated 95% CIs will be presented by treatment arm. PFS rates at different time points will be estimated with corresponding 2-sided 95% CIs.

Sensitivity/Supplementary Analyses

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

- The PFS analysis will be repeated based on the Centrally Assessed *BRAF* V600E Positive analysis set.
- The same methodology and summary as the main analysis will be used, but PD or death that occurs after the intercurrent events of starting new anticancer therapy will be considered PFS events. All other intercurrent events will be addressed in the same approach as the primary estimand of PFS.

ORR is defined as the proportion of participants who have achieved a BOR of confirmed CR or PR per RECIST v1.1 as assessed by BICR. The BOR is the best response obtained among all tumor assessment visits after date of randomization until documented PD, or start of subsequent anticancer therapy, or death. Confirmation of the response will be no sooner than 4 weeks after the initial documentation of CR or PR.

A BOR of SD requires that an overall response of SD has been determined at a time point at least 6 weeks after the date of randomization.

A BOR of PD requires that the documented progression should be within 12 weeks after the date of randomization and not qualifying as CR, PR or SD. The ORR will be calculated along with corresponding 2-sided Wilson score 95% CI.

The treatment effect of the Arm B compared to Arm C, as measured by stratified (by the randomization strata) odds ratio and its 95% CI in terms of OR defined as the odds of OR with Arm B divided by the odds of OR with Arm C will be tested using Cochran-Mantel-Haenszel statistics stratified by the randomization strata at 1-sided 0.001 level of significance considering the first 110 randomized participants each in Arm B and in Arm C.

Cohort 3

The primary endpoint is ORR, defined as the proportion of participants who have achieved a BOR of confirmed CR or PR per RECIST v1.1 as assessed by BICR. The BOR is the best response obtained among all tumor assessment visits after date of randomization until documented PD, or start of subsequent anticancer therapy, or death. Confirmation of the response will be no sooner than 4 weeks after the initial documentation of CR or PR.

A BOR of SD requires that an overall response of SD has been determined at a time point at least 6 weeks after the date of randomization.

A BOR of PD requires that the documented progression should be within 12 weeks after the date of randomization and not qualifying as CR, PR or SD. The ORR will be calculated along with corresponding 2-sided Wilson score 95% CI.

The treatment effect of Arm D compared to Arm E, as measured by stratified (by the randomization strata) odds ratio and its 95% CI in terms of OR defined as the odds of OR

PFIZER CONFIDENTIAL

CT02-GSOP Oncology Clinical Protocol Template (01 May 2024)

with Arm D divided by the odds of OR with Arm E will be tested using Cochran-Mantel-Haenszel statistics stratified by the randomization strata at 1-sided 0.025 level of significance.

9.4.3. Secondary Endpoints

9.4.3.1. PFS Arm A versus Arm C, Arm A versus Arm B, and Cohort 3

PFS by BICR and by investigator of Arm A versus Arm C and of Arm A versus Arm B, and PFS by investigator for Cohort 3 will be analyzed using the same analysis method described in Section 9.4.2, however, as these comparisons are not part of the multiple testing strategy as outlined in Section 9.4.1.1, no formal testing will be performed to compare PFS of these treatment arms.

As the key secondary endpoint in Cohort 3, PFS by BICR will be compared between Arm D and Arm E, only if ORR analysis is statistically significant, using the same analysis method described in Section 9.4.2, and 1-sided $\alpha=0.025$.

9.4.3.2. OS

OS is defined as the time from the date of first dose (SLI) or the date of randomization (Phase 3 and Cohort 3) to death due to any cause. If a participant is not known to have died at the time of the cutoff for analysis, then OS will be censored at the date of last contact when the participant was known to be alive. OS will be calculated in months as follows:

$$\text{OS (months)} = [\text{date of death or censoring} - \text{date of first dose (SLI) or randomization date (Phase 3, Cohort 3)} + 1] / 30.4375$$

For SLI, OS time will be estimated using the Kaplan-Meier method for Cohort 1 (EC + FOLFIRI) and Cohort 2 (EC + mFOLFOX6) and by prior treatment line (0 or 1), separately.

Final OS analysis for SLI and Cohort 3 will be performed for each portion of the study approximately 24 months after the enrollment of last participant of that portion.

As the key secondary endpoint in Phase 3 portion of the study, OS will be compared between Arm B and Arm C using a 1-sided stratified log-rank test.

The treatment effect will be estimated using a Cox's proportional hazards model stratified by randomization strata to calculate the hazard ratio for OS of Arm B versus Arm C. In order to account for the group sequential design on this endpoint, the repeated CI method⁸⁶ will be used to construct the 2-sided repeated CI for the hazard ratio at the interim and the final analyses of OS.

In addition, the unadjusted 95% CIs for the hazard ratios will also be reported at the interim and the final analyses for OS.

OS time will be estimated using the same Kaplan-Meier method as described for PFS. Timing of OS analyses for Phase 3 are outlined in Section 9.5.1.

OS of Arm A versus Arm C, Arm A versus Arm B, Arm D versus Arm E will also be analyzed using the same analysis method described above. However, as these comparisons are not part of the multiple testing strategy as outlined in Section 9.4.1.1, no formal testing will be performed to compare OS of these treatment arms.

Sensitivity/Supplementary Analyses

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

- The OS analysis will be repeated based on the Centrally Assessed *BRAF* V600E Positive analysis set.

9.4.3.3. Objective Response Rate

ORR is defined as the proportion of participants who have achieved a confirmed BOR of CR or PR per RECIST v1.1. The BOR is the best response obtained among all tumor assessment visits after the date of first dose (SLI) or the date of randomization (Phase 3, Cohort 3) until documented disease progression, death, or start of subsequent anticancer therapy. Clinical deterioration or clinical progression noted on the completion eCRF will not be considered as documented disease progression. Confirmation of the response will be performed per RECIST v1.1, 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.

A BOR of SD requires that a time point overall response of SD has been determined at a time point at least 6 weeks after the date of first dose (SLI) or the date of randomization (Phase 3, Cohort 3).

A BOR of PD requires that the documented progression should be within 12 weeks after the date of first dose (SLI) or the date of randomization (Phase 3, Cohort 3) and not qualifying as CR, PR or SD.

The ORR will be calculated along with corresponding 2-sided Wilson score 95% CI.

9.4.3.4. Duration of Response

DOR is defined as the time from the date of first radiographic evidence of response (CR or PR) to the earliest documented disease progression per RECIST v1.1, or death due to any cause. DOR will be calculated for participants with a confirmed response (CR or PR).

DOR will be calculated in months as follows:

$$\text{DOR (months)} = (\text{date of event or censoring} - \text{date of first CR or PR} + 1) / 30.4375$$

The same censoring rules specified for PFS in Section 9.4.2 apply to DOR. Kaplan-Meier method will be used to estimate DOR time. The median DOR and its 95% CIs will be

presented by treatment arm and cohorts. DOR rates at different time points will be estimated with corresponding 2-sided 95% CIs.

9.4.3.5. Time to Response

TTR is defined as the time from the date of first dose (SLI) or the date of randomization (Phase 3, Cohort 3) to first radiographic evidence of response (CR or PR) per RECIST v1.1. TTR will be calculated for participants with a confirmed response (CR or PR).

TTR will be calculated in weeks as follows:

$$\text{TTR (in weeks)} = (\text{data of first CR or PR} - \text{date of first dose (SLI) or date of randomization (Phase 3, Cohort 3)} + 1) / 7$$

TTR will be summarized using simple descriptive statistics (mean, standard deviation, median, minimum, maximum, first quartile, third quartile).

9.4.3.6. PFS (SLI)

PFS in the SLI is defined as the time from the date of first dose to the earliest documented disease progression per RECIST v1.1, or death due to any cause. PFS will be calculated in months as follows:

$$\text{PFS (months)} = (\text{date of event or censoring} - \text{date of first dose} + 1) / 30.4375$$

PFS time in the SLI will be estimated using the Kaplan-Meier method for Cohort 1 (EC + FOLFIRI) and Cohort 2 (EC + mFOLFOX6) and by prior treatment line (0 or 1), separately. The same censoring rules specified for PFS in [Section 9.4.2](#) will be used with the date of first dose date as the starting date.

9.4.3.7. PFS2

PFS2 is defined as the time from the date of randomization to the date of discontinuation of next-line treatment after first objective PD by investigator assessment, to second objective disease progression, or death from any cause, whichever occurs first. Second objective disease progression is PD after the start of subsequent systemic anticancer therapy. PFS2 will be calculated in months as follows:

$$\text{PFS2 (months)} = [\text{minimum of (date of death, date of second objective PD, date of discontinuation of next treatment) or censoring} - \text{randomization date} + 1] / 30.4375$$

Participants alive, on next treatment and for whom a second objective PD has not been observed will be censored at the last time known to be alive and without second objective PD. In addition, participants who die after missing 2 or more tumor assessments while on study treatment will remain censored for PFS2.

PFS2 time will be estimated using the same Kaplan-Meier method as described for PFS.

9.4.3.8. Patient Reported Outcomes

FAS will be the primary set for PRO analyses in Phase 3 and Cohort 3. Detailed methodology for summary and statistical analyses of the PRO data collected in this study is outlined here and further detailed in the SAP.

The EORTC QLQ-C30, EQ-5D-5L, PGIC and PGIS will be scored according to their respective user guides/scoring manuals. For the EORTC QLQ-C30 and EQ-5D-5L, missing items will be handled per the respective scoring manuals of each questionnaire. For the PGIS and PGIC, no adjustments for missing data will be performed.

9.4.3.9. Pharmacokinetic Analyses

Plasma concentrations of encorafenib and a metabolite LHY746, irinotecan and an active metabolite SN-38, and total and free plasma concentrations of platinum of oxaliplatin will be determined using validated assays. Descriptive statistics of concentrations of encorafenib and LHY746, irinotecan and SN-38, and oxaliplatin will be reported and summarized graphically. Pharmacokinetic parameters from the SLI arms and in the up to 16 Chinese participants in Phase 3 Arm A and Arm B will be generated by noncompartmental and/or compartmental approaches as appropriate, summarized and reported. Potential drug interactions between encorafenib and irinotecan or oxaliplatin will be assessed in the respective SLI arms by intra-participant comparisons or comparisons to historical results. Details of analyses will be included in statistical analysis plans and results will be reported.

9.4.3.10. Exposure-Response of Encorafenib

Descriptive statistics of trough plasma concentrations of encorafenib and a metabolite LHY746 will be reported for the Phase 3 portion of this study and in Cohort 3 Arm D. Phase 3 and Cohort 3 Arm D PK parameters will be estimated for encorafenib and LHY746 as appropriate using a population model-based approach and will be included in separate population PK reports, if appropriate. Relationships between PK of encorafenib and biomarkers, clinical response and/or safety will be conducted using post hoc exposure estimates (eg, C_{max} , AUC or C_{min}) from population PK modeling, if possible and appropriate. Measures of efficacy may include but are not limited to OS, PFS and ORR. Selection of safety measures will be based on frequency of observations or by selection of safety measures of interest. If appropriate, the impact of mFOLFOX6 on encorafenib exposure or responses will be evaluated by comparing Arm B to Arm A, or to historical data. Analyses will be described in separate stand-alone modeling plans and specific reports will be produced. In addition, if data permits, ER analysis with select safety and efficacy endpoints from Cohort 3 Arm D will be conducted and included in a separate report.

