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1. TITLE PAGE

STATISTICAL ANALYSIS PLAN

NCT Number : NCT03693170

Reference:	**W00090 GE 2 01**
Author: Name (First & Last name)	PII [redacted]
Title	**Statistician**
Version n°:	**5**
Date:	**22JAN2021**

2. SIGNATURES

	Title	Name (First & Last name)	Consistency between SAP and study protocol	Date	Signature
Author	**Statistician**	PII [redacted]	**NA**		
Reviewer	**Clinical Program Director**	PII [redacted]	**NA**		
Approving Officer	**Head of Biometry Department DMPC**	PII [redacted]	☐ **Confirmed**		

3. VERSIONING

Version	Date	Author (First & Last name)	Pages or sections concerned	Nature (*)	Reason(s) for change (**)
1	24OCT2018	PII [redacted] PII	All	C	
2	15FEB2019 (draft V2)	PII [redacted]	section 15.4 (Vital Signs)	M	"both direction" was deleted in "shift table based on NCI-CTCAE v4.03 grade for hypertension at baseline and worst post-baseline values (both direction) will be produced." Because Not Applicable to gradable Hypertension
			Appendix 5 (List of TFLs)	M	All titles were updated to be shorter and display the more relevant information. A rule was added for Stage 1/Stage 2 analyses and analyses performed on Japanese subjects, to display this information in the Title.
			Section 9.2 (Reporting conventions)	M	For qualitative variables, percentages will be computed on the analysis population (instead of the number of non-missing observations).
			Section 13 (Demographics and Baseline Characteristics)	M	MSI status to be described as "Disease characteristics" instead of "BRAF mutation".
			Section 15.6 (MUGA/Echo) + Appendix 5 (List of TFLs)		Listing 12_5_3_1 (Subjects with LVEF abnormalities [FAS]) and 12_5_3_8 (Listing of subjects with grade 2 or above NCI-CTCAE v4.03 abnormalities [FAS]) were similar in SAP v1. Listing 12_5_3_8 was deleted and 12_5_3_1 was replaced by a Listing of subjects with grade 2 or above NCI-CTCAE v4.03 abnormalities [FAS]. Section 15.6 was reworded to clarify.
			Section 15.10 (Ophthalmologic examination) + Appendix 5 (List of TFLs)	M	Visual Field, fundoscopy and slit lamp: Section was reworded to be more explicit on the analyses to be performed. Title of Tables was also updated to be more accurate.

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			Section 15.10 (Ophthalmologic examination) + Appendix 5 (List of TFLs)	M	LogMAR analysis: the section was reworded to be more explicit on the analyses to be performed. "The number of patients reporting at least once an increase in score of <=0 (no deterioration), >0 to <0.1, 0.1 to <0.2, 0.2 to <0.3 and ≥0.3 LogMAR will be summarized in shift table" now reads: " LogMAR results will be summarized in a shift table from Baseline score (≤0, >0 to <0.1, 0.1 to <0.2, 0.2 to <0.3 and ≥0.3) to worst post-baseline value (≤0 (no deterioration), >0 to <0.1, 0.1 to <0.2, 0.2 to <0.3 and ≥0.3)." Title of Table was also updated to be more accurate.
			Section 9.1.2 (Dates and Period) + section 15.2 (Adverse Events) + section 15.11 (Concomitant Therapies and diagnostic procedures) + section 18 (Healthcare resource utilization)	A	Clarification was added to the definition of the study period (30 days post-last study treatment administration included) so that the definition of the treatment period is unequivocal and consistent across the document.
			Section 5 (List of Abbreviations)	A	TA = Tumor Assessment added to the List of Abbreviations.
			Section 13 (Demographics and Baseline Characteristics)	D	TNM classification at study entry not required to be described. Stage at study entry is sufficient.
			Section 13 (Demographics and Baseline Characteristics)	M	ECOG Performance Status to be described as "Disease characteristics".

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			Any section	M	When referring to study drug/treatment: "definitive discontinuation replaced by "discontinuation "temporary discontinuation" replaced by "interruption"
			Section 9.1.1 (Reporting conventions)	M	Treatment label updated, to start each drug name with a capital letter ("Encorafenib + Binimetinib + Cetuximab"). Label was also provided for summaries by study drug (when applicable): respectively "Encorafenib", "Binimetinib" and "Cetuximab".
			Section 13 (Demographics and Baseline Characteristics)	M	Time since initial diagnosis: typo was corrected in the derivation rule: "date of initial diagnosis of primary site diagnosis" now reads "date of initial diagnosis of primary site".
			Section 15.1 (Treatment Exposure)	A	Duration of study drug exposure to be also be described as a discrete variable, with modalities t to < t+4 weeks (t being the duration of exposure, in weeks), such as: < 4 weeks / 4 - < 8 weeks / - < 12 weeks / etc
			Section 13 (Demographics and Baseline Characteristics) + Section 15.2 (Adverse Events) + section 15.11 (Concomitant Therapies and diagnostic procedures)	M	Descriptions by WHO-Drug ATC1, ATC2 and ATC3 replaced by descriptions by ATC2, ATC4 and Preferred Term.

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			Section 15.2 (Adverse Events)	A	Clarification was added regarding the description of AE leading to Death (by SOC and PT): on-treatment deaths will be summarized (i.e. occurring during treatment and up to 30 days after last study treatment).
			Section 15.2 (Adverse Events)	A	Definitions of Related AE, AE leading to discontinuation/interruption/dose reduction for a specific drug were not explicitly stated in the SAP and were added.
			All document	M	Following Audit Clinical Quality Assurance (DEC2018): line spacing was harmonized across document.
			Appendix 4 (Table 2)	D	Following Audit Clinical Quality Assurance (DEC2018): Wording: "QTcF *" replaced by "QTcF"
			Section 6.1 (Study Design)	A	Following Audit Clinical Quality Assurance (DEC2018): A paragraph was added to explicitly state how data collected from BRAF negative subjects will be used: "Subjects with an unconfirmed BRAFV600E mutation status will be included in the Full Analysis Set when they have received at least one dose of study treatment (partial or full), and will then be analyzed for efficacy, safety, quality of life, biomarkers and healthcare resource utilization (cf. section 7)."
			Section 13 (Demographics	A	"Blood sample for MSI testing (control sample) will not be processed until the

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			and Baseline Characteristics)		End of the Study. MSI Status will thus remain undetermined during the study and will be described when available (End Of Study analysis)."
			Section 6.6 (Cut-off dates)	M	Reworded, to match the study protocol wording (version 5 of study protocol): "have either discontinued or have four post-baseline tumor assessments" now reads "had the opportunity to complete four post-baseline tumor assessments, and after subjects with an initial objective response have had an opportunity to have a confirmation scan"
			Section 15.3 (Laboratory Data)	A	Table updated according to version 5 of study protocol: add Myoglobin, Serum CK isoenzymes
			Section 6.1 (Study Design)	M	According to version 5 of study protocol: Update of the paragraph on the lack of confirmation of mutation / discordance between local and central (threshold before requirement to perform assessment using central laboratory).
			Section 12 (Disposition of subjects)	M	Clarification added: The number of subjects in each analysis set detailed in section 7 will be described on the Screened Subjects Set, so this does not apply to the Screened Subjects Set.
2	27FEB2019 (draft V2)	PII [redacted]	Section 6.9 (Study flow-chart)	M	Update with flow-charts from study protocol V5.

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			Section 6.5 (Sample Size) + Section 6.6 (Cut-off dates)	A	Definition of cut-off from the study Protocol completed to explicitly mention discontinued subjects.
			Section 15.2 (Adverse Events)	M	Paragraph on analysis of AE leading to death / Deaths reworded for a better understanding.
			Section 15.10 (Ophthalmic examination)	M	Added clarification on the definition of "subjects at risk of developing the abnormality": "with baseline not missing and not being significantly abnormal in both eyes, and with at least one post-baseline value".
			Section 15.10 (Ophthalmic examination)	A	Following protocol amendment version 5: Add analysis for: General inspection, Motility examination, Alignment examination Visual disturbance (assessments not planned in previous versions of the study protocol).
			Section 14.1 (Primary endpoint)	M	"UNK" replaced by "NE" to be consistent with RECIST terminology. Derivation rules for BOCR aligned with those used in previous studies: PR to capture early progression (< 9 weeks after first study treatment administration). Progressions ≥ 9 weeks after first study treatment administration will be "NE" ("NE: not qualifying for confirmed CR or PR and without SD after more than 6 weeks or progression" now reads "NE: not qualifying for confirmed CR or PR and without SD after more than 6 weeks or early progression < 9 weeks")