9.4.3.11. Biomarker Analyses

Patient plasma samples collected at C1D1 and C2D15 will be assayed to determine if ctDNA is detectable or not detectable. If ctDNA is detected it will be further assayed for the presence of tumor biomarkers such as *BRAF* V600 VAF and/or tumor-specific methylation. Patients will be assigned to subgroups based on whether ctDNA was detected or not at C1D1 and C2D15.

Summary statistics will be reported by subgroups for each arm. Analyses of ORR, PFS, and/or OS by treatment arm will be performed in subgroups considered to be adequately powered to provide informative results. Details of these analyses will be described in the SAP.

9.4.4. Tertiary/Exploratory Endpoints

The details of tertiary/exploratory endpoints analyses will be described in the SAP or in a separate exploratory analysis plan.

Results from exploratory analyses will be reported in the CSR where possible. However, given the exploratory nature of the objective and endpoints, the analyses may not be completed at the time of the CSR. Results from exploratory analyses that are not included in the CSR will be shared with the scientific community through publication at scientific conferences and/or in peer-reviewed scientific journals.

9.4.5. Safety Analyses

All safety analyses will be performed on the safety analysis set.

Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

9.4.5.1. Adverse Events

Adverse events will be coded using current MedDRA. Severity of AEs will be graded using the NCI CTCAE v 4.03 toxicity grading scale. Incidence tables will be presented for all AEs by maximum severity, SAEs, AEs assessed as related to study intervention and AEs resulting in discontinuation of study intervention. Details will be described in the SAP.

9.4.5.2. Clinical Laboratory Results

Clinical laboratory data will be classified by grade according to NCI CTCAE version 4.03 and will be analyzed using summary statistics. The worst on-treatment grades during the treatment period will be summarized. Shifts in toxicity grading from baseline to highest grade during the on-treatment period will be displayed. Results for laboratory tests that are not part of NCI CTCAE will be presented as below, within, or above normal limits. Only participants with post-baseline laboratory values will be included in these analyses. Further details of analyses for all the laboratory parameters will be provided in the SAP.

9.4.5.3. Electrocardiogram Analyses

ECG parameters QT interval, heart rate, QTcF interval, PR interval, and QRS complex will be summarized by treatment and time point. Further details of analyses for ECG parameters will be provided in the SAP.

9.4.6. Other Analyses

Descriptive statistics will be used to summarize all participant characteristics, treatment administration/compliance, vital signs, body weight and ECOG performance status. Data will also be displayed graphically, where appropriate.

Other exploratory PRO analyses may be performed subsequently as needed.

Pharmacogenomic or biomarker data from Banked Biospecimens may be collected during or after the trial and retained for future analyses; the results of such analyses are not planned to be included in the CSR.

9.4.6.1. Subgroup Analyses

Subgroup analyses will be performed to further assess the comparisons described by the primary and key secondary objectives. The HR of PFS and OS and the corresponding 95% CI will be computed and displayed per subgroup level using a forest plot. Further details including the precise subgroups used will be detailed in the SAP.

9.5. Interim Analyses

9.5.1. Interim Efficacy Analysis for OS (Phase 3)

The trial allows for stopping the study for a superior OS result, provided the primary ORR and/or PFS endpoint has already been shown to be statistically significant. A Lan-DeMets (O'Brien-Fleming) alpha-spending function⁸⁷ stopping boundaries will be used to control the overall type I error rate.

A maximum of three analyses are planned for OS as described below:

- 1) a first interim analysis at the time of ORR analysis if that analysis is positive;
- 2) if ORR analysis and/or the PFS result is positive, a second/first interim analysis could be performed at the time of PFS analysis;
- 3) a final analysis when 297 deaths are observed.

The exact boundaries will be calculated based on the actual number of events and the information fraction. The exact nominal p-values that will need to be observed to declare statistical significance at the time of these analyses for OS will depend on the number of OS events that have been observed at the time of these analyses and, the alpha for OS that can be used for this comparison and that already spent at the time of earlier analyses.

Interim analysis results may be used for decisions regarding stopping for early success, or adapting the study after the interim analysis. Participants may be discontinued from the study as a result of the interim analysis.

Before any interim analysis is conducted, the details of the objectives, decision criteria, dissemination plan and method of maintaining the study blind as per Pfizer's SOPs will be

documented. In addition, the analysis details will be documented and approved in the study SAP.

9.6. Data Monitoring Committee or Other Independent Oversight Committee

There will be an E-DMC to review cumulative safety data during the study conduct for the SLI, Phase 3, and Cohort 3, as well as review the efficacy at the interim analyses according to the charter. The E-DMC is independent of the study (ie, does not include any investigators in the study) and includes only members external to study Sponsors. The E-DMC will evaluate the safety data and PK data as it is available at pre-specified intervals and at additional points during the conduct of the SLI. During the Phase 3 portion of the study, the E-DMC will assess safety/tolerability after the first 30 participants have been randomized and treated for at least 1 cycle and then approximately every 6 or 12 months, as specified in the charter.

ORR and DOR for Phase 3 and Cohort 3 portions will be evaluated by E-DMC.

The recommendation made by the E-DMC to alter the conduct of the study will be forwarded to the appropriate Pfizer personnel for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of safety data, to regulatory authorities, as appropriate. The E-DMC charter describes the role of the E-DMC in more detail.

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 and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor, submitted to an IRB/ethics committee by the investigator, and reviewed and approved by the IRB/ethics committee before the study is initiated.

Any amendments to the protocol will require IRB/ethics committee approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/ethics committee annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/ethics committee;
- Notifying the IRB/ethics committee of SAEs or other significant safety findings as required by IRB/ethics committee procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH GCP guidelines, the IRB/ethics committee, European regulation 536/2014 for clinical studies, European Medical Device Regulation 2017/745 for clinical device research, and all other applicable local regulations.

10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of the ICH GCP that the investigator becomes aware of.

10.1.2. Financial Disclosure

Investigators and sub-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 regulatory 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.

10.1.3. Informed Consent/Assent Process

10.1.3.1. Adult Participants

The investigator or the investigator's representative will explain the nature of the study including the risks and benefits, to the participant or their legally authorized representative and answer all questions regarding the study. The participant or their legally authorized representative should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative (if allowed by local regulations) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH GCP guidelines, privacy and data protection requirements, where applicable, and the IRB/ethics committee or study center.

The investigator must ensure that each study participant or their legally authorized representative is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant or their legally authorized representative must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant or their legally authorized representative.

The participant or their legally authorized representative must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/ethics committee members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant or their legally authorized representative is fully informed about his or her right to access and correct their personal data and to withdraw consent for the processing of his or her personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date on which the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants or their legally authorized representative must be reconsented to the most current IRB/ethics committee version of the IRB/ethics committee-approved ICD(s) during their participation in the study as required per local regulations.

A copy of the ICD(s) must be provided to the participant or their legally authorized representative (if allowed by local regulations).

A participant who is rescreened is not required to sign another ICD if the rescreening occurs within 28 days from the previous ICD signature date.

Unless prohibited by local requirements or IRB/ethics committee decision, the ICD will contain a separate section that addresses the use of samples for optional additional research. The optional additional research does not require the collection of any further samples. The investigator or authorized designee will explain to each participant the objectives of the additional research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow specimens to be used for additional research. Participants who decline to participate in this optional additional research will not provide this separate signature.

10.1.3.2. Pediatric Participants

The investigator or their representative will explain the nature of the study to the participant and their parent(s)/legal guardian and answer all questions regarding the study. The participant and their parent(s)/legal guardian should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

When consent is obtained from a participant's parent(s)/legal guardian, the participant's assent (affirmative agreement) must be subsequently obtained when the participant has the capacity to provide assent, as determined by the IRB/ethics committee. If the investigator determines that a participant's decisional capacity is so limited they cannot reasonably be consulted, then, as permitted by the IRB/ethics committee and consistent with local regulatory and legal requirements, the participant's assent may be waived with source documentation of the reason assent was not obtained. If the study participant does not provide their own assent, the source documents must record why the participant did not provide assent (for example, the child is not of assenting age per local regulations or policies), how the investigator determined that the person signing the consent was the participant's parent(s)/legal guardian, the consent signer's relationship to the study participant, and that the participant's assent was obtained or waived. If assent is obtained verbally, it must be documented in the source documents.

If study participants are minors who reach the age of majority or if a child reaches the age of assent (per local IRB/ethics committee requirements) during the study, as recognized under local law, the child or adolescent must then provide the appropriate assent or consent to document their willingness to continue in the study. For an adolescent, who reaches the age of consent, parental consent would no longer be valid. If the enrollment of emancipated minors is permitted by the IRB/ethics committee and local law, the participant must provide documentation of legal status to give consent without the permission of a legally authorized representative.

Participants and their parent(s)/legal guardian must be informed that their participation is voluntary. The participant's parent(s)/legal guardian will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/ethics committee or study center.

The investigator must ensure that each study participant's parent(s)/legal guardian and the study participant as applicable are fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant's parent(s)/legal guardian must be informed that the participant's personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant's parent(s)/legal guardian.

The participant's parent(s)/legal guardian must be informed that the participant's medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/ethics committee members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant's parent(s)/legal guardian is fully informed about their right to access and correct their child's personal data and to withdraw consent for the processing of their child's personal data, keeping in mind the privacy rights that may restrict access of older adolescents' medical records by their parent(s)/legal guardian in certain regions.

The source documentation must include a statement that written informed consent, and as applicable assent, was obtained before the participant was enrolled in the study and the date the written consent/assent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Parent(s)/legal guardian and the participant must be reconsented to the most current version of the ICD(s)/assent during their participation in the study as required per local regulations.

A copy of the ICD(s) and assent, if written, must be provided to the parent(s)/legal guardian and the participant.

A participant who is rescreened is not required to sign another ICD if the rescreening occurs within 28 days from the previous ICD signature date.

Unless prohibited by local requirements or IRB/ethics committee decision, the ICD will contain a separate section that addresses the use of samples for optional additional research. The optional additional research does not require the collection of any further samples. The investigator or authorized designee will explain to each participant the objectives of the additional research. Participants will be told that they are free to refuse to participate and may withdraw their consent/assent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow specimens to be used for additional research. Participants who decline to participate in this optional additional research will not provide this separate signature.

10.1.4. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to their actual identity and medical record ID. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

The sponsor maintains SOPs on how to respond in the event of unauthorized access, use, or disclosure of sponsor information or systems.

10.1.5. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT/CTIS, and/or www.pfizer.com, and other public registries and websites in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT/CTIS

Pfizer posts clinical trial results on EudraCT/CTIS for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

www.pfizer.com

Pfizer posts CSR synopses and plain-language study results summaries on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov. CSR synopses will have personally identifiable information anonymized.

Documents within marketing applications

Pfizer complies with applicable local laws/regulations to publish clinical documents included in marketing applications. Clinical documents include summary documents and CSRs including the protocol and protocol amendments, sample CRFs, and SAPs. Clinical documents will have personally identifiable information anonymized.