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					Add description of reasons for having unknown status in Non-Evaluable patients.
			Section 12 (Disposition)	D	"Prematurely discontinued" now reads "discontinued"
			Section 12 (Disposition)	M	Analysis Sets (except Screened Subjects Set) to be described on the FAS and not on the Screened Subjects Set.
			Appendix 5	M	List of TFLs moved in an excel file.
			Section 14.1.3 (Exploratory Analysis)	M	Subgroup analysis using MSI status at screening to be performed upon availability of MSI Status.
2	22MAR2019 (Draft V2)	PII [redacted]	Section 14.2.4 (PFS)	M	Rewording: "PFS rates" replaced by "PFS estimated probabilities" to be consistent with the other sections of the document. 25th and 75th percentiles to be displayed too.
			Section 14.2.4 (PFS)	A	Censoring rules for PFS were detailed.
			Section 14.2.7 (DOR)	M	Censoring rules for DOR updated, to be consistent with the definition of DOR (study protocol and SAP section 6.3.2): "Patients who are lost to follow-up, or reach the time point of analysis without a known record of progression or death will have the duration of response censored at the date of last adequate tumor assessment." (and not "at the date of last tumour assessment or last

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					contact of a follow-up showing no progression, whichever occur last")
			Section 14.2.7 (DOR)	M	Definition of DOR updated to be consistent with the definition given in section 6.3.2 and in the study protocol.
			Section 9.3 (Analysis Visits)	M	"overall lesion response equal to 'Unknown'" replaced by "overall lesion response equal to 'Not Evaluable'" to be consistent with the wording used in the derivation rules for overall response (section 14).
			Section 14.2.7 (DOR)	A	Clarification added in text: median, 25th and 75th percentiles to be described, and estimated probabilities to be displayed, to be consistent with analyses performed on other endpoints.
			Section 15.2 (Adverse Events)	M	Clarification: description of related SAEs by SOC and PT to be performed overall and by study drug.
			Section 15.2 (Adverse Events)	M	Wording: "onset day" used everywhere (to replace "onset time", "time to onset", etc) to harmonize wording across document.
			Section 17 (Biomarkers) & Appendix 5 (List of TFLs)	D	Delete analyses performed on $BRAF^{V600E}$ mutation status in circulating tumor DNA (ctDNA). These analyses will not be part of the CSR but summarized in a separate report under the supervision of translational medicine department.
			Section 13 (Demographics and Baseline)	A	The number and percentage of subjects with at least one prior antineoplastic therapy (Radiotherapy) used prior to study entry to be tabulated by Best Overall Response too.
			Section 15.10 (Ophthalmic Examination)	M	Definition of subjects at risk of developing an abnormality (OCT, FA assessments) updated (compared to the initial definition written in draft V2, 27FEB2019) to be consistent with the definition used for Fundoscopy and slit lamp, as OCT and FA are considered as

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					non-optional assessments in protocol version 5.
2	29MAR2019 (Draft V2)	PII [redacted]	Section 15.3 (Laboratory Data)	D	Footnote b under Table 16 was deleted as not of interest for Statistical Analysis.
			Section 13 (Demographics) and Section 14.1.3 (Exploratory Analysis on primary endpoint)	M	Footnote on MSI Status reworded so that there is no reference to the timing of analysis for this variable + refer to appendix 5 (no need of an update of the SAP for changes (not major) in Appendix 5).
2	05APR2019 (Draft V2)	PII [redacted]	Section 14.2.4 (PFS) ; section 14.2.7 (DOR) ; section 14.2.9 (TTR)	A	Censoring rules were displayed using tables (in order to ease the understanding). No change in the definition of censoring/events.
2	05APR2019 (Final V2)	PII [redacted]	All	NA	Clean version 2 of the document.
3	22JUL2019 (Draft V3)	PII [redacted]	Section 14.2.1 (ORR for confirmed+unconfirmed)	A	Add detailed rules for derivation of BOR (confirmed+unconfirmed responses)
3	22JUL2019 (Draft V3)	PII [redacted]	Section 11.2.4 (missing or incomplete dates)	A	Correction: incomplete/missing end dates of Concomitant Medications should be imputed using the same rules as for AEs (not only applicable to start dates) Add imputation rules for Procedures (same as for Medications).
3	22JUL2019 (Draft V3)	PII [redacted]	Section 9.1.2 (Dates and Period)	A	Following dates should also be taken into account in the derivation of the last contact date: • Cardiac evaluation date with non-missing parameter value • ECG evaluation date with non-missing parameter value • Ophtalmologic evaluation date with non-missing parameter value

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					• Physical examination date with non-missing parameter value • Questionnaire evaluation date with non-missing parameter value (QS)
3	22JUL2019 (Draft V3)	PII [redacted]	Section 9.1.2 (Dates and Period)	M	"Assessment dates after the cut-off date will not be used to derive the last contact date" replaced by "If after derivation, the last contact date is posterior to the cut-off date, then the last contact date will be taken to be the cut-off date".
3	22JUL2019 (Draft V3)	PII [redacted]	Section 14 (Efficacy)	A	Clarification that "new antineoplastic therapy" refers to any additional secondary antineoplastic medication or surgery or radiotherapy, as collected in the e-CRF.
3	22JUL2019 (Draft V3)	PII [redacted]	Section 15.2 (Adverse Events)	A	Add in summary Table of AEs: - AEs leading to discontinuation of all study drugs - related AEs leading to discontinuation of all study drugs - AEs leading to discontinuation of Binimetinib and Encorafenib - related AEs leading to discontinuation of Binimetinib and Encorafenib
3	22JUL2019 (Draft V3)	PII [redacted]	Section 15.2 (Adverse Events) + Appendix 5 (List of TFLs)	M	SAE description by SOC and PT should be performed only on TESAEs. Idem for SAESIs.
3	29JUL2019 (Draft V3)	PII [redacted]	Section 9.3 (Analysis Visits)	M	Time windows for Chemistry: "Study days 9 to 222" corrected into "Study days 9 to 22"
3	30AUG2019 (Draft V3)	PII [redacted]	Section 12 (Disposition)	A	Number of subjects in PK set to be described only when PK analyses are performed (not relevant otherwise, as per definition of PK set)

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3	30AUG2019 (Draft V3)	PII [redacted]	Section 13 (Demographics and Baseline)	A	Added in description of disease characteristics, as per iDSMC recommendation (iDSMC #1): - Number of subjects with metastases at initial diagnosis - Time from initial diagnosis to first metastasis (days)
3	30AUG2019 (Draft V3)	PII [redacted]	Section 14.2.4 (PFS)	A	Censoring rules for PFS: wording updated to avoid any confusion: - "second scheduled tumor assessment" update in "second scheduled post-Baseline tumor assessment" - "new antineoplastic therapy given" updated in "new antineoplastic therapy given, prior progression of death without progression observed"
3	30AUG2019 (Draft V3)	PII [redacted]	Section 14.2.7 (DOR)	A	Censoring rules for DOR: wording updated to avoid any confusion: - "new antineoplastic therapy given" updated in "new antineoplastic therapy given, prior progression or death without progression observed"
3	27SEP2019 (draft V3)	PII [redacted]	Section 15.2 (Adverse Events)	A	Added in the summary table of AEs (these were already described in other tables): - Subjects with at least one AE leading to study drug discontinuation (respectively: binimetinib, encorafenib, cetuximab) - Subjects with at least one AE leading to death
3	27SEP2019 (draft V3)	PII [redacted]	Section 11.2.4 (Missing dates)	A	Add rules for imputation of missing dates of death
3	27SEP2019 (draft V3)	PII [redacted]	Section 11.2.4 (Missing dates)	A	Added: 'For adverse event with a start date and which are "ongoing", completely missing AE end date will be imputed to the cut-off date.'

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3	27SEP2019 (draft V3)	PII [redacted]	Section 11.2.4 (Missing dates)	A	Rules for imputation of prior/concomitant therapies and for prior/subsequent antineoplastic therapies were detailed.
3	27SEP2019 (draft V3)	PII [redacted]	Section 14.2.9 (Time to Response)	M	Clarification: "FAS responders" are "FAS confirmed responders"
3	08OCT2019 (draft V3)	PII [redacted]	Section 14.2.9 (Time to Response)	M	Censoring time for patients who do not achieve a CR or PR, and who have a PFS event (i.e. progressed or died due to any cause), assigned to maximum follow-up time, to be consistent with previous studies. Add case where no post-Baseline assessment
3	11OCT2019 (draft V3)	PII [redacted]	Section 15.1 (Treatment Exposure)	A	Definition of dose reduction and interruption were added, as missing in previous versions.
3	11OCT2019 (draft V3)	PII [redacted]	Section 14.2.4 (PFS)	A	A table with censoring rules for the sensitivity analysis of the PFS was added.
3	11OCT2019 (draft V3)	PII [redacted]	Section 15.11 (Concomitant therapies)	A	Time to Disease Progression after next regimen detailed (PFS after next line of treatment) Time to subsequent therapy was added.
3	18OCT2019 (draft V3)	PII [redacted]	Appendix 3 (AESI)	M	Corrections. Appendix displayed in a separate excel file.
3	28OCT2019 (draft V3)	PII [redacted]	Section 16 (QoL)	A	Add derivation of missing/incomplete/complete questionnaire
3	28OCT2019 (draft V3)	PII [redacted]	Section 17 (Biomarkers)	A	Add definition of Nadir
3	28OCT2019 (draft V3)	PII [redacted]	Section 15.4 (Vital Signs)	A	Add grading rules for hypertension, as per NCI-CTCAE
3	28OCT2019 (draft V3)	PII [redacted]	Appendix 4	M	Clarification: increase/decrase "from Baseline"