Data Sharing

Pfizer provides researchers secure access to participant-level data or full CSRs for the purposes of “bona-fide scientific research” that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make data from these trials available 18 months after study completion. Participant-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information anonymized.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.6. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Guidance on completion of CRFs will be provided in the CRF Completion Requirements document.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password protected or secured in a locked room to prevent access by unauthorized third parties.

QTLs are predefined parameters that are monitored during the study. Important deviations from the QTLs and any remedial actions taken will be summarized in the CSR.

The investigator must permit study-related monitoring, audits, IRB/ethics committee review, and regulatory agency inspections and provide direct access to source records and documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy including definition of study-critical data items and processes (eg, 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 noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the data management plan and monitoring plan maintained and utilized by the sponsor or designee.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional 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. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.7. 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 investigator site.

Data reported on the CRF or entered in the eCRF that are 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. Also, current medical records must be available.

Definition of what constitutes source data can be found in the clinical monitoring plan.

Description of the use of computerized system is documented in the Data Management Plan.

10.1.8. Study and Site Start and Closure

The study start date is the date of the first participant's first visit.

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, including (but not limited to) regulatory authority decision, change in opinion of the IRB/ethics committee, or change in benefit-risk assessment. 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.

The investigator may initiate study-site closure at any time upon notification to the sponsor or designee/CRO if requested to do so by the responsible IRB/ethics committee or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/ethics committee or local health authorities, the sponsor's procedures, or the ICH GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ethics committees/IRBs, the regulatory authorities, and any 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.

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.9. Publication Policy

For multicenter trials, the primary publication will be a joint publication developed by the investigator and Pfizer reporting the primary endpoint(s) of the study covering all study sites. The investigator agrees to refer to the primary publication in any subsequent publications. Pfizer will not provide any financial compensation for the investigator's participation in the preparation of the primary congress abstract, poster, presentation, or primary manuscript for the study.

Investigators are free to publish individual center results that they deem to be clinically meaningful after publication of the overall results of the study or 12 months after primary completion date or study completion at all sites, whichever occurs first, subject to the other requirements described in this section.

The investigator will provide Pfizer an opportunity to review any proposed publication or any other type of disclosure of the study results (collectively, "publication") before it is submitted or otherwise disclosed and will submit all publications to Pfizer 30 days before submission. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days upon request from Pfizer. This allows Pfizer to protect proprietary information and to provide comments, and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study-intervention or Pfizer-related information necessary for the appropriate scientific presentation or understanding of the study results. For joint publications, should there be disagreement regarding interpretation and/or presentation of specific analysis results, resolution of, and responsibility for, such disagreements will be the collective responsibility of all authors of the publication.

For all publications relating to the study, the investigator and Pfizer will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors. The investigator will disclose any relationship with Pfizer and any relevant potential conflicts of interest, including any financial or personal relationship with Pfizer, in any publications. All authors will have access to the relevant statistical tables, figures, and reports (in their original format) required to develop the publication. The results of this study may be published or presented at scientific meetings by the investigator after publication of the overall study results or 1 year after the end of the study (or study termination), whichever comes first.

10.1.10. Sponsor's Qualified Medical Personnel

The sponsor will designate a medically qualified individual (MQI, also known as the medical monitor) to advise the investigator on study-related medical questions. The contact information for the study medical monitor is documented in the Study Team Contact List located in the Investigator Site File.

Participants are provided with a Pfizer study information card at the time of informed consent which includes contact information for their investigator in case of study-related medical questions. The study information card contains, at a minimum, (a) study number, (b) participant's study identification number, and (c) principal investigator contact information.

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10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests will be performed at times defined in the [SoA](#) section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory, or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

Table 35. Protocol-Required Safety Laboratory Assessments

Hematology	Chemistry	Urinalysis	Coagulation	Other
<ul style="list-style-type: none"> • Hemoglobin • Hematocrit • RBC count • Platelet count • WBC count • Total neutrophils (Abs) 	<ul style="list-style-type: none"> • BUN^a • Creatinine • Glucose • Calcium • Sodium • Magnesium • Potassium • Chloride • Total CO₂ (bicarbonate)^b • AST, ALT • Albumin • Total bilirubin • Direct bilirubin (if total bilirubin values are above normal) • Alkaline phosphatase • Uric acid • Total protein • Lipase • LDH 	<ul style="list-style-type: none"> • pH • Glucose (qual) • Protein (qual) • Blood (qual) • Ketones 	<ul style="list-style-type: none"> • PT or INR • PTT or aPTT 	<ul style="list-style-type: none"> • Pregnancy test (β-hCG)^c <p><u>At screening only:</u></p> <ul style="list-style-type: none"> • FSH^d • Hepatitis B surface antigen (at Screening)^e • Hepatitis C antibody (at Screening)^f • HIV, as applicable per local regulations <p><u>Tumor markers:</u></p> <ul style="list-style-type: none"> • CRP • CEA

a Urea may be collected for local laboratory testing

b Not required if not included in the chemistry panel at the site laboratory. Investigators should follow up per institutional standard of care (eg, blood gas analysis) if warranted by required laboratory test results.

c Serum at screening and urine β-hCG during the study for female participants of childbearing potential.

Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/ethics committee.

d For confirmation of postmenopausal status only.

e If HBsAg positive, HBV DNA must be measured

f If HCV antibody positive, HCV RNA must be measured

The investigator must review the central laboratory report, document this review and record any clinically significant changes occurring during the study in the AE section of the CRF.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
<ul style="list-style-type: none">• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.• NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>Meeting</u> the AE Definition
<ul style="list-style-type: none">• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:<ul style="list-style-type: none">• Is associated with accompanying symptoms.• Requires additional diagnostic testing or medical/surgical intervention.• Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.• Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.• New conditions detected or diagnosed after study intervention administration 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. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events **NOT** Meeting the AE 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 (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Worsening of signs and symptoms of the malignancy under study should be recorded as AEs in the appropriate section of the CRF. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as AEs.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. 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 that hypothetically might have caused death if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization 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 hospitalization are AEs. If a

complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether “hospitalization” occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person’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, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised 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 hospitalization but may jeopardize 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 hospitalization, or development of drug dependency or drug abuse.
- Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the active collection period. Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE. If the malignancy has a fatal outcome during the study or within the active collection period, then the event leading to death must be recorded as an AE on the CRF, and as an SAE with CTCAE Grade 5 (see the Assessment of Intensity section).
- Suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms “suspected transmission” and “transmission” are considered synonymous. These cases are considered unexpected and handled as

serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the CT SAE Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious adverse events (AEs); and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure	All AEs/SAEs associated with exposure during pregnancy or breastfeeding Occupational exposure is not recorded.	All (and EDP supplemental form for EDP) Note: Include all SAEs associated with exposure during pregnancy or breastfeeding. Include all AEs/SAEs associated with occupational exposure.

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.

- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the CT SAE Report Form/AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.
- 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 AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

GRADE	Clinical Description of Severity
1	MILD adverse event
2	MODERATE adverse event
3	SEVERE adverse event
4	LIFE-THREATENING consequences; urgent intervention indicated
5	DEATH RELATED TO adverse event

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/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 IB and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE 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. 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.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as “related to study intervention” for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.

- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as the data become available.
- After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via CT SAE Report Form

- Facsimile transmission of the CT SAE Report Form is the preferred method to transmit this information to Pfizer Safety.
- In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Report Form pages within the designated reporting time frames.

10.4. Appendix 4: Contraceptive Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 6 months after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention(s):

- Refrain from donating sperm.

PLUS either:

- Be abstinent from heterosexual intercourse with a female of childbearing potential as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

OR

- Must agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.

10.4.2. Female Participant Reproductive Inclusion Criteria

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Is not a WOCBP (see definitions below in [Section 10.4.3](#)).

OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency, as described below during the intervention period and for at least 9 months after the last dose of study intervention, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention(s). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.
- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with high user dependency, as described below during the intervention period and for at least 9 months after the last dose of study intervention, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention(s). In addition, a second effective method of contraception, as described below, must be used. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

10.4.3. Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenarchal.
2. Premenopausal female with 1 of the following:
 - Documented hysterectomy;
 - Documented bilateral salpingectomy;
 - Documented bilateral oophorectomy.

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

3. Postmenopausal female:
 - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition, a
 - high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years of age and not using hormonal contraception or HRT.
 - Female on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen 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.

10.4.4. Contraception Methods

Contraceptive use by men or women should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

Highly Effective Methods That Have Low User Dependency

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.
2. Intrauterine device.
3. Intrauterine hormone-releasing system.
4. Bilateral tubal occlusion.
5. Vasectomized partner.
 - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

Highly Effective Methods That Are User Dependent

6. Combined (estrogen and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
 - Oral;
 - Intravaginal;
 - Transdermal;
 - Injectable.
7. Progestogenonly hormone contraception associated with inhibition of ovulation:
 - Oral;
 - Injectable.

8. Sexual abstinence:

- Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

One of the following effective barrier methods must be used in addition to the highly effective methods listed above:

- Male or female condom with or without spermicide;
- Cervical cap, diaphragm, or sponge with spermicide;
- A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

10.5. Appendix 5: Genetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Therefore, where local regulations and IRBs/ethics committees allow, blood and tumor tissue samples will be collected for DNA and/or RNA analysis.
- The scope of the genetic research may be narrow (eg, 1 or more candidate genes) or broad (eg, the entire genome), as appropriate to the scientific question under investigation.
- The samples may be analyzed as part of a multistudy assessment of genetic factors involved in the response to the study interventions or study interventions of this class to understand treatments for the disease(s) under study or the disease(s) themselves.
- The results of genetic analyses may be reported in CSR or in a separate study summary, or may be used for internal decision making without being included in a study report.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained as indicated:
 - Samples for biomarker analyses (see Section 8.8) will be stored for up to 10 years following the last participant's last visit for the study or for another period as per local requirements.
 - Samples for banking will be stored indefinitely or for another period as per local requirements.
- Participants may withdraw their consent/assent for the storage and/or use of their Banked Biospecimens at any time by making a request to the investigator; in this case, any remaining material will be destroyed. Data already generated from the samples will be retained to protect the integrity of existing analyses.
- Banked Biospecimens will be labeled with a code. The key between the code and the participant's personally identifying information (eg, name, address) will be held at the study site and will not be provided to the sample bank.

10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury, but adapt are termed “adaptors.” In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are “susceptible” to progressive and serious liver injury, commonly referred to as DILI. Participants who experience a transaminase elevation above $3 \times \text{ULN}$ should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

In the majority of DILI cases, elevations in AST and/or ALT precede TBili elevations ($>2 \times \text{ULN}$) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above $3 \times \text{ULN}$ (ie, AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy’s law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant’s individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy’s law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values $\geq 3 \times \text{ULN}$ AND a TBili value $\geq 2 \times \text{ULN}$ with no evidence of hemolysis and an alkaline phosphatase value $< 2 \times \text{ULN}$ or not available.
- For participants with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:
 - Preexisting AST or ALT baseline values above the normal range: AST or ALT values ≥ 2 times the baseline values AND $\geq 3 \times \text{ULN}$; or $\geq 8 \times \text{ULN}$ (whichever is smaller).
 - Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of $\geq 1 \times \text{ULN}$ **or** if the value reaches $\geq 3 \times \text{ULN}$ (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment. The possibility of hepatic neoplasia (primary or secondary) should be considered.