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3	30OCT2019 (draft V3)	PII [redacted]	Section 15.2 (Adverse Events)	A	Clarification in AESI analyses
3	06NOV2019 (draft V3)	PII [redacted]	Section 15.2 (Adverse Events)	M	KM analysis of time to first occurrence of AESI by grouping replaced by a description of onset day of AESI
3	06NOV2019 (draft V3)	PII [redacted]	Section 18 (Healthcare resource)	A	Parameters to be described were clarified.
3	06NOV2019 (draft V3)	PII [redacted]	Section 15.1 (Treatment exposure)	M	Duration of planned exposure and number of planned doses were clarified for Cetuximab.
3	06NOV2019 (draft V3)	PII [redacted]	Section 15.2 (Adverse Events)	D	Description of (general) medications started > 30 days after the EOT was deleted (not planned in Appendix 5). A listing of Medications is sufficient.
3	12NOV2019 (draft V3)	PII [redacted]	Section 11.2.4 (Missing or incomplete dates)	A	Add imputation rules for Date of initial diagnosis of primary site
3	12NOV2019 (draft V3)	PII [redacted]	Section 15.2 (Adverse Events)	M	Analyses of onset day of AESI and maximum duration of AESI were harmonized: to be performed by grouping an PT, overall and maximum Grade 3 or higher.
3	28NOV2019 (draft V3)	PII [redacted]	Section 15.7 (ECOG)	M	Shift table by visit replaced by a shift table of worst post-baseline grade
3	28NOV2019 (draft V3)	PII [redacted]	Section 15.9 (Dermatological examination)	A	Post-Baseline skin abnormalities to be described.
3	02DEC2019 (draft V3)	PII [redacted]	Section 14.1.3 (Exploratory)	M	Primary tumor location "Rectum" will be considered as Left-colon.
3	02DEC2019 (draft V3)	PII [redacted]	Section 17 (Biomarkers)	M	Population clarified for Scatter plots highlighting individual results will display baseline CEA vs baseline CA19-9 Levels, each BOCR being identified differently: will be produced on the FAS,
3	13JAN2020 (draft V3)	PII [redacted]	Section 13 (Demographics)	A	Primary tumor location for "other": "caecum" or "cecum" will be

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					considered as "colon, right" and "sigmoid" as "colon, left"
3	13JAN2020 (draft V3)	PII [redacted]	Section 11.2.4 (Missing or incomplete dates)	A	Add imputation rules for date of first metastasis
3	28JAN2020 (draft V3)	PII [redacted]	Section 15.3 (Laboratory)	A	Clarify that Drug Induced Injuries will be flagged using the SMQ "Drug related hepatic disorders"
3	28JAN2020 (draft V3)	PII [redacted]	Section 6.5 (Sample Size) and section 14.1.1 (Primary Analysis)	A	NB: Due to the time needed to get the central confirmation of the BRAFV600E mutation, more than 90 subjects with centrally confirmed BRAFV600E mutation may be treated. If so, the nominal alpha and power will be computed. The Clopper-Pearson (exact) binomial 95% confidence interval will be computed with 37 confirmed responders observed among the N patients and the lower limit will be compared to the clinically relevant response rate of 30%. Moreover, the primary analysis at Stage 2 will be repeated when excluding the overrunning patients (i.e. on the 90 first treated subjects with a centrally confirmed BRAFV600E mutation, see section 14.1.1) and differences between the two analyses will be discussed.
3	03MAR2020 (draft V3)	PII [redacted]	Section 15.2 (Adverse Events)	M	Imputation of end date of TEAESI for the calculation of duration. Paragraph replaced with reference made to section 11.2.4 (where imputation rules for AE end dates are described).
3	03MAR2020 (draft V3)	PII [redacted]	Section 15.3 (Laboratory)	A	Clarify that Drug Induced Injuries will be flagged using the SMQ "Drug related hepatic disorders" + narrow terms
3	03MAR2020 (draft V3)	PII [redacted]	Section 14.1.3 (Exploratory Analyses)		Added after Steering Committee Stage1: "At the time of the primary analysis (i.e. Stage 2 or at Stage 1 if study stops for futility), analysis of cORR based on investigator-assessed tumor evaluation will be repeated on the ES, when excluding the patients

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					with no confirmed metastatic disease at inclusion (i.e. Inclusion criterion #3 not filled)."
3	04MAR2020	PII [redacted]	-	-	Final Version 3
4	23MAR2020	PII [redacted]	Appendix 1 (Prior antineoplastic therapy Combinations)	M	Rewording of derivation rules: To ease the understanding and to take into consideration coding specificities
4	14APR2020	PII [redacted]	Section 9.3 (Analysis Visits)	D	Correction in derivation of Time windows for weight, ECOG PS, ophthalmic and dermatological examination, ECHO/MUGA, coagulation, urinalysis, EORTC QLQ-C30; EQ-5D-5L, PGIC: C1D1 post-dose deleted as not applicable for these assessments. Idem for hematology
4	14APR2020	PII [redacted]	Section 15.4 (Vital Signs)	A	Clarification added for derivation of grade for Systolic and diastolic BP combined (mmHg): "Maximum grade based on SBP and DBP values will be considered"
4	14APR2020	PII [redacted]	Appendix 4 (VITAL SIGNS AND ECG CLINICALLY NOTABLE ABNORMALITIES)	M	Correction typo for body temperature abnormal low value: ≤ 36°C.
4	14APR2020	PII [redacted]	Title page	D	Remove PII [redacted] (author of SAP V1) from the signature page
4	18MAY2020	PII [redacted]	Section 14.2.1 (cORR as per central review)	A	Add a paragraph to describe how to handle central review data (two different readers)
4	18MAY2020	PII [redacted]	Section 15.6 (ECHO/MUGA)	M	Clarification of rules to define LVEF abnormality, to take into account decimal values (not only integer). Clarification of rules to define LVEF abnormality: change from baseline

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					mean absolute change, not relative change.
4	18MAY2020	PII [redacted]	Section 13 (Demographics & baseline characteristics)	A	Add description of age using new categories Add description of number of subjects with lung metastases only.
4	18MAY2020	PII [redacted]	Section 7 (Analysis sets)	A	Clarify that subjects with no central confirmation of the BRAF V600E status will be excluded from the PP set (not a protocol deviation, as initially considered. So subjects were not excluded from the PP set in previous version).
4	19MAY2020	PII [redacted]	Section 10 (deviations and reasons for exclusion from Analysis sets)	A	Add analysis to assess impact of COVID-19 pandemic on the study.
4	19MAY2020	PII [redacted]	Section 14.1.2 (Supportive Analyses of the primary endpoint)	A	Add an analysis performed on the subjects who benefited from the USM implemented because of the COVID-19 pandemic
4	19MAY2020	PII [redacted]	Section 15.2 (Adverse Events)	A	Add a listing of AEs related to COVID-19
4	19MAY2020	PII [redacted]	Section 15.11 (Concomitant therapies and procedures)	A	Add a listing of procedures related to COVID-19
4	19MAY2020	PII [redacted]	Section 13 (Demographics & baseline characteristics)	A	Add the description of news items collected in the eCRF (related to history of stomies)
4	20MAY2020	PII [redacted]	Section 13 (Demographics & baseline characteristics)	M	Result of prior antineoplastic surgery to be described by location and not on all prior surgeries (=> result of surgery on primary site, result of surgery on metastatic site)
4	21MAY2020	PII [redacted]	Section 15.1 (Treatment Exposure)	M	Update derivation for cetuximab, to take into account the USM implemented because of the COVID-19 pandemic

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4	15JUN2020	PII [redacted]	Section 13 (Demographics & baseline characteristics)	A	Add derivation of time since creation of stomy.
4	15JUN2020	PII [redacted]	Section 13 (Demographics & baseline characteristics)	M	Update definition of subjects with metastasis at first diagnosis, to include metastases diagnosed within 30 days after cancer diagnosis (provided no antineoplastic therapy taken during that time interval)
4	22JUN2020	PII [redacted]	Section 15.3 (Laboratory data)	M	Clarification of parameters to be displayed in shift tables
4	28JUN2020	PII [redacted]	Section 15.11 (subsequent antineoplastic therapies)	A	Add a description of combination of interest, as the analysis by ATC is not relevant because some investigators enter the combination on a single row, and some enter each single agent on different records.
4	28JUN2020	PII [redacted]	Appendix 1	A	Appendix for prior and subsequent antineoplastic therapies. + Add several combinations of interest
4	03JUL2020	PII [redacted]	Section 11.2.4 (Missing or incomplete dates)	M	Update of derivation rules for imputation of missing/incomplete dates for prior therapies (not antineoplastic) (ticked "taken prior to study entry"): reference date is date of ICF signed, not first study treatment.
4	09JUL2020	PII [redacted]	Section 13 (Demographics & baseline characteristics)	A	Add description of baseline CRP level, CEA and CA19-9 according to local ULN (variables used for subgroups analysis of primary endpoint)
4	09JUL2020	PII [redacted]	Section 15.10 (Ophthalmic Examination)	M	Clarification regarding the definition of subjects at risk of developing the abnormality as not explicit (all abnormalities vs. clinically significant abnormalities)
4	24AUG2020	PII [redacted]	Section 15.10 (Ophthalmic Examination)	M	Wording updates

Version	Date	Author (First & Last name)	Pages or sections concerned	Nature (*)	Reason(s) for change (**)
4	01SEP2020	PII [redacted]	Appendix 1 (Antineoplastic combinations)	A	Add codes for folinic acid, after review by IQVIA medic
4	01SEP2020	PII [redacted]	Section 15.3 (Laboratory data)	A	Hy's Law and drug-induced liver injuries will be considered after the first study treatment administration.
4	07SEP2020	PII [redacted]	Section 15.1 (Treatment Exposure)	M	Clarifications in derivation to take into account implementation of USM (COVID-19 related) regarding cetuximab exposure parameters
4	28SEP2020	PII [redacted]	Section 12 (Demographics and other baseline characteristics) and Section 15.11 (subsequent antineoplastic therapies)	A	Add classification of location of antineoplastic surgeries, as done for primary tumor location, for consistency between tables.
4	06OCT2020	PII [redacted]	Section 15.1 (Treatment Exposure)	M	Clarifications in derivation to take into account implementation of USM (COVID-19 related) regarding cetuximab exposure parameters
4	30OCT2020	PII [redacted]	-		update of signature page, due to change in study team/company organization
4	10NOV2020	PII [redacted]	Section 15.1 (Treatment Exposure) And Section 13 (Demographics and Baseline Characteristics)	A	Add rounding convention for BSA if calculated
5	22JAN2021	PII [redacted]	SIGNATURES	M	Following changes of responsibilities, modification of the statistician. Limitation of this version signatures page to only the concerned department.
5	22JAN2021	PII [redacted]	Appendix 1	M	Update of the list of antineoplastic combinations including monotherapies and resulting from the import of a medical review through an excel file prepared on the basis of the reviex of

Version	Date	Author (First & Last name)	Pages or sections concerned	Nature (*)	Reason(s) for change (**)
					the data extracted for the Data Review Meeting before the Database Lock
5	22JAN2021	PII	Appendix 5	M	Title was modified subsequently for tables 12_5_7_12, 14_1_6_5, 14_1_6_6
5	22JAN2021	PII	Appendix 6	A	As version 5 concerns only modification of appendix 1, the signatures will be restricted to only the concerned departments. The full signature page from SAP V4 is added in appendix in order to prove that Statistical analysis has been approved by all the concerned departments.

(*) *C: Creation, M: Modification, A: Addition, D: Deletion*

(**) *If the modifications are requested by external representatives (authorities), specify the organism name.*

4. TABLE OF CONTENTS

List of Tables

5. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical classification
BID	*Bis in Die*
BMI	Body Mass Index
BOR	Best Overall Response
BOCR	Best Overall Confirmed Response
BP	Blood Pressure
BSA	Body Surface Area
CK	Creatine Kinase
CI	Confidence Interval
COVID-19	Coronavirus Disease 2019
CR	Complete Response
CtDNA	Circulating tumor DNA
CT scan	Computed Tomography scan
DBP	Diastolic Blood Pressure
DI	Dose Intensity
eCRF	Electronic case report form
ECG	Electrocardiogram
EQ VAS	EuroQol Visual Analog Scale
ES	Efficacy Set
FA	Fluorescein Angiography
FAS	Full Analysis Set
FPFV	First Patient First Visit
HR	Heart Rate
ICH	International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use
KM	Kaplan-Meier
LLT	Lowest Level Term
LPLV	Last Patient Last Visit
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Regulatory Activities
MSI	MicroSatellite Instability
NGS	Next Generation Sequencing
OCT	Optical Coherence Tomography
ORR	Overall/Objective Response Rate
PD	Progressive Disease
PDI	Planned Dose Intensity
PFS	Progression-Free Survival
PGIC	Patient Global Impression Change

PK	Phamacokinetic
PP	Per Protocol Set
PCR	Polymerase Chain Reaction
PR	Partial Response
PT	Preferred Term
QD	*Quaque Die* (once daily)
QoL	Quality of Life
QTcF	QT interval corrected for heart rate using Fridericia's formula
QW	*Quaque* Week *(*once a week)
Q2W	*Quaque 2* Week*s* (once every 2 weeks)
RBC	Red blood cells
RDI	Relative Dose Intensity
RECIST	Response Evaluation Criteria In Solid Tumours
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SC	Steering Committee
SD	Stable Disease
StD	Standard Deviation
SEM	Standard Error of Mean
SOC	System Organ Class
SPC	Summary Of Product Characteristics
TA	Tumor Assessment
TEAE	Treatment Emergent Adverse Event
TESAE	Treatment Emergent Serious Adverse Event
ULN	Upper Limit Normal
USM	Urgent Safety Measure
VAS	Visual Analysis Scale
WBC	White Blood Cells
WHODrug	World Health Organisation Drug

6. INTRODUCTION

This document describes the interim and final statistical analyses of the study, including pharmacokinetic analysis, that will be performed after the Stage 1 and Stage 2 snapshots, and final lock of the clinical database.

This statistical analysis plan will be approved, finalised and signed before the first subject is screened in the study.

6.1. STUDY DESIGN

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

The study will include two stages according to a two-stage design.

Stage 1: In the first stage, 40 subjects will be treated. In case of discordance in the results between the local assay and the central laboratory (potential false-positive local result), or lack of *BRAF*^{V600E} confirmation, subject will be replaced for the interim primary analysis (futility analysis). If there are 11 or fewer confirmed responses (CR or PR) in the 40 treated subjects with a centrally confirmed *BRAF*^{V600E} mutation, the study will be stopped. Otherwise, additional subjects will enter stage 2. Stage 2 may be initiated as soon as 40 subjects with a centrally confirmed *BRAF*^{V600E} mutation are treated and confirmed responses are observed in at least 12 subjects.

Stage 2: 50 additional subjects will be treated, for a total of 90 subjects with a centrally confirmed *BRAF*^{V600E} mutation. In case of discordance in the results between the local assay and the central laboratory (potential false-positive local result), or lack of *BRAF*^{V600E} confirmation, subject enrolled in the stage two of the trial will be replaced for the primary analysis.

If at any time there is lack of confirmation of the BRAF^{V600E} mutation in a total of 6 subjects (≥ 6% of the total planned enrollment) or discordance between the local assay and the central laboratory in 3 subjects (≥ 3% of the total planned enrollment), all subsequent subjects will be required to have

BRAF^{V600E} determined by the central laboratory prior to study treatment assignment (i.e., local *BRAF* testing will no longer be accepted for trial eligibility).

Subjects will be eligible for the study based on identification of a *BRAF*^{V600E} mutation in the tumor tissue as determined by local laboratory result obtained at any time prior to Screening. Only polymerase chain reaction (PCR) and next generation sequencing (NGS)-based results will be acceptable. The BRAF mutation status must be confirmed by central laboratory no later than 30 days after the first dose of study treatment. In cases where there is a discordance between local assay and central laboratory results (i.e. either no BRAF mutation identified or not a *BRAF*^{V600E} mutation), or if the central laboratory is not able to confirm presence of a *BRAF*^{V600E} mutation due to inadequate or poor sample condition or absence of available material within 30 days of initiating study therapy, subjects may only continue treatment if there is no clinical indication of deterioration or disease progression and the Investigator determines that the subject is deriving benefit. In such instances, subjects must be informed that the *BRAF*^{V600E} mutation status is unconfirmed and must sign a separate informed consent form (ICF) that includes this information and describes alternative treatment options. Subjects with an unconfirmed *BRAF*^{V600E} mutation status will be included in the Full Analysis Set (when they have received at least one dose of study treatment (partial or full), cf. section 7).

Treatment will be administered in 28-day cycles until disease progression, unacceptable toxicity, subject's decision, withdrawal of consent, initiation of subsequent anticancer therapy or death. After discontinuation of study treatment, there will be a 30-day safety follow-up period. Subjects will then enter a survival follow-up period after the completed 30 days safety follow up and will be followed for at least 1 year after the start of study treatment of the last subject enrolled. If a subject discontinues the treatment for a reason other than progressive disease, tumor assessment must be performed (as per local and central review) until the start of new anti-cancer therapy, disease progression, death, lost to follow-up, subject decision or withdrawal consent.

The investigational products in this study are encorafenib and binimetinib in combination with cetuximab. Dose schedule is the following:

- Encorafenib: 300 mg PO (oral capsule 4X 75 mg) QD.
- Binimetinib: 45 mg PO (oral tablet 3X 15 mg) BID.
- Cetuximab: 400 mg/m^2 intravenous (IV) at Cycle 1 day 1 then 250 mg/m^2 IV every week (QW) for the first 28 weeks. Then, 500mg/m^2 IV every two weeks (Q2W) from week 29 (Cycle 8 day 1).

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

The *end of the study* is defined as the time point when all subjects have been followed for at least 1 year after the start of study treatment of the last subject enrolled (including survival status).