In addition to repeating measurements of AST and ALT and TBili for suspected cases of Hy's law, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

10.7. Appendix 7: ECG Findings of Potential Clinical Concern

ECG Findings That <u>May</u> Qualify as Adverse Events
<ul style="list-style-type: none"> Marked sinus bradycardia (rate <40 bpm) lasting minutes. New PR interval prolongation >280 msec. New prolongation of QTcF to >480 msec (absolute) or by >60 msec from baseline. New-onset atrial flutter or fibrillation, with controlled ventricular response rate: ie, rate <120 bpm. New-onset type I second-degree (Wenckebach) AV block of >30 seconds' duration. Frequent PVCs, triplets, or short intervals (<30 seconds) of consecutive ventricular complexes.
ECG Findings That <u>May</u> Qualify as Serious Adverse Events
<ul style="list-style-type: none"> QTcF prolongation >500 msec. New ST-T changes suggestive of myocardial ischemia. New-onset left bundle branch block (QRS >120 msec). New-onset right bundle branch block (QRS >120 msec). Symptomatic bradycardia. Asystole: <ul style="list-style-type: none"> In awake, symptom-free patients in sinus rhythm, with documented periods of asystole ≥3.0 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node; In awake, symptom-free patients with atrial fibrillation and bradycardia with 1 or more pauses of at least 5 seconds or longer; Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm. Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute).

- Ventricular rhythms >30 seconds' duration, including idioventricular rhythm (heart rate <40 bpm), accelerated idioventricular rhythm (HR 40 bpm to <100 bpm), and monomorphic/polymorphic ventricular tachycardia (HR >100 bpm (such as torsades de pointes)).
- Type II second-degree (Mobitz II) AV block.
- Complete (third-degree) heart block.

ECG Findings That Qualify as Serious Adverse Events

- Change in pattern suggestive of new myocardial infarction.
- Sustained ventricular tachyarrhythmias (>30 seconds' duration).
- Second- or third-degree AV block requiring pacemaker placement.
- Asystolic pauses requiring pacemaker placement.
- Atrial flutter or fibrillation with rapid ventricular response requiring cardioversion.
- Ventricular fibrillation/flutter.
- At the discretion of the investigator, any arrhythmia classified as an adverse experience.

The enumerated list of major events of potential clinical concern are recommended as “alerts” or notifications from the core ECG laboratory to the investigator and Pfizer study team, and not to be considered as all inclusive of what to be reported as AEs/SAEs.

10.8. Appendix 8: Country-Specific Requirements

10.8.1. France Contract Unique

1. GCP Training

Before enrolling any participants, the investigator and any subinvestigators will complete the Pfizer-provided Good Clinical Practice training course (“Pfizer GCP Training”) or training deemed equivalent by Pfizer. Any investigators who later join the study will do the same before performing study-related duties. For studies of applicable duration, the investigator and subinvestigators will complete Pfizer GCP Training or equivalent every 3 years during the term of the study, or more often if there are significant changes to the ICH GCP guidelines or course materials.

2. Study Intervention

No participants or third-party payers will be charged for study intervention.

3. Urgent Safety Measures

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

4. Termination Rights

Pfizer retains the right to discontinue development of encorafenib at any time.

10.8.2. Mainland China Specific Procedures

In mainland China, central laboratory results should be used to confirm participant eligibility, however, local laboratory results will be acceptable throughout the remainder of the study for clinical safety laboratory assessments and captured in the eCRF.

The below samples, collected for testing as per [Section 8.8](#) Biomarkers, will be sent to Personalis, Inc. laboratory in the United States for testing. The samples left over after analysis will be destroyed by Sharps Solutions LLC in the United States.

- Pre-treatment tumor tissue samples to enable retrospective genomic profiling (eg, *RAS* mutations, MSI status) and expression analyses (eg, gene, protein).
- Approximately 4 mL whole blood samples at baseline for filtering of somatic mutation data.

10.9. Appendix 9: RECIST 1.1

CATEGORIZING LESIONS AT BASELINE

Measurable Lesions

Lesions that can be accurately measured in at least one dimension.

- Lesions with longest diameter twice the slice thickness and at least 10 mm or greater when assessed by computed tomography or MRI (slice thickness 5-8 mm).
- Lesions with longest diameter at least 20 mm when assessed by chest X-ray.
- Superficial lesions with longest diameter 10 mm or greater when assessed by caliper.
- Malignant lymph nodes with the short axis 15 mm or greater when assessed by computed tomography.

NOTE: The shortest axis is used as the diameter for malignant lymph nodes, longest axis for all other measurable lesions.

Non-measurable disease

Non-measurable disease includes lesions too small to be considered measurable (including nodes with short axis between 10 and <15 mm) and truly non-measurable disease such as pleural or pericardial effusions, ascites, inflammatory breast disease, leptomeningeal disease, lymphangitic involvement of skin or lung, clinical lesions that cannot be accurately measured with calipers, abdominal masses identified by physical exam that are not measurable by reproducible imaging techniques.

- **Bone disease:** Bone disease is non-measurable with the exception of soft tissue components that can be evaluated by computed tomography or MRI and meet the definition of measurability at baseline.
- **Previous local treatment:** A previously irradiated lesion (or lesion subjected to other local treatment) is non-measurable unless it has progressed since completion of treatment.

Normal sites

- **Cystic lesions:** Simple cysts should not be considered as malignant lesions and should not be recorded either as target or non-target disease. Cystic lesions thought to represent cystic metastases can be measurable lesions, if they meet the specific definition above. If non-cystic lesions are also present, these are preferred as target lesions.
- **Normal nodes:** Nodes with short axis <10 mm are considered normal and should not be recorded or followed either as measurable or non-measurable disease.

RECORDING TUMOR ASSESSMENTS

All sites of disease must be assessed at baseline. Baseline assessments should be done as close as possible prior to study start. For an adequate baseline assessment, all required scans should be done within 28 days prior to treatment and all disease must be documented appropriately. If baseline assessment is inadequate, subsequent statuses generally should be indeterminate.

Target lesions

- All measurable lesions up to a maximum of 2 lesions per organ, 5 lesions in total, representative of all involved organs, should be identified as target lesions at baseline. Target lesions should be selected on the basis of size (longest lesions) and suitability for accurate repeated measurements. Record the longest diameter for each lesion, except in the case of pathological lymph nodes for which the short axis should be recorded. The sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions at baseline will be the basis for comparison to assessments performed post-baseline.
- If two target lesions coalesce the measurement of the coalesced mass is used. If a large target lesion splits, the sum of the parts is used.
- Measurements for target lesions that become small should continue to be recorded. If the lesion is considered to have disappeared, 0 mm should be recorded; otherwise if a lesion is determined to be present but too small to measure, the lesion status will indicate “too small to measure and judged to be less than 10 mm” and 5 mm will be used in the calculation of the sum of the diameters.

NOTE: When nodal lesions decrease to <10 mm (normal), the actual measurement should still be recorded.

Non-target disease

- All non-measurable disease is non-target. All measurable lesions not identified as target lesions are also included as non-target disease. Measurements are not required but rather assessments will be expressed as ABSENT, INDETERMINATE, PRESENT/NOT INCREASED, INCREASED. Multiple non-target lesions in one organ may be recorded as a single item on the case report form (eg, ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

OBJECTIVE RESPONSE STATUS AT EACH EVALUATION.

Disease sites must be assessed using the same technique as baseline, including consistent administration of contrast and timing of scanning. If a change needs to be made the case must be discussed with the Investigator or radiologist and the sponsor to determine if substitution is possible. If not, subsequent objective statuses are not evaluable.

Target disease

- Complete Response (CR): Complete disappearance of all target lesions with the exception of nodal disease. All target nodes must decrease to normal size (short axis <10 mm). All target lesions must be assessed.
- Partial Response (PR): Greater than or equal to 30% decrease under baseline of the sum of diameters of all target measurable lesions. All target lesions must be assessed.
- Stable Disease (SD): Does not qualify for CR, PR or Progression. All target lesions must be assessed. Stable can follow PR only in the rare case that the sum increases by less than 20% from the nadir (smallest sum of diameters; consider baseline and all assessments prior to the time point under evaluation), but enough that a previously documented 30% decrease no longer holds.
- Objective Progression (PD): 20% increase in the sum of diameters of target measurable lesions above the smallest sum observed (over baseline if no decrease in the sum is observed during therapy), with a minimum absolute increase of 5 mm.
- Not evaluable (NE): Progression has not been documented, and
 - one or more target lesions have not been assessed or
 - assessment methods used were inconsistent with those used at baseline or
 - one or more target lesions cannot be measured accurately (eg, poorly visible unless due to being too small to measure) or
 - one or more target lesions were excised or irradiated and have not reappeared or increased.

Non-target disease

- CR: Disappearance of all non-target lesions and normalization of tumor marker levels (if being followed). All lymph nodes must be 'normal' in size (<10 mm short axis).
- Non-CR/Non-PD: Persistence of any non-target lesions and/or tumor marker level (if being followed) above the normal limits.
- PD: Unequivocal progression of pre-existing lesions. Generally the overall tumor burden must increase sufficiently to merit discontinuation of therapy. In the presence of SD or PR in target disease, progression due to unequivocal increase in non-target disease should be rare.
- Not evaluable (NE): Progression has not been determined and
 - one or more non-target lesion sites have not been assessed or
 - assessment methods used were inconsistent with those used at baseline or
 - one or more non-target lesions cannot be assessed (eg, poorly visible or unclear images) or

- one or more non-target lesions were excised or irradiated and have not reappeared or increased.

New Lesions

The appearance of any new unequivocal malignant lesion indicates PD. If a new lesion is equivocal, for example due to its small size, continued assessment will clarify the etiology. If repeat assessments confirm the lesion, then progression should be recorded on the date of the initial assessment. A lesion identified in an area not previously scanned will be considered a new lesion.

Supplemental Investigations

- If CR determination depends on a residual lesion that decreased in size but did not disappear completely, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate. If no disease is identified, objective status is CR.
- If progression determination depends on a lesion with an increase possibly due to necrosis, the lesion may be investigated with biopsy or fine needle aspirate to clarify status.

Subjective progression

Participants requiring discontinuation of treatment without objective evidence of disease progression should not be reported as PD on tumor assessment CRFs. This should be indicated on the end of treatment CRF as off treatment due to Global Deterioration of Health Status. Every effort should be made to document PD even after discontinuation of study treatment.

Determination of Tumor Response by RECIST

When both target and non-target lesions are present, individual assessments will be recorded separately. New lesions will also be recorded separately. Determination of tumor response at each assessment based on target, non-target and new lesions is summarized below:

Table 36. Objective Response Status at Each Assessment for Participants With Measurable Disease at Baseline

Target Lesions	Non-target Lesions	New Lesions	Objective status
CR	CR	No	CR
CR	Non-CR/Non-PD or 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

* Non-PD includes CR and Non-CR/Non-PD

** New lesions must be unequivocal

10.10. Appendix 10: Patient Global Impression of Severity and Patient Global Impression of Change

Patient Global Impression of Severity

Please choose the response below that best describes the severity of your colorectal cancer over the past 7 days.

Select only ONE response.