6.2. STUDY OBJECTIVES

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

The **secondary objectives** of the study are:

- To evaluate the cORR by central radiologist assessment.
- To evaluate ORR (for confirmed and unconfirmed responses) by local radiologist/investigator and central assessment.
- To assess the effect of the combination of encorafenib, binimetinib and cetuximab on the duration of response (DOR).
- To assess the effect of the combination of encorafenib, binimetinib and cetuximab on other time-related efficacy parameters: time to response (TTR), progression-free survival (PFS) and overall survival (OS).

- To characterize the safety and tolerability of the combination of encorafenib, binimetinib and cetuximab.
- To assess the effect on quality of life (QoL).
- To explore health care resource utilization.
- To describe the pharmacokinetics (PK) of encorafenib, binimetinib, a metabolite of binimetinib (AR00426032) and cetuximab.

Exploratory objectives:

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

6.3. STUDY ENDPOINTS

6.3.1. Primary endpoint

The primary endpoint is the confirmed Objective Response Rate (cORR) as assessed by local radiologist/investigator review as per Response Evaluation Criteria in Solid Tumours (RECIST 1.1[1]).

The cORR is defined as the number of subjects achieving a best overall confirmed response of CR or PR divided by the total number of analysed subjects.

6.3.2. Secondary endpoints

The following secondary efficacy endpoints will be determined:

- cORR as assessed by central radiologist review as per RECIST 1.1.
- ORR (for confirmed and unconfirmed responses) as per local radiologist/investigator-assessment.

- ORR (for confirmed and unconfirmed responses) as per central assessment.
- Overall survival (OS) defined as the time from first dose to death due to any cause. If a subject is not known to have died, survival will be censored at the date of last known date the subject was alive or at the cutoff date, whatever is earlier.
- Progression-free survival (PFS), defined as the time from first dose to the earliest documented date of disease progression or death due to any cause, assessed based on local radiologist/investigator review.
- PFS defined with tumor assessment assessed based on central review will be also used in a supportive analysis of PFS.
- Duration of response (DOR) defined as the time from first radiographic evidence of response assessed based on local radiologist/investigator review to the earliest documented PD or death due to underlying disease and is calculated for responders only. Responders who do not have a PD or death date by the data cutoff date will be censored for DOR at their last adequate tumor assessment of CR, PR or SD prior to the cutoff date.
- Duration of response assessed based on central radiologist review.
- Time to response (TTR) defined as the time from first dose until first documented radiographic evidence of response of CR or PR assessed based on local radiologist/investigator review. Subjects who do not have a CR or PR by the cutoff date will be censored for TTR at their last adequate tumor assessment date if they didn't have a PFS event, and at maximum follow-up (i.e. FPFV to LPLV used for the analysis) if they had a PFS event.
- Time to response assessed based on central review.
- Type and severity of adverse events (AEs) and serious adverse events (SAEs), changes in hematology and chemistry values, physical examinations, vital signs, electrocardiogram (ECGs) and echocardiogram (ECHO)/ multi-gated acquisition (MUGA) scans and ophthalmological examinations graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v4.03 (NCI-CTCAE v4.03).
- Change from baseline in the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire for Cancer subjects (QLQ-C30), EuroQol-5D-5L (EQ-5D-5L), and Patient Global Impression of Change (PGIC).
- Resource utilization focused on hospitalizations occurring during the study treatment phase.

- Plasma concentrations of encorafenib, binimetinib and the active metabolite of binimetinib (AR00426032) and serum concentration of cetuximab.

6.3.3. Exploratory endpoints

The following exploratory efficacy endpoints will be determined:

- Changes from baseline in blood tumor markers (carcinoembryonic antigen [CEA] and carbohydrate antigen 19-9 [CA19-9]) at the beginning of each cycle and at the end of treatment.
- *BRAF* ^{V600E} mutation status in blood circulating tumor DNA (ct-DNA) at baseline.
- MSI status in formalin-fixed paraffin-embedded (FFPE) samples via established PCR assays in tumor sample versus germline control at screening.

6.4. STUDY TIMEPOINTS

Table 1: Study Timepoints

Analysis Visit Number	***Study Phase Number***	***Study Phase***	***Visit Label for Statistical Output***
1	*1*	*Screening*	*Screening*
x.1	*2*	*Treatment*	*CxD1*
x.2			*CxD8*
x.3			*CxD15*
x.4			*CxD22*
901			*End of treatment*
902			*Safety follow-up*
91y	*3*	*Long-term follow-up*	*Survival y*

6.5. SAMPLE SIZE

The sample size is based on a two-stage design with nominal risks alpha=2.5% and beta=20%.

The null hypothesis that the true response rate is 30% will be tested against a one-sided alternative. In the first stage, 40 subjects will be treated. Subjects in whom the presence of *BRAF*^{V600E} is not confirmed (discordance or lack confirmation) by central laboratory will be replaced. If there are 11 or fewer confirmed responses in these 40 treated subjects, inactivity will be declared, and the study will be stopped for futility.

The time point for the futility analysis will be after all 40 treated patients of stage 1 with centrally confirmed BRAF^{V600E} mutation had the opportunity to complete four post baseline tumor assessment[1]. And in case the last subject required for the concerned stage has an objective response, it should be confirmed in the following tumor assessment before the analysis is being performed. However, it will be possible to proceed to Stage 2 as soon as 40 subjects with a centrally confirmed *BRAF*^{V600E} mutation are treated and 12 confirmed responses are observed.

Subjects data that will be analyzed during the futility analysis will be reviewed on an ongoing basis in order to determine as soon as possible (even before the inclusion of the 40th patient) whether the criteria for continuing to stage 2 (12 confirmed responses) are satisfied or not.

As it may take several treatment cycles for subjects to achieve a confirmed response, then a limited number of subjects (maximum 12) from stage 2 may be treated while waiting for all subjects in the initial cohort of 40 subjects in Stage 1 to be evaluable for a confirmed response. These additional subjects will not count towards responses in Stage 1 but will be included as part of the Stage 2 cohort, should the study move forward into Stage 2.

If at any time it becomes evident that the threshold of 12 responses is unlikely to be met, then additional patients may not be recruited (e.g.: 6 or fewer responses among 35 patients with sufficient follow-up [potential for at least 2 post-baseline assessments]).

[1] NB: This means that patients who discontinued are to be taken into account

If the study continues to the second stage, 50 additional subjects will be treated for a total of 90 subjects with a centrally confirmed *BRAF*^{V600E} mutation.

The null hypothesis will be rejected if 37 or more confirmed responses are observed in 90 treated subjects. This design yields a 1-sided type I error rate equal to 1.6% and power of 80% when the true response rate is 45%.

NB: Due to the time needed to get the central confirmation of the *BRAF*^{V600E} mutation, more than 90 subjects with centrally confirmed *BRAF*^{V600E} mutation may be treated. If so, the nominal alpha and power will be computed. The Clopper-Pearson (exact) binomial 95% confidence interval will be computed with 37 confirmed responders observed among the N patients and the lower limit will be compared to the clinically relevant response rate of 30%.

Moreover, the primary analysis at Stage 2 will be repeated when excluding the overrunning patients (i.e. on the 90 first treated subjects with a centrally confirmed *BRAF*^{V600E} mutation, see section 14.1.1) and differences between the two analyses will be discussed.

The cut-off for stage 2 analysis will be after all 90 treated patients of stage 1 and 2 with centrally confirmed *BRAF*^{V600E} mutation had the opportunity to complete four post-baseline tumor assessments1, and after subjects with an initial objective response have had an opportunity to have a confirmation scan. The sample size calculation was based on binomial probabilities calculated in R (version 3.2.3).

This binomial design matches the O'Brien-Fleming design (O'Brien, 1979[2]) for one sample obtained using East software (version 6.4) [3] with a 1-sided type I error rate equal to 2.5% and a power of 81%.

6.6. CUT-OFF DATES

3 statistical analyses are planned: Stage 1 analysis (futility analysis), Stage 2 analysis and analysis at the end of the study.

The cut-off date for Stage 1 and Stage 2 analyses is estimated to occur approximately when all treated subjects with a centrally confirmed *BRAF*^{V600E} mutation of the concerned stage (i.e. 40

patients for Stage 1 and 90 patients for Stage 2) had the opportunity to complete four post baseline tumor assessment). And in case the last subject required for the concerned stage has an objective response, it should be confirmed in the following tumor assessment before the analysis is being performed.

The end of the study is defined as the time point when all subjects have been followed for at least 1 year after the start of study treatment of the last subject enrolled (including survival status).

Scope of each cut-off analysis is described in Appendix 5 (List of statistical Tables, figures and Listings).

6.7. STEERING COMMITTEE (SC)

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

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

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

6.8. INDEPENDENT DATA SAFETY MONITORING COMMITEE (IDSMC)

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

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

Analyses for iDSMC will be based on safety, thus this will not affect the statistical operating characteristics of the Stage 1 and Stage 2 analyses.