- None
- Mild
- Moderate
- Severe

Patient Global Impression of Change

Please choose the response below that best describes the overall change in your colorectal cancer since you started taking the study medication.

Select only ONE response.

- Much better
- A little better
- No change
- A little worse
- Much worse

10.11. Appendix 11: Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
5-FU	fluorouracil
Abs	absolute
ACE	angiotensin-converting enzyme
ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
Arm C	Control Arm
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the concentration-time curve
AV	atrioventricular
AxMP	auxiliary medicinal product
BBB	bundle-branch block
BCRP	breast cancer-resistance protein
β-hCG	beta-human chorionic gonadotropin
BICR	blinded independent central review
BID	twice a day
BOR	best overall response
Bpm	beats per minute
<i>BRAF</i>	B-Raf proto-oncogene
BRAF	serine/threonine-protein kinase B-Raf
BSA	body surface area
BUN	blood urea nitrogen
CAP	College of American Pathologists
CAPOX	capecitabine/oxaliplatin
CD4	cluster of differentiation 4
CDx	companion diagnostic
CE	Conformité Européene
CEA	carcinoembryonic antigen
cfDNA	circulating free DNA
CFR	Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CLIA	Clinical Laboratory Improvement Amendments

Abbreviation	Term
C _{max}	maximum concentration
C _{min}	minimum concentration
CNS	central nervous system
CO ₂	carbon dioxide (bicarbonate)
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CR	complete response
CRC	colorectal cancer
CRF	case report form
CRO	contract research organization
CRP	C-reactive protein
CSR	Clinical Study Report
CT	clinical trial; computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
CYP	cytochrome P450 enzyme (1A2, 2B6, 2C8, 2C9, 2C19 and 3A4 refer to isoforms)
DDI	drug-drug interaction
DDR	DNA damage response and repair
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
dMMR	deficient mismatch repair
DOR	duration of response
DPD	dihydropyrimidine dehydrogenase
DRE	disease-related event
EC	encorafenib plus cetuximab
ECG	electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group performance status
eCRF	electronic case report form
E-DMC	External Data Monitoring Committee
EDP	exposure during pregnancy
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 – 30 Item Core Questionnaire
EOT	end of treatment
EQ-5D-5L	EuroQol-5D-5L
EQ VAS	EuroQol-visual analogue scale
ERK	extracellular signal-regulated kinase
ESMO	European Society for Medical Oncology
EU	European Union
EudraCT	European Clinical Trials Database

Abbreviation	Term
FAS	full analyses set
FDA	Food and Drug Administration
FDG-PET	fluorodeoxyglucose-positron emission tomography
FFPE	formalin-fixed paraffin-embedded
FOLFIRI	fluorouracil/leucovorin/irinotecan
FOLFOX	fluorouracil/leucovorin/oxaliplatin
FOLFOXIRI	fluorouracil/leucovorin/oxaliplatin/irinotecan
FSH	follicle-stimulating hormone
G-CSF	granulocyte colony-stimulating factor
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GI	gastrointestinal
GM-CSF	granulocyte-macrophage colony stimulating factor
HA	health authority
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HFSR	hand foot skin reaction
HGRAC	Human Genetics Resources Administration of China
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HR	hazard ratio; heart rate
HRT	hormone replacement therapy
IA	Interim Analysis
IB	Investigator's Brochure
ICD	informed consent/assent document
ICH	International Council for Harmonisation
ID	identification
IEC	Independent Ethics Committee
IMP	investigational medicinal product
IND	Investigational New Drug
INR	international normalized ratio
IP manual	investigational product manual
IPAL	Investigational Product Accountability Log
IRB	Institutional Review Board
IRT	Interactive Response Technology
IV	intravenous
JSMO	Japanese Society of Medical Oncology
KA	keratoacanthoma
KRAS	KRAS proto-oncogene
LDH	lactate dehydrogenase

Abbreviation	Term
LFT	liver function test
LHY746	encorafenib metabolite
LPLV	last participant last visit
LQTS	long QT syndrome
LV	left ventricular
mCRC	metastatic colorectal cancer
MDRD	modification of diet in renal disease
MedDRA	Medical Dictionary for Regulatory Activities
MEK	mitogen-activated protein kinase kinase
mFOLFOX6	modified fluorouracil/leucovorin/oxaliplatin
MHRA	Medicines & Healthcare products Regulatory Agency
MMR	mismatch repair
mOS	median overall survival
mPFS	median progression-free survival
MQI	medically qualified individual
MRI	magnetic resonance imaging
MSI	microsatellite instability
MSI-H	microsatellite instability-high
MSS	microsatellite stable
MTD	maximum tolerated dose
n, N	number
NaF-PET	sodium fluoride-positron emission tomography
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCIC	National Cancer Information Center
NE	not evaluable
NGS	next generation sequencing
NIMP	noninvestigational medicinal product
NK1	neurokinin-1
NR	not reached
NRAS	NRAS Proto-Oncogene, GTPase
NTI	narrow therapeutic index
NYHA	New York Heart Association
OAT	organic anion transporter (1 and 3 refer to isoforms)
OATP	organic anion transporting polypeptide (1B1 and 1B3 refer to isoforms)
OCT	organic cation transporter (2 refers to isoform)
OR	objective response
ORR	objective response rate
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease
PD-L1	programmed death-ligand 1

Abbreviation	Term
PFS	progression-free survival
PFS2	progression after next line of therapy
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
P-gp	P-glycoprotein
PICC	peripherally inserted central catheter
PK	pharmacokinetic(s)
pMMR	proficient mismatch repair
PO	oral
PR	partial response
PRES	posterior reversible encephalopathy syndrome
PRO	patient reported outcome
PT	preferred term; prothrombin time
PTT	partial thromboplastin time
PVC	premature ventricular contraction/complex
Q2W	every 2 weeks
Q6W	every 6 weeks
Q8W	every 8 weeks
QALY	quality-adjusted life-year
QD	once daily
QoL	quality of life
QT	QT interval
QTc	corrected QT interval
QTcF	QTc corrected using Fridericia's formula
<i>RAS</i>	RAS family of proto-oncogenes
RAS	RAS GTPase
<i>RAF</i>	RAF family of proto-oncogenes
RAF	RAF GTPase
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RGQ	Rotor-Gene Q
RP2D	recommended Phase 2 dose
RPLS	reversible posterior leukoencephalopathy syndrome
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SC	steering committee
SCC	squamous cell carcinoma
SD	standard deviation; stable disease
SEER	surveillance, epidemiology, and end results
SLI	Safety Lead-in
SmPC	Summary of Product Characteristics

Abbreviation	Term
SN-38	active metabolite of irinotecan
SN-38G	inactive metabolite of irinotecan
SoA	schedule of activities
SOC	standard of care
SOP	standard operating procedure
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
T	temperature
TBili	total bilirubin
TdP	Torsades de Pointes
TKI	tyrosine kinase inhibitor
TME	tumor microenvironment
TOC	table of contents
TTR	time to response
UGT	uridine 5'-diphospho-glucuronosyltransferase (1A1 refers to isoform)
UK	United Kingdom
ULN	upper limit of normal
US	United States
USA	United States of America
USPI	United States Prescribing Information
VAF	variant allele fraction
VEGF	vascular endothelial growth factor
WBC	white blood cell
WHO	World Health Organization
WOCBP	woman of childbearing potential
wt	wild type

10.12. Appendix 12: Alternative Measures During Public Emergencies

The alternative study measures described in this section are to be followed during public emergencies, including the COVID-19 pandemic globally, if allowed by local regulation. This appendix applies for the duration of the COVID-19 pandemic and will become effective for other public emergencies only upon written notification from Pfizer.

Use of these alternative study measures are expected to cease upon the return of business as usual circumstances (including the lifting of any quarantines and travel bans/advisories).

10.12.1. Eligibility

While SARS-CoV-2 testing is not mandated for this study, local clinical practice standards for testing should be followed. A participant should be excluded if he/she has a positive test result for SARS-CoV-2 infection, is known to have asymptomatic infection, or is suspected of having SARS-CoV-2. Participants with active infections are excluded from study participation as per exclusion criterion 13. When the infection resolves, the participant may be considered for re-screening.

10.12.2. Telehealth Visits

In the event that in-clinic study visits cannot be conducted, every effort should be made to follow up on the safety of study participants at scheduled visits per the Schedule of Activities (Section 1.3) or unscheduled visits. Telehealth visits may be used to continue to assess participant safety and collect data points. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (e.g., audio, video, video-conferencing software) remotely, allowing the participant and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. The following assessments must be performed during a telehealth visit:

- Review and record study intervention(s), including compliance and missed doses.
- Review and record any AEs and SAEs since the last contact. Refer to Section 8.3.
- Review and record any new concomitant medications or changes in concomitant medications since the last contact.
- Review and record contraceptive method and results of pregnancy testing. Confirm that the participant is adhering to the contraception method(s) required in the protocol. Refer to Section 8.2.9, Appendix 4 (Section 10.4) and Section 10.12.3 of this appendix regarding pregnancy tests.

Study participants must be reminded to promptly notify site staff about any change in their health status.

10.12.3. Alternative Facilities for Safety Assessments

10.12.3.1. Laboratory Testing

If a study participant is unable to visit the site for protocol-specified safety laboratory evaluations, testing may be conducted at a local laboratory if permitted by local regulations. The local laboratory may be a standalone institution or within a hospital. Refer to

Section 8.2.8 Clinical Safety Laboratory Assessments and Section 10.12.3, for the list of safety laboratory evaluations, including pregnancy testing required per protocol.

If a local laboratory is used, qualified study site personnel must order, receive, and review results. Site staff must collect the local laboratory reference ranges and certifications/accreditations for filing at the site. Laboratory test results are to be provided to the site staff as soon as possible. The local laboratory reports should be filed in the participant's source documents/medical records. Relevant data from the local laboratory report should be recorded on the CRF.

If a participant cannot visit a local laboratory for pregnancy testing, a home urine pregnancy testing kit with a sensitivity of at least 25 IU/mL may be used by the participant to perform the test at home, if compliant with local regulatory requirements. The pregnancy test outcome should be documented in the participant's source documents/medical records and relevant data recorded on the CRF. Confirm that the participant is adhering to the contraception method(s) required in this protocol.

10.12.3.2. Imaging

If the participant is unable to visit the study site for safety imaging assessments, the participant may visit an alternative facility to have the safety imaging assessment(s) performed. Qualified study site personnel must order, receive, and review results.

10.12.3.3. Electrocardiograms

If the participant is unable to visit the study site for ECGs, the participant may visit an alternative facility to have the ECGs performed. Qualified study site personnel must order, receive, and review results.

10.12.4. Study Intervention

If the safety of a trial participant is at risk because they cannot complete required evaluations or adhere to critical mitigation steps, then discontinuing that participant from study intervention must be considered.

Study intervention may be shipped by courier to study participants if permitted by local regulations and in accordance with storage and transportation requirements for the study intervention. Pfizer does not permit the shipment of study intervention by mail. The tracking record of shipments and the chain of custody of study intervention must be kept in the participant's source documents/medical records.

The following is recommended for the administration of study intervention for participants who have active confirmed (positive by regulatory authority-approved test) or presumed (test pending/clinical suspicion) SARS-CoV-2 infection:

- For symptomatic participants with active SARS-CoV-2 infection, study intervention should be delayed for at least 14 days from the start of symptoms. This delay is intended to allow the resolution of symptoms of SARS-CoV-2 infection.

- Prior to restarting treatment, the participant should be afebrile for 72 hours, and SARS-CoV-2-related symptoms should have recovered to \leq Grade 1 for a minimum of 72 hours. Notify the study team when treatment is restarted.
- Continue to consider potential drug-drug interactions as described in Section 6.5 for any concomitant medication administered for treatment of SARS-CoV-2 infection.

10.12.5. Home Health Visits

A home health care service may be utilized to facilitate scheduled visits per the Schedule of Activities. Home health visits include a healthcare provider conducting an in-person study visit at the participant's location, rather than an in-person study visit at the site. The following may be performed during a home health visit:

- Physical exam including dermatological lesions and vital signs
- Review and record study treatment(s), including compliance and missed doses.
- Review and record any AEs and SAEs since the last contact. Refer to Section 8.3.
- Review and record any new concomitant medications or changes in concomitant medications since the last contact.
- Review and record contraceptive method and results of pregnancy testing. Confirm that the participant is adhering to the contraception method(s) required in the protocol. Refer to Section 8.2.9 and Section 10.12.3 of this appendix regarding pregnancy tests.

10.12.6. Adverse Events and Serious Adverse Events

If a participant has COVID-19 during the study, this should be reported as an adverse event (AE) or serious adverse event (SAE) and appropriate medical intervention provided. Study treatment should continue unless the investigator/treating physician is concerned about the safety of the participant, in which case temporary or permanent discontinuation may be required.

It is recommended that the Investigator discuss temporary or permanent discontinuation of study intervention with the Pfizer medical monitor.

10.12.7. Efficacy Assessments

If the participant is unable to visit the study site for imaging assessments (e.g., CT, MRI, X-ray, FDG-PET), the participant may visit an alternative facility to have the imaging assessments performed. Qualified study site personnel must order, receive, and review results.

10.12.8. Independent Oversight Committees

There will be no impact on the Steering Committee Charter or E-DMC Charter. The Steering Committee and E-DMC will continue to be consulted during public health emergencies.

10.13. Appendix 13: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the table of contents (TOC). The protocol amendment summary of changes tables for past amendment(s) can be found below:

Amendment 6	13 March 2024	<p>The main purpose of Protocol Amendment 6 is to modify the required number of PFS events by BICR needed to conduct the primary PFS analysis for the Phase 3 portion of the study to enable a timely readout of the PFS given a slower-than-expected accrual of events.</p> <ol style="list-style-type: none"> Section 9.2 Sample Size Determination <ul style="list-style-type: none"> Modified the power and the number of PFS events by BICR required for the Phase 3 PFS primary endpoint and removed the sentence about duration of follow up. Section 9.4.1.1 Statistical Testing Strategy <ul style="list-style-type: none"> Modified the number of PFS events by BICR required for the Phase 3 PFS primary endpoint and added the condition about minimal follow-up. Added a sentence that PFS of Cohort 3 will be analyzed descriptively if ORR analysis is not significant. Section 1.1 Synopsis, Objectives, Endpoints, and Estimands; Section 3 Objectives, Estimands, and Endpoints <ul style="list-style-type: none"> Updated the secondary objective and endpoint pertaining to the correlation between ctDNA and outcome for both Phase 3 and Cohort 3. Section 3 Objectives, Estimands, and Endpoints <ul style="list-style-type: none"> Added a new tertiary/exploratory objective and endpoint pertaining to the surgical conversion rate for both Phase 3 and Cohort 3 Section 9.1.1 Estimands <ul style="list-style-type: none"> Updated the population for the OR for Arm B vs Control Arm to the first 110 participants who are randomized in the Phase 3 portion of the study into each of Arm B and Arm C (Full Analysis Set, ORR Subset). Section 9.1.1, Table 32: PFS Outcome and Event Dates – Primary Analysis <ul style="list-style-type: none"> Updated the situation pertaining to ‘no adequate baseline’ assessment to include no disease at baseline.
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		<p>7. Section 9.1.1, Table 32: PFS Outcome and Event Dates – Primary Analysis; Section 9.4.2 Primary Endpoints</p> <ul style="list-style-type: none"> Modified the definition of new anticancer therapy by removing reference to target/non-target lesions. <p>8. Section 9.3 Analysis Sets</p> <ul style="list-style-type: none"> Added a ‘Full Analysis Set, ORR Subset’. <p>9. Section 9.4.1.4 Definition of Baseline</p> <ul style="list-style-type: none"> Added a rule in the event that no efficacy assessment was performed before randomization, but was done before the start of study treatment. <p>10. Section 9.4.3.11 Biomarker Analyses</p> <ul style="list-style-type: none"> Added a more detailed description of planned ctDNA analyses. <p>11. Section 9.5.1 Interim Efficacy Analysis for OS (Phase 3)</p> <ul style="list-style-type: none"> Removed that details of IA for OS will be documented and approved in an E-DMC charter. <p>12. Section 9.6 Data Monitoring Committee or Other Independent Oversight Committee</p> <ul style="list-style-type: none"> Added that cumulative safety data will be reviewed by the E-DMC for Phase 3 and Cohort 3, in addition to the SLI. Added that ORR and DOR for Phase 3 and Cohort 3 will be evaluated by E-DMC. <p>13. Title page</p> <ul style="list-style-type: none"> Added regulatory agency identification numbers and Sponsor address. <p>14. Section 1.1 Synopsis</p> <ul style="list-style-type: none"> Defined abbreviations at first use and removed cross references to sections and literature citations outside the synopsis. Added protocol title, brief title, and regulatory agency identification numbers. Removed tertiary/exploratory objectives and endpoints from the table in the synopsis for all 3 phases of the study.
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		<ul style="list-style-type: none"> Added section on study population. Added section on ethical considerations. <p>15. Section 2.3 Benefit/Risk Assessment</p> <ul style="list-style-type: none"> Removed DDIs as a potential risk as this was removed from Section 2.3.1 in Protocol Amendment 5. <p>16. Section 4.2.5 Biomarkers</p> <ul style="list-style-type: none"> Updated the description and rationale for the ctDNA analyses. <p>17. Section 6.1 Study Interventions Administered</p> <ul style="list-style-type: none"> Added AxMP as a potential intervention classification type. Added a new row to include SRSD for each study intervention. <p>18. Section 6.5.1.4 Drugs with a Conditional or Possible Risk to Prolong the QT Interval and/or Induce Torsade de Pointes</p> <ul style="list-style-type: none"> Updated the website link for CredibleMeds. <p>19. Section 6.5.2 Prohibited Concomitant Therapy</p> <ul style="list-style-type: none"> Updated the website link for Drug Interactions Solutions. <p>20. Section 8.8.3 Circulating Free DNA (cfDNA)</p> <ul style="list-style-type: none"> Updated the analyses of cfDNA and added methylation changes to the description of possible assessments. <p>21. Section 10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations</p> <ul style="list-style-type: none"> Incorporated protocol template updates throughout this section. <p>22. Section 10.13, Appendix 13: Protocol Amendment History, Amendment 5</p> <ul style="list-style-type: none"> Removed all text regarding the removal of Cohort 4. Corrected text pertaining to number of participants in Phase 3. <p>23. References</p>
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		<ul style="list-style-type: none"> The list of references was updated accordingly. <p>24. Throughout Protocol</p> <ul style="list-style-type: none"> Editorial revisions and typographical errors were corrected. <p>25. Section 8.2.7 Electrocardiograms</p> <ul style="list-style-type: none"> Modified the resting period prior to an ECG from 10 minutes to 5 minutes. <p>26. Section 10.1.10 Sponsor's Qualified Medical Personnel</p> <ul style="list-style-type: none"> Modified the process for contacting a medically qualified individual from a medical escalation process via a Pfizer Call Center to direct clinical team contact using a Study Team Contact List.
Amendment 5	20 December 2022	<p>1. Overall Protocol: Study design revision: Enrollment in Arm A was discontinued.</p> <p>2. Section 1.1 Synopsis:</p> <ul style="list-style-type: none"> Revised rationale text to include Cohort 3 Arms D and E. Revised Estimand text to include the Primary Estimand for Cohort 3. Revised Overall Design text to include Cohort 3 design and primary objective. Decreased the number of Phase 3 participants from 870 to 620: 150 participants in Arm A (enrollment discontinued), 235 each in Arm B and in Arm C. Added text for Cohort 3. Revised Intervention Groups and Duration text to include Arms D and E in Cohort 3. <p>3. Section 1.1 Objectives, Estimands, and Endpoints:</p> <ul style="list-style-type: none"> Added ORR as primary objective and endpoint. Removed reference to Arm A as key secondary objective and PFS as endpoint. Added OS as secondary objective and ORR as secondary endpoint for Arm A vs Control Arm and Arm B. Added objectives and endpoints (ORR, DOR, PFS, TTR, & OS) for Cohort 3.

		<ul style="list-style-type: none"> Added Tertiary/Exploratory objectives/endpoints. <p>4. Section 1.1 Estimands: Added discussion of OR and ORR for Arm B and Control Arm.</p> <p>5. Section 1.1 Overall Design: Added text about FOLFIRI and mFOLFOX6 for use in Cohort 3.</p> <p>6. Section 1.1 Number of Participants: Revised number of participants for Phase 3 and added number of participants for Cohort 3.</p> <p>7. Section 1.1 Intervention Groups and Duration: Added information for Cohort 3.</p> <p>8. Section 1.1 Data Monitoring Committee or Other Independent Oversight Committee: Removed study phase specification in the paragraph that describes imaging.</p> <p>9. Section 1.2 Schema: Revised study design figure to show revision of Phase 3 study design and to include Cohort 3.</p> <p>10. Section 1.3 Schedule of Activities: Clarified +3 day window applies to a study visit. Revised Table 3 to reflect the addition of Cohort 3 Arm D:</p> <ul style="list-style-type: none"> Specified Cetuximab infusion is for Arm A, Arm B, and Cohort 3 Arm D Only and FOLFIRI is only applicable to Cohort 3 Arm D. Removed optional Bevacizumab dosing for Cohort Arm E. Removed Arm and Cohort specific details from tumor radiographic assessment (CT, MRI) timing. <p>Revised Table 4. To reflect the addition of Cohort 3 Arm E:</p> <ul style="list-style-type: none"> Specified mFOLFOX6 and FOLFOXIRI are Arm C only and FOLFIRI is Arm E only. <p>11. Section 2.3.1 Risk Assessment: Removed Potential Risk of Drug-Drug Interaction section for over-exposure of irinotecan/SN-38 due to CYP3A4 inhibition by encorafenib. Rationale expanded in 4.2.2.</p> <p>12. Section 3 Objectives, Estimands, and Endpoints: Changes as detailed above in Section 1.1.</p> <p>13. Section 4.1 Overall Design:</p> <ul style="list-style-type: none"> Revised text to include Cohort 3 (Arms D and E).
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		<ul style="list-style-type: none"> Decreased the number of Phase 3 participants from 870 to 620: 150 participants in Arm A (enrollment discontinued), 235 each in Arm B and in Arm C. Added text for Cohort 3. <p>14. Section 4.2.2 Assessment of Potential DDI with Encorafenib:</p> <ul style="list-style-type: none"> Revised text to include in vitro studies indicating encorafenib is reversible inhibitor of some CYP450 enzymes and UGT1A1. Added text on observed reduction in irinotecan exposure when co-administered with encorafenib at steady state. Added text that encorafenib does not inhibit CYP3A on Day 1 at clinically relevant doses. <p>15. Section 4.2.4 Progression-Free Survival and Objective Response Rate as Primary Endpoints: Section modified to account for addition of ORR as primary endpoint for Phase 3 and addition of Cohort 3 endpoints.</p> <p>16. Section 4.4 End of Study Definition: Revised definition to be based on LSLV, not on number of events.</p> <p>17. Section 5.1.1 Molecular Prescreening Inclusion Criteria:</p> <ul style="list-style-type: none"> Included Cohort 3 in criterion #1 Replaced text regarding the central laboratory requirement for BRAF V600E confirmation from criterion # 10 with a reference to 8.7.2 for further clarification. Added text specifying a minimum of 10 tumor sample slides for mainland China is inserted for criterion #5. <p>18. Section 5.1.2 Screening Inclusion Criteria:</p> <ul style="list-style-type: none"> Added additional text to patients with oligometastatic colorectal cancer. Added text concerning prior systemic regimens and measurable disease for Cohort 3. Added text specifying a minimum of 10 tumor sample slides for mainland China is inserted for criterion #10. <p>19. Section 5.2.1 Molecular Prescreening Exclusion Criteria: Added text on Gilbert's syndrome for Cohort 3.</p> <p>20. Section 5.2.1 Medical Conditions Exclusion Criteria: Updated HBV DNA test result parameter for one of the active HBV definitions.</p>
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CT02-GSOP Oncology Clinical Protocol Template (01 May 2024)