6.9. STUDY FLOW-CHART

STUDY FLOW-CHART FOR SCREENING

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

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

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

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

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

STUDY FLOW-CHART FOR TREATMENT AND FOLLOW-UP PERIOD

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

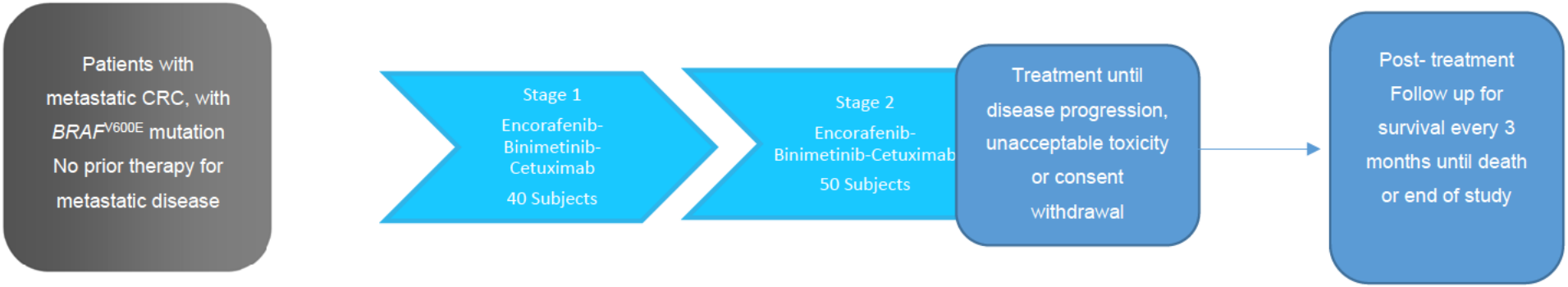
Cycle/Period	*Cycle 1[a]*					*Subsequent Cycles[a]*						
Visit	*C1 D1*		*C1 D8*	*C1 D15*	*C1 D22*	*Cn D1*	*Cn D8*	*Cn D15*	*Cn D22*	*End of treatment*	*Safety Follow-Up[q]* (EOS)	*Survival (Every 3 Months)*
Cycle Days	*D1*		*D8*	*D15*	*D22*	*D1*	*D8[v]*	*D15*	*D22[v]*	*Dxx*	*Dxx*	*Dxx*
Epochs	*SCREENING*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

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

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

p	For subjects who discontinue study treatment due to disease progression the survival follow up phase will start after the 30-days safety follow up is complete The subject will be contacted by phone for collection of information This may be conducted more frequently as needed. For subjects who discontinue study treatment due to reasons other than disease progression, tumor assessment must be performed until start of new anti cancer therapy,disease progression, death, lost to follow-up, subject's decision or consent withdrawn.
q	To be performed 30-day after end of treatment (EOT) , when clinically appropriate, it is recommended subjects be monitored with physical examinations, dermatological examinations and chest CT scans for cutaneous and non-cutaneous secondary malignancies for up to 6 months after the last encorafenib dose or until initiation of another antineoplastic therapy.
r	To be performed prior to study treatment administration. Only for vital signs: not to be performed at D8 and D22 starting week 29.
s	The questionnaires should be completed by the subjects at the beginning of the study visit prior to receiving any study treatment, prior to any other study assessment or consultation with the Investigator, and prior to being informed of their current disease status.
t	Cetuximab wil be administered as a weekly schedule for the first 28 weeks. Subjects on study will switch to a biweekly schedule starting on week 29 (Cycle 8 day 1). If there was a dose modification prior to switching to the biweekly schedule, the total dose per cycle should be maintained (i.e. 200mg/m2 QW, may be changed to a 400mg/m2 Q2W)
u	Information related to the length of stay, hospital facilities used, reasons for hospitalization, and hospital discharge information will be collected
v	From Week 29 (cycle 8), D8 and D22 visits will not be performed (biweekly infusions of cetuximab: no cetuximab infusion on D8 and D22)
Abbreviations: BSA = body surface area; CA19-9 = cancer antigen 19-9; CEA = carcinoembryonic antigen; CT = computed tomography; ECG = electrocardiogram; ECHO = echocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-5L = EuroQol-5D-5L; HIV= Human immuno deficiency virus; IV = intravenous(ly); MRI = magnetic resonance imaging; MSI = microsatellite instability; MUGA = multi-gated acquisition; PD = progressive disease; PGIC = Patient's Global Impression of Change; PK = pharmacokinetic(s).	

6.10. STUDY SCHEME



7. ANALYSIS SETS

The following analysis sets are defined:

• The **Screened subjects set (SCR)** consists of all subjects who have signed any informed consent.

• The **Full Analysis Set (FAS)** is composed of all subjects having received at least one dose of study treatment (partial or full). The analysis of efficacy, safety, quality of life, biomarkers and healthcare resource utilization will be done on the FAS.

Note: Partial dose is defined as at least one dose of encorafenib, binimetinib or cetuximab.

• The **Efficacy Set (ES)** is composed of all FAS subjects with a centrally confirmed *BRAF*^{V600E} mutation. The analysis of efficacy, including the primary analysis of the primary endpoint, will be done on the ES.

• The **Per Protocol set (PP set)** is composed of all FAS subjects without any major protocol deviations. The PP set will be defined prior to the database lock supporting the primary analysis, and will be used for the supportive analyses of primary efficacy endpoint. *Note*: In this SAP, the term "major protocol deviations" describes all deviations likely to significantly bias the interpretation of the primary efficacy endpoint results leading to exclusion of PP set. There may be protocol deviations identified as major by the clinical team (in CTMS) that will not lead to exclusion of PP set. All deviations recorded in CTMS will be reviewed prior to database snapshot/lock to identify any potential deviations leading to exclusion of PP set.

Continuation of the study despite *BRAF*^{V600E} -mutant status not centrally confirmed is allowed by the protocol (i.e. not a protocol deviation), provided the subject had signed the appropriate ICF. As the study investigates "encorafenib, binimetinib plus cetuximab in subjects with previously untreated *BRAF*^{V600E} -mutant Metastatic Colorectal Cancer", subjects with no central confirmation of the *BRAF*^{V600E} -mutant status (i.e. unconfirmed or negative) will be excluded from the PP set.

• The **Pharmacokinetics Set (PK Set)** will consist of all subjects who receive at least 1 dose of encorafenib, binimetinib or cetuximab and who have at least 1 post-dose PK blood collection with associated bioanalytical results.

8. INFERENTIAL PRINCIPLES

Only the test on the primary efficacy endpoint, on which is based the sample size justification, may lead to a causal interpretation. All other statistical results are to be regarded within an exploratory perspective.

9. REPORTING CONVENTIONS AND DEFINITIONS

9.1. DEFINITIONS

9.1.1. General

Study treatment will refer to the combination of encorafenib (LGX818 or W0090), binimetinib (MEK162 or W0074) and cetuximab.

The treatment label for all Tables, Listings and Figures will be: **"**Encorafenib + Binimetinib + Cetuximab".

Study drug will refer to encorafenib, binimetinib or cetuximab.

When displaying summaries for each study drug, drug labels to be used are: Encorafenib, Binimetinib and Cetuximab, respectively.

9.1.2. Dates and period

Date of first administration of study treatment is derived as the first date when a non-zero dose of any study drug was administered and recorded on the eCRF.

Date of last administration of study treatment is defined as the last date when a non-zero dose of any study drug was administered and recorded on the eCRF. Note: if at a given analysis time point, the patient has a start date but with no end date and no EOT page is filled-in, the patient will be

considered as ongoing and the end date will be imputed to the cut-off date for the calculation of treatment duration.

Last contact date will be derived for patients (known to have died or not) at the analysis cut-off. Imputed date (e.g. analysis cut-off date programmatically imputed to replace the missing end date of a dose administration record) will **not** be considered for the determination of last contact date. Only dates associated with patient visits or actual examinations of the patient will be used in the derivation. If after derivation, the last contact date is posterior to the cut-off date, then the last contact date will be taken to be the cut-off date. Last contact date will only be derived using the latest complete date among the following:

- Start/end date of study medication with non-missing dose (doses of 0 are allowed);
- RECIST assessment date with evaluation marked as “done”;
- Laboratory/PK collection date with sample collection marked as “done”;
- Vital sign date with non-missing parameter value;
- Cardiac evaluation date with non-missing parameter value;
- ECG evaluation date with non-missing parameter value;
- Ophthalmologic evaluation date with non-missing parameter value;
- Physical examination date with non-missing parameter value;
- Questionnaire evaluation date with non-missing parameter value;
- Performance status date with non-missing performance status;
- Start/end date of adverse events with non-missing/non-“None” verbatim term and outcome different from “Fatal” and grade less than 5
- Start date of fatal AE (i.e. outcome “Fatal” and grade 5) when the Start date is strictly before the end date
- Start/end date of antineoplastic therapies administered after study treatment discontinuation with non-missing medication/procedure term;
- Date of contact in survival status when the patient is marked as alive;

- Treatment assigned date.

FPFV used for analysis will be defined as the earliest date of first study treatment administration.

LPLV used for analysis will be defined as the greatest Last Contact Date.