Page 221

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		<p>21. Section 5.2.1 Prior/Concomitant Therapy Exclusion Criteria: Updated major surgery criteria.</p> <p>22. Section 5.3.1 Contraception: Added text requiring the use of hormonal agents when combined with other highly effective methods for patients taking encorafenib.</p> <p>23. Section 5.3.2 Meals and Dietary Restrictions: Added mention for Cohort 3.</p> <p>24. Section 5.3.3 Photosensitivity: Updated wording in alignment with encorafenib and 5-FU SRSDs.</p> <p>25. Section 6.1 Study Interventions Administered:</p> <ul style="list-style-type: none"> Added Cohort 3 where applicable in column headers. Updated footnote a regarding different presentations of leucovorin. <p>26. Section 6.1.2 Treatment Regimens: Added Tables 14 and 15 for Cohort 3 treatment regimens.</p> <p>27. Section 6.1.3.1 Administration of Encorafenib:</p> <ul style="list-style-type: none"> Revised text to include mention of Cohort 3. Removed text relating to DDI of encorafenib and irinotecan in SLI. <p>28. Section 6.3.1 Allocation to Study Intervention: Added information for Cohort 3.</p> <p>29. Section 6.5.1.2 CYP and UGT Substrates and Inhibitors: Added information regarding CYP3A based on recent data from ongoing DDI study.</p> <p>30. Section 6.5.1.3 Transporter Substrates and Inhibitors: Added text on dose reductions of drugs used concomitantly with encorafenib.</p> <p>31. Section 6.5.2 Prohibited Concomitant Therapy: Irinotecan was added to the last 2 bullet points in the section.</p> <p>32. Section 6.5.3.1 Premedication for Cetuximab Administration: Added Cohort 3 Arm D.</p> <p>33. Section 6.6: Dose Modification: Added mention of Cohort 3.</p> <p>34. Section 6.6.2 Dose Modification for Cetuximab: Added information for Cohort 3 as well as re-worded this section for clarity.</p>
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		<ul style="list-style-type: none"> Revised information for Phase 3 Arms and added information on analyses of ORR for Cohort 3. Revised information for statistical testing strategy. <p>50. Section 9.4.1.3 Stratification Factors: Added stratification information for Cohort 3.</p> <p>51. Section 9.4.2 Primary Endpoints: Added information on ORR and its use in Phase 3 and Cohort 3.</p> <p>52. Section 9.4.3 Secondary Endpoints: Added information on OS, ORR, TTR, PFS, and PROs in Cohort 3.</p> <p>53. Section 9.5.1 Interim Efficacy Analysis for OS (Phase 3): Removed interim analysis for PFS.</p> <p>54. Section 9.5.2 Interim Efficacy Analysis for OS: Revised text for analyses planned for OS and removed table for planned efficacy boundaries for OS.</p> <p>55. Throughout Protocol: Editorial revisions and typographical errors corrected.</p> <p>56. REFERENCES: The list of references has been updated accordingly.</p>
Amendment 4	28 February 2022	<p>Based on the safety lead-in (SLI) data showing the tolerability of encorafenib and cetuximab (EC)+chemotherapy treatment, the primary purpose of this amendment is to modify the primary and key secondary endpoints, the statistical procedure to preserve overall study alpha and update the sample size to align with the new statistical plan.</p> <p>Additionally, based on review of the totality of the SLI data, Arm B will consist of EC + mFOLFOX6; therefore, references to the use of FOLFIRI in Arm B and Arm C have been removed throughout. Clarifications and other administrative modifications have also been included throughout.</p> <ol style="list-style-type: none"> Section 1 Protocol Summary, Section 3 Objectives, Estimands and Endpoints, Section 4 Study Design, Section 5.2.1 Molecular Prescreening Exclusion Criteria 6b, 6.1 Study Intervention, Section 6.6 Dose Modifications, Section 9.4.3.10 Exposure-Response Relationship of Encorafenib: Removed references to FOLFIRI in Arm B and Arm C of Phase 3 Section 1.1 Synopsis, Section 4.1 Overall Design: Added paragraph regarding SLI data review and decision that Arm B will consist of EC in combination with mFOLFOX6 Section 1.1 Synopsis, Section 3 Objectives, Estimands and Endpoints and Section 4.1 Overall Design: Modified to align

		<p>with the primary and key secondary endpoints, testing strategy and updated sample size</p> <ol style="list-style-type: none"> 4. Section 1.1 Synopsis and Section 3 Objectives, Estimands and Endpoints and Section 8.5 Pharmacokinetics: Clarified, where appropriate, that the Phase 3 PK objective is for mainland China sites 5. Section 1.1 Synopsis: Clarified E-DMC review to be done according to the charter 6. Section 1.2 Schema: Updated figure to remove reference to FOLFIRI and updated Phase 3 sample size 7. Table 1 Schedule of Activities: Removed the DPD documentation row due to the heterogeneity in DPD testing practice worldwide 8. Table 2 Schedule of Activities: Removed BICR from radiological assessment row for consistency with Section 8.1.1 9. Table 2, 3 and 4 Schedule of Activities and Section 8.2.3 Physical Examination: Added weight assessment on Day 15 to align with standard practice 10. Table 4 Schedule of Activities: Added an X for bevacizumab administration to Day 15 to align with standard practice 11. Table 3, 4, 5 Schedule of Activities: <ul style="list-style-type: none"> • Added clarification on Cycle 1 Day 1 window • Added clarification on new anticancer therapy • Added clarification on when on-treatment biopsies should be collected 12. Table 3, 4, 5 Schedule of Activities and Section 8.8 Biomarkers, Section 8.8.3 Circulating Free DNA (cfDNA) and Section 8.8.5 Specified Protein Research: Clarified the collection volume of the cfDNA and protein biomarkers samples for mainland China 13. Table 5 Schedule of Activities: Added an X for contraceptive check at EOT Visit for consistency with other SoA tables 14. Section 4.4 End of Study Definition: Modified end of study definition to align with revised statistical analysis 15. Section 5.1.1 Molecular Prescreening Exclusion Criteria and 5.1.2 Screening Inclusion Criteria: Added clarification in criteria 5 and 10 on sample type, age of specimen and number of slides
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CT02-GSOP Oncology Clinical Protocol Template (01 May 2024)

Page 226

090177e1a0d4d2e4Approved\Approved On: 31-May-2024 20:59 (GMT)

		<p>26. Section 6.6 Dose Modification:</p> <ul style="list-style-type: none"> • Clarified recommendations regarding dosing on Day 1 of each cycle • Added dosing guidance in instance of cetuximab infusion reaction <p>27. Section 6.6.1 Dose Modifications for Encorafenib: Added guidance for encorafenib dose re-escalation</p> <p>28. Section 6.6.2 Dose Modifications for Cetuximab: Moved the sentence regarding cetuximab discontinuation instructions to Section 6.6.3</p> <p>29. Section 6.6.3 Dose Modifications for Oxaliplatin, Irinotecan and 5-FU and Capecitabine as Part of mFOLFOX6, FOLFIRI, and FOLFOXIRI and CAPOX Regimens: Modified entire section for clarification and alignment with standard-of-care practice</p> <p>30. Section 7.1 Discontinuation of Study Intervention: Added language regarding treatment beyond progression</p> <p>31. Section 8.1.1 Tumor Response Assessments:</p> <ul style="list-style-type: none"> • Added clarification on new anticancer therapy • Added radiologist guidance • Clarified BICR timing • Added language regarding treatment beyond progression <p>32. Section 8.1.2 Patient Reported Outcomes: removed paragraphs that were not applicable to the study</p> <p>33. Section 8.2.6 Vital Signs: Added flexibility on sequence of assessment with regards to laboratory tests</p> <p>34. Section 8.3.7. Disease Related Events and/or Disease Related Outcomes Not Qualifying as AEs or SAEs: Added clarification regarding when to collect fatal outcomes</p> <p>35. Section 8.5 Pharmacokinetics: Added clarification to the timing of predose samples to Table 28, Table 29 and Table 30 footnotes</p> <p>36. Section 8.7.3 Molecular Prescreening: Modified language for consistency with Section 5.1.2 and laboratory manual</p> <p>37. Section 8.8.2 Tumor Tissue Assessments: Added language regarding optional on-treatment de novo tumor biopsies</p>
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Amendment 3	24 February 2021	<p>The primary purpose of this amendment is to incorporate HA recommendations. The majority of HA comments were with regards to aligning recommendations (dosing, patient management) with locally approved labels/prescribing information (hereafter referred to as labels). In addition, clarifications and administrative modifications have also been included.</p> <ol style="list-style-type: none"> Section 1.1 Synopsis and Section 3 Objectives, Estimands and Endpoints: <ul style="list-style-type: none"> Added clarification that the PFS by BICR and OS Phase 3 Secondary objectives are for Arm A vs Arm B Removed that PFS2 is per RECIST v1.1 Section 1.1 Synopsis, Number of Participants and Section 4.1 Overall Design: added clarification that if neither SLI regimen is tolerated, Phase 3 will proceed without Arm B Table 1 Schedule of Activities: <ul style="list-style-type: none"> The X in the Contact IRT row has been moved from prescreening to the correct screening column A row for discussion of fertility preservation at screening has been added to align with locally approved product labels as requested by multiple health authorities Table 2, 3, 4 and 5 Schedule of Activities: <ul style="list-style-type: none"> Added a definition of End of Treatment for clarity Clarified visit windows

		<ul style="list-style-type: none"> Added windows and combined notes in the tumor radiographic assessment row Added clarification that PK sampling must occur on the day of dosing Clarified that blood samples for germline comparator and banked biospecimen only need to be collected at Cycle 1 <p>The following changes were made in response to health authority feedback:</p> <ul style="list-style-type: none"> Added a contraceptive check row to align with locally approved product labels Added that physical exam should include a visual assessment to align with encorafenib approved label Added a urine pregnancy test at 28-day follow-up visit <p>5. Table 3, 4 and 5 Schedule of Activities: Added clarification that the PROs should be done with the same frequency as the tumor assessments not visits</p> <p>6. Table 5 Schedule of Activities: clarified that verification of inclusion/exclusion and demography only need to be collected at Cycle 1</p> <p>7. Section 2.2.2.1 Current Recommendations for Treatment of BRAF V600E-mutant mCRC: added rationale for not including cetuximab in the control arm per health authority feedback</p> <p>8. Section 2.3 Benefit/Risk Assessment:</p> <ul style="list-style-type: none"> Clarified that levo-leucovorin and calcium folinate may be supplied in other countries and not limited to Japan and added definition of leucovorin. Added clarity that investigators should refer to locally approved product labels for the management of patients <p>9. Section 2.3.1 Risk Assessment: added adolescent participation discussion per health authority feedback</p> <p>10. Section 5.1 Inclusion Criteria:</p> <ul style="list-style-type: none"> Criteria 11 was updated to simplify definition of prior therapy <p>The following changes were made in response to health authority feedback:</p> <ul style="list-style-type: none"> Criteria 1 was updated to only allow participants ≥ 16 years in countries where permitted
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CT02-GSOP Oncology Clinical Protocol Template (01 May 2024)

Page 229

		<ul style="list-style-type: none"> Criteria 4 was updated to clarify participants must have stage IV disease and a note added for patients with oligometastatic disease <p>11. Section 5.2 Exclusion Criteria:</p> <ul style="list-style-type: none"> Criteria 9 was clarified to exclude patients with unknown dMMR or MSI-H status Criteria 11e was updated to add clarification around eligibility of participants with bundle-branch block (BBB) or with an implanted cardiac pacemaker Criteria 18 was edited to further define prior treatments excluded in the SLI Criteria 21 was edited to exclude radiation therapy that included > 30% of the bone marrow <p>The following changes were made in response to health authority feedback:</p> <ul style="list-style-type: none"> Criteria 8 was updated to add unknown RAS mutation status Criteria 17 was updated to clarify participants with residual Grade 2 peripheral neuropathy may only be treated in the FOLFIRI cohort in SLI Criteria 22 was modified to clarify definition of investigational products <p>12. Section 5.3 Lifestyle Considerations:</p> <p>The following changes were made in response to health authority feedback:</p> <ul style="list-style-type: none"> Added a statement regarding participant fertility preservation prior to study intervention Section 5.3.1 Contraception: added recommendations for duration of contraception follow-up to align with locally approved product labels Added Section 5.3.3 regarding avoiding extended exposure to ultraviolet light to align with locally approved product labels <p>13. Section 6 Study Intervention:</p> <ul style="list-style-type: none"> Added clarity that investigators should refer to locally approved product labels for the management of patients Table 6.1: oxaliplatin dose formulation was corrected
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		<ul style="list-style-type: none"> Table 6.1: added clarification that all study interventions except encorafenib may be provided as non-IMP in the USA only Table 6.1 added that calcium folinate may also be supplied and clarified that levo-leucovorin and calcium folinate may be supplied in other countries and not limited to Japan <p>14. Section 6.1.1 Safety Lead-In: in response to health authority feedback, clarified that a decision to proceed as a 2-arm study will be made prior to the start of Phase 3</p> <p>15. Table 9 DLT Criteria: updates have been made to align with CTCAE dictionary terms</p> <p>16. Section 6.1.2 Treatment Regimens:</p> <ul style="list-style-type: none"> Have added text to indicate that study interventions should be administered in accordance with respective locally approved label or local institutional standards Table 10, 12, and 13: added that calcium folinate may also be supplied and removed Japan to allow flexibility for future use in other countries Table 10, 11, 12, and 13: have added clarification that all infusion times are approximate infusion times <p>17. Section 6.1.3.1 Administration of Encorafenib: Modified to align with recommended encorafenib dosing instructions</p> <p>18. Section 6.1.3.2 Administration of Capecitabine, Cetuximab, 5-Fluorouracil, Irinotecan, Leucovorin, Oxaliplatin and Bevacizumab: have added that these study interventions may also be administered per local institutional standards</p> <p>19. Section 6.5.1.4 Drugs with a Conditional or Possible Risk to Prolong the QT Interval and/or Induce Torsade de Pointes: added investigators should also use caution when administering oxaliplatin in response to health authority feedback</p> <p>20. Section 6.5.2 Prohibited Concomitant Therapy: guidance has been added regarding the administration of COVID-19 vaccines</p> <p>21. Section 6.5.3.5 Hematopoietic Growth Factors: added section to outline the use of hematopoietic growth factors on the study</p> <p>22. Table 15 Recommended Encorafenib Dose Modifications: edits have been made to align with approved encorafenib label</p> <p>23. Section 6.6 Dose Modifications: A statement previously inserted in Amendment 2 has been removed as it now conflicts with</p>
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		<p>instruction that study interventions should be administered in accordance with local institutional standards</p> <p>24. Section 6.6.2, 6.6.3, 6.6.3, 6.6.4, and 6.6.5 Dose Modifications for the other study interventions: added instruction to refer to the locally approved product labels for adverse reactions not specifically mentioned in response to health authority feedback</p> <p>25. Table 20, 21 and 22 Recommended Dose Modifications: edits have been made to align with locally approved product labels</p> <p>26. Table 21 Recommended Capecitabine Dose Reductions: table has been removed based it conflicted with the previous Table 22 Recommended Capecitabine Dose Modifications</p> <p>27. Section 7.1 Discontinuation of Study Intervention: clarifications have been made throughout regarding the end of treatment and follow-up visits.</p> <p>28. Section 8.1.1 Tumor Response Assessments: added clarification that skeletal target lesions should be imaged by CT, MRI or X-ray</p> <p>29. Section 8.2.3 Physical Examinations: In response to health authority feedback, added clarification that new or worsening visual disturbances should be assessed</p> <p>30. Section 8.2.7 Electrocardiograms: added guidance per locally approved product labels in response to health authority feedback</p> <p>31. Section 8.2.9 Pregnancy Testing: redundant language has been removed</p> <p>32. Section 8.5 Pharmacokinetics</p> <ul style="list-style-type: none"> Added clarification that PK sampling must occur on the day of dosing and that samples should not be drawn from the same arm as the IV is being administered Added clarification around timepoints relative to dosing Added a table for Phase 3 sampling schedule Added tables for PK sampling schedules for participants in China <p>33. 8.7.3 Molecular Prescreening: Moved the statement regarding registration in the IRT to the appropriate section 8.7.2 Screening</p> <p>34. Section 8.8 Biomarkers: clarified that genomic profiling is to be done retrospectively</p>
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		<ul style="list-style-type: none"> Text has been updated to align with the text in Section 8.2.8 <p>43. Appendix 4, Section 10.4.2 Female Participant Reproductive Inclusion Criteria: duration of contraception in female participants was extended to until 9 months after the last dose of study intervention in compliance with locally approved product labels</p> <p>44. Appendix 10:</p> <ul style="list-style-type: none"> Updated instructions for completion of the PROs Updated the PRO scores to reflect actual forms being used <p>45. Appendix 12: added that alternative study measures are to be followed if allowed by local regulations.</p>
Amendment 2	12 November 2020	<p>The primary purpose of this amendment is to incorporate MHRA recommendations.</p> <ol style="list-style-type: none"> Added Section 2.2.2.3 Management of Cancer Patients During COVID-19 Pandemic. <p>Rationale: to provide information to consider in the treatment of participants during the COVID-19 pandemic.</p> <ol style="list-style-type: none"> Section 2.3.1 Risk Assessment: revised to add risks associated with COVID-19 and potential mitigation strategies. Section 2.3.3 Overall Benefit/Risk Conclusion: added statement regarding benefit/risk for participants during the current COVID-19 pandemic. Section 6.6.6 Guidance for Administration of Study Intervention in Participants with SARS Cov-2 Infection: added reference to Appendix 12 for further mitigation strategies. Section 8.7.2 <i>BRAF</i> Testing: added clarification that the kit used is partially CE-marked for its analytical performance according to 98/79/EC Annex VIII and is an US FDA approved medical device. Section 8.7.5 Companion Diagnostic for Eligibility: added clarification that BRAF V600E test kit is partially CE marked. Appendix 4, Section 10.4.1 Male Participant Reproductive Inclusion Criteria: duration of contraception in male participants was extended to until six months after the last dose of study intervention in compliance with the SmPCs of oxaliplatin and 5-fluorouracil. Added Appendix 12, Alternative Measures During Public Emergencies: to describe possible alternative study measures to

		be followed during public emergencies, including the COVID-19 pandemic.
Amendment 1	07 August 2020	<p>The primary purpose of this amendment is to incorporate CHMP Scientific Advice recommendations. In addition, clarifications and administrative modifications have also been included.</p> <ol style="list-style-type: none"> 1. Table 1 Schedule of Activities and Exclusion Criteria (Section 5.2, Criteria 5): Added that, where recommended by local label or guidelines, patients must be tested for dihydropyrimidine dehydrogenase (DPD) deficiency before initiating treatment with fluorouracil or capecitabine. <p>Rationale: Alignment with recent EMA guidance (EMA recommendations on DPD testing prior to treatment with fluorouracil, capecitabine, tegafur and flucytosine- 30 April, 2020).</p> <ol style="list-style-type: none"> 2. Risk/Benefit Assessment (Section 2.3) and Study Interventions Administered (Section 6.1): Added clarification that levo-leucovorin may be supplied only in Japan. <p>Rationale: To provide clarification levo-leucovorin will not be supplied as an IMP in other participating countries.</p> <ol style="list-style-type: none"> 3. Table 13 Treatment Regimens (Control Arm): Added a clarifying statement that the 5-FU dose used in FOLFOXIRI regimen may be administered per local standard of care. <p>Rationale: As per CHMP Scientific Advice that pointed out different doses are considered standard-of-care in Europe and US.</p> <ol style="list-style-type: none"> 4. Dose Modifications (Section 6.6): Added a statement to the dose modification that Day 1 and Day 15 chemotherapy infusions may not begin until serum potassium and magnesium are within institutional normal limits (replacement permitted). <p>Rationale: To maintain alignment with inclusion/exclusion criteria.</p> <ol style="list-style-type: none"> 5. Genetics (Section 8.7): Added the following: Molecular profiling will be performed as described in Section 8.8. There is no intent to perform specific free-standing germline genomic analyses, but will be used as controls to assist in identifying and profiling somatic tumor mutations (See Section 8.8.2 for further details). No additional specified genetics will be evaluated in this study. <p>Rationale: To update text with recently revised standard language from Pfizer Translational Oncology.</p> <ol style="list-style-type: none"> 6. Table 31 OS – Summary of Planned Efficacy Boundaries: A data entry error regarding the number of cumulative OS events was corrected.
Original protocol	15 July 2020	N/A

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