Unless otherwise stated, reference dates are defined as:

- For the *Reference Start Date/Time*: the date/time of first study treatment administration for treated subjects and the date/time of first visit in other case
- For the *Reference End Date/Time*: the date/time of last administration to study treatment.

Study treatment period will refer to the period from first study treatment administration date up to last study treatment administration date + 30 days (included).

9.1.3. Durations and times

Some analysis may require the computation of a duration from a reference day to a post-reference day.

Duration will be defined in days (or in seconds, if applicable) as following:

- Duration (in days) = Date - Reference date + 1 day
- Duration (in seconds) = (DateTime) – (Reference DateTime) + 1 sec

Unless specified otherwise, durations of events (e.g., duration of treatment) will be calculated in days. Conversions to weeks, months, years will be days/7, days/30.4375, days/365.25, respectively.

The *onset day of AE* is calculated from the date of first study treatment administration up to the start date of the AE notification, as follows:

- If start date ≥ Date of first administration: onset day = Date AE notification – Date of first study treatment administration + 1
- If start date < Date of first administration: onset day = Date AE notification – Date of first study treatment administration

S*tudy day* is defined in the following manner:

- On or after the start date of study treatment: the study day will be calculated as (date of safety assessment) – (start date of study treatment) + 1. Study day 1 will therefore be the first day of study treatment.
- Before the start date of study treatment: the study day will be calculated as (date of safety assessment) – (start date of study treatment).

Time to event is defined in the following manner:

- The time from event i to an event j (in days) will be calculated as (date of event j – date of event i) + 1

9.2. REPORTING CONVENTIONS

Summary statistics will be summarized by visit when appropriate and will consist of values for:

- number of subjects, mean, standard deviation, median, lower and upper quartiles, minimum and maximum for quantitative parameters (95% confidence interval around the mean will be presented when relevant)
- number and percentage of subjects for qualitative parameters

Summary statistics will be presented in tabular and/or graphics format when appropriate.

Mean and standard error of mean (SEM) will be represented graphically by time windows for relevant criteria.

Qualitative variables must be displayed by increasing order of modalities if ordinal, and by alphabetical order otherwise.

All tables describing events by MedDRA System Organ Class (SOC) and/or Preferred Term (PT), or by WHODrug "Anatomical Therapeutic Chemical" (ATC) classification, should be displayed by

decreasing order of frequency (%) of SOC and PT, or ATC, and by alphabetical order when similar frequencies.

For quantitative variables:

- Calculated statistics (mean, std, median, lower and upper quartiles and 95% confidence interval) will be displayed with one more significant figure than the observed data.
- For description of changes over time, baselines and values for present changes will be also described at a given visit.
- For description of values over time, baselines for present values will be also described at a given visit.

For percentages,

- One decimal digit should be given,
- No percentage should be given for cells with 0 subjects.
- They will be computed on the analysis population.

Individual data listings will be provided for all analyzed criteria, sorted by treatment group, subject identifier, parameter and corresponding date of assessment.

When results are graphically represented, time units (Days, Weeks, Months...) must be used for horizontal axis and scale of axis must be proportional to time interval duration. Number of subjects (N=xx) per timepoint should be displayed on the horizontal axis.

9.3. ANALYSIS VISITS

Time windows

Except for ECG baseline, if two or more assessments are performed within a time window then the assessment closest to the planned visit is used in analyses by time window. For worst post-baseline assessment all on-treatment values are considered regardless of time windows.
Time windows for criteria are defined in Table 2 to Table 7.

Table 2: Time windows for weight, ECOG PS, ophthalmic and dermatological examination, ECHO/MUGA, coagulation, urinalysis, EORTC QLQ-C30; EQ-5D-5L, PGIC

Time Window	Planned Visit Timing	Time Window Definition
Baseline	Study day 1 pre-dose	Before first study treatment administration
Cycle 2 Day 1	Study day 29	Study day 1 post-dose to 43
Cycle x Day 1	Study day (x-1)*28+1 = k	Study days k-13 to k+14
Safety follow-up	Post treatment study day 30*	Last administration of study treatment day+1 to Post treatment study day 37

* Study day *i* = First day of study treatment administration + (i-1) day(s)
Post treatment study day *i* = Last administration of study treatment day + *i* day

Table 3: Time windows for vital signs

Time Window	Planned Visit Timing	Time Window Definition
Baseline	Study day 1 pre-dose	Before first study treatment administration
Up to week 28		
Cycle 1 Day 8	Study day 8	Study days 1 post dose to 11
Cycle 1 Day 15	Study day 15	Study days 12 to 18
Cycle 1 Day 22	Study day 22	Study days 19 to 25
Cycle 2 Day 1	Study day 29	Study days 26 to 32
Cycle x Day y *(except C1D8)*	Study day (x-1)*28+y = k	Study days k-3 to k+3
From week 29 (Cycle 8 Day 1)		
Cycle 8 Day 1	Study day 197	Study days 194 to 204
Cycle 8 Day 15	Study day 211	Study days 205 to 218
Cycle 9 Day 1	Study day 225	Study days 219 to 233
Cycle x Day y from cycle 8 Day 15	Study day Study day (x-1)*28+y = k	Study days k-6 to k+7
Safety follow-up	Post treatment study day 30	Last administration of study treatment day+1 to Post treatment study day 37

* Study day *i* = First day of study treatment administration + (i-1) day(s)
Post treatment study day *i* = Last administration of study treatment day + *i* day

Table 4: Time windows for ECG

Time Window	Planned Visit Timing	Time Window Definition
Baseline	Study day 1 pre-dose	Before first study treatment administration
Cycle 1 Day 1 post-dose	Study day 1 post-dose	Study days 1 post dose to 8
Cycle 1 Day 15	Study day 15	Study days 9 to 22
Cycle 2 Day 1 pre-dose	Study day 29 pre-dose	Study days 23 to before C2D1 study treatment administration
Cycle 2 Day 1 post-dose	Study day 29 post-dose	Study days 29 C2D1 post dose to 43
Cycle x Day 1 from cycle 3	Study day (x-1)*28+1 = k	Study days k-13 to k+14
Safety follow-up	Post treatment study day 30*	Last administration of study treatment day+1 to Post treatment study day 37

* Study day *i* = First day of study treatment administration + (i-1) day(s)
Post treatment study day *i* = Last administration of study treatment day + *i* day

Table 5: Time windows for hematology

Time Window	Planned Visit Timing	Time Window Definition
Baseline	Study day 1 pre-dose	Before 1rst administration
Cycle 1 Day 15	Study day 15	Study day 1 post-dose to 18
Cycle 1 Day 22	Study day 22	Study days 19 to 25
Cycle 2 Day 1	Study day 29	Study days 26 to 43
Cycle x Day 1 from cycle 3	Study day (x-1)*28+1 = k	Study days k-13 to k+14
Safety follow-up	Post treatment study day 30*	Last administration of study treatment day+1 to Post treatment study day 37

* Study day *i* = First day of study treatment administration + (i-1) day(s)
Post treatment study day *i* = Last administration of study treatment day + *i* day

Table 6: Time windows for chemistry

Time Window	Planned Visit Timing	Time Window Definition
Baseline	Study day 1 pre-dose	Before 1rst administration
Cycle 1 Day 1	Study day 1 post-dose	Study days 1 post dose to 8
Cycle 1 Day 15	Study day 15	Study days 9 to 22
Cycle 2 Day 1	Study day 29	Study days 23 to 43
Cycle x Day 1 from cycle 3	Study day (x-1)*28+1 = k	Study days k-13 to k+14
Safety follow-up	Post treatment study day 30*	Last administration of study treatment day+1 to Post treatment study day 37

* Study day *i* = First day of study treatment administration + (i-1) day(s)
Post treatment study day *i* = Last administration of study treatment day + *i* day

Table 7: Time windows for CEA, CA19-9

Time Window	Planned Visit Timing	Time Window Definition
Baseline	Study day 1 pre-dose	Before 1rst administration
Cycle 2 Day 1	Study day 29	Study days 1 post dose to 43
Cycle x Day 1 from cycle 3	Study day (x-1)*28+1 = k	Study days k-13to k+14
Safety follow-up	Post treatment study day 30*	Last administration of study treatment day+1 to Post treatment study day 37

* Study day *i* = First day of study treatment administration + (i-1) day(s)
Post treatment study day *i* = Last administration of study treatment day + *i* day

Determination of Missing Adequate Tumor Assessments

The term 'adequate Tumor Assessments (TA)' is defined as TA with overall lesion response different from missing and 'Unknown'. The term 'missing adequate TA' is defined as TA not done or TA with overall lesion response equal to 'Not Evaluable'. For the sake of simplicity, the 'missing adequate TA' will also be referred as 'missing TA'. An exact rule to determine whether there is one or two missing TAs is therefore needed.

This rule will be based on the distance between the last adequate TA date and the event date.

Let D_1 be the largest distance (relative to the last adequate TA date) that a patient can have a tumor assessment and not be classified as having missed an assessment. Let D_2 be the largest distance (relative to the last adequate TA date) that a patient can have a tumor assessment and not be classified as having missed two assessments. If the distance exceeds threshold D_1 or D_2 then the analysis will assume one or two missing TAs, respectively.

The threshold D1 will be defined as the protocol specified interval between the TAs plus the protocol allowed window around the assessments. Similarly, the threshold D2 is defined as two

times the protocol specified interval between the TAs plus the protocol allowed window around the assessments.

As per protocol, post-screening assessments are expected to be performed every ***A***=6 weeks (±***B***=7 days) from the first dose for the first 12 weeks of treatment (***I***=84 days); except for first tumor evaluation for which the time-window allowed is day 42 +7 days from first dose, then every ***X***=8 weeks (±***Y***=7 days) thereafter until disease progression, subject decision, withdrawal of consent, initiation of subsequent anticancer therapy, subject is lost to follow-up, death or defined end of study.

Therefore:

- if the last adequate tumor assessment before the event date is performed on or before study day 21 (=7**A/*2) then D_1=49 (=***A****7+***B)*** days and D_2=91 (=2**A**7+***B)*** days;
  - This accounts for the scenario where the last adequate tumor assessment is the baseline assessment. This also allows for the rare instance where an additional assessment occurred early in the study.
- if the last adequate tumor assessment before the event date is performed between study day ***M***+1 (where M= *I*- (1.5**A*)*7) to study day ***N*** then D1=A*7+2*B days and D2=(A+X)*7+B+Y days;
  - Day N is calculated as N = *I*– (0.5**A*)*7.
  - This accounts for the scenario where only the first scheduled assessments after the last adequate tumor assessment occur prior to month *I*.
- if the last adequate tumor assessment before the event date is performed between study day ***N***+1 and study day ***P*** then D_1=***X****7+***B***+***Y*** days and D_2=2**X**7+***B***+***Y*** days;
  - Day *P* is calculated as *P* = *I*+ (0.5*X)*7.
  - This accounts for the scenario where only the last adequate tumor assessment occurs prior to month *I*/7.
- otherwise, when the last adequate tumor assessment before the event date is performed after study day ***P***+1, then D_1=***X****7+2**Y*** days and D_2=2**X**7+2**Y*** days.

Using the D_2 definition above, an event is censored as occurring after ≥2 missing tumor assessments if the distance between the last adequate tumor assessment date and the event date is larger than D_2.

Table 8: Illustration of D1 and D2 Criteria

If the last tumor assessment before the event date occurs between Study Days	D1	D2
1 – 21	49	91
22 – 63	56	112
>=64	70	126

Example: For a patient with a tumor assessment SD at Day 21(last tumor assessment before PFS event), and PD at the next tumor assessment on

- *Scenario 1: Day 46 (i.e. 25 days after SD). Patient is classified as not having missed tumor assessment between both scans. PFS is not censored.*
- *Scenario 2: Day 76 (i.e. 55 days after SD). Patient is classified as having missed 1 tumor assessment between both scans. PFS event is not observed after more than 1 missing or inadequate tumor assessment. PFS is not censored.*
- *Scenario 3: Day 113 (i.e. 92 days after SD). Patient is classified as having 2 missing tumor assessments between both scans. PFS event is observed after more than 1 missing or inadequate tumor assessment. Using the D2 definition, PFS is censored at the last adequate tumor assessment (at SD scan).*

9.4. BASELINE

Baseline is defined as the last available assessment before the first study treatment administration, unless otherwise specified.

If an assessment is planned to be performed prior to the first dose of study treatment in the protocol and the assessment is performed on the same day as the first administration of study drug, it will be assumed that it was performed prior to study treatment administration (if time is not available).

Unscheduled assessments will be used in the determination of baseline.

ECG Baseline will be the mean of the triplicate measurements at Cycle 1 Day 1 before the first study treatment administration.

Change from baseline will be defined as the difference between the value of the endpoint at the time point of interest and the baseline value.

9.5. CUT-OFF CONVENTIONS

All available data will be included at the time of the cut-off date.

Subjects continuing to receive study treatment at the time of analysis will have time-to-event data (e.g., PFS, DOR) censored at the time of last tumor assessment prior to the data cut-off point used, if the event has not been observed before. Ongoing events (e.g., AEs, concomitant medication, etc.) will be summarized for analysis using the data cut-off date as the date of completion, with an indication that the event is ongoing.

For subjects who drop out from the study with ongoing events, the discontinuation date will be used as the completion date of the event with the appropriate censoring.

Data obtained after the cut-off will not be displayed in any listings or used for summary statistics (e.g. laboratory values of samples taken after data cut-off, AE with onset date after data cut-off, etc.).

For exposure data, if the treatment was started before the cut-off date and ended after the cut-off date, the end date will be imputed by the cut-off date. This imputed date will be used for duration and cumulative dose derivations.

10. DEVIATIONS AND ADDITIONAL REASONS OF EXCLUSION FROM ANALYSIS SETS

The protocol deviations will be reviewed prior to database lock. These will be classified as major or minor.

A deviation will be considered as major if it is likely to significantly bias the interpretation of the primary efficacy endpoint results.

Note: In this SAP, major protocol deviations described all deviations leading to exclusion of PP set. There may have protocol deviations identified as major by clinical team (in CTMS) that will not lead to exclusion of PP set. All deviations recorded in CTMS will be reviewed prior to database snapshot/lock to identify any potential deviations leading to exclusion of PP set.

Major protocol deviations and additional reasons of exclusion from analysis sets will be qualified in accordance with the list of pre-defined reasons for exclusion from analysis sets for the study. This list, as large as possible, will be described in a specific document, separately from the statistical analysis plan.

The number and percentage of subjects with at least one major deviation will be tabulated by type of major deviations on the Full Analysis Set.

The number and percentage of subjects with at least one minor deviation will be also tabulated by type of minor deviations on the Full Analysis Set.

The number and percentage of subjects with at least one reason of exclusion from analysis sets will be tabulated by type of reason of exclusion on the Full Analysis Set.

In order to describe the impact of the COVID-19 pandemic on the study, the number and percentages of subjects with at least one deviation related to COVID-19 will be tabulated on the Full Analysis Set, for minor deviations, major deviations and both combined. Type of minor and major deviations will also be described on the Full Analysis Set.

Same description will be performed for the number of deviations reported. Deviations related to COVID-19 pandemic are reported with a prefix “COVID19”. Prefix will not be displayed in the outputs.

11. HANDLING OF MISSING DATA AND ANALYSIS OF DROP-OUTS

11.1. DROP-OUTS

No missing data due to drop out will be imputed.

11.2. MISSING DATA (OTHER THAN DROP-OUT)

11.2.1. Missing efficacy data

Missing values will not be substituted by estimated values but considered as missing in statistical analysis.

Note: For tumor assessment, when no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point and will be analysed as such.

11.2.2. Missing Safety data

For laboratory data, in the case that an upper limit is mentioned in the associated character variable, missing numerical value will be replaced by the limit mentioned in the character variable. (For lower limit, missing numeric value will be replaced by the lower limit).

Example: for a measure of ALAT with a character variable “<4”, missing numeric value will be replaced by 4.

Missing numeric values with an associated character variable “>50” will be replaced by 50. In listings, character variable will be displayed.

In case of missing BSA at an assessment time, the measurement at the previous assessment time will be used for the Cetuximab exposure analysis.

11.2.3.Missing QoL data

EORTC QLQ-C30

For each of the 15 scores:

- if at least half of the items from the score have been answered, the score will be calculated based on the mean of the present items.
- If more than half of the items are missing, the score will be missing.
- None single-item scores can be imputed

EQ-5D-5L and PGIC

Missing item scores will not be substituted by estimated values but considered as missing for statistical analysis.

11.2.4.Missing or incomplete dates

Replacement of missing or incomplete dates presented hereafter is defined in a conservative approach.

- **Missing dates of first study treatment administration**

Missing dates of the first study treatment administration will be considered equal to the Cycle1 Day 1 visit date for subjects assigned to treatment and with confirmation that this subject actually received treatment.

- **Missing dates of start of adverse event**

In case of completely missing date, it will be estimated by the date of first study treatment administration.

If the day and the month are missing,

- If the year is the same as the year of first study treatment administration, it will be estimated by the date of first study treatment administration.
- If the year is prior to the year of first study treatment administration, it will be estimated by the 31 December.
- If the year is after the year of first study treatment administration, it will be estimated by the 1st January.

If only the day is missing,

- If the month/year are the same as the month/year of first study treatment administration, it will be estimated by the date of first study treatment administration.
- If the month/year are prior to the month/year of first study treatment administration, it will be estimated by the 15th day of the month.
- If the month/year are after to the month/year of first study treatment administration, it will be estimated by the first day of the month.

If after imputation, the estimated start date is after the end date of the adverse event, it will be replaced by the end date of the adverse event

- **Missing dates of end of adverse event**

For adverse events that are not "ongoing" at the end of the study (i.e. with an outcome other than "Not recovered/not resolved" or "Recovering/resolving"), completely missing AE end dates will be estimated by the last contact date.

For adverse event with a start date and which are "ongoing", completely missing AE end date will be imputed to the cut-off date.

If the day and the month are missing,

- If the year is the same as the year of last contact date, it will be estimated by the last contact date

- If the year is prior to the year of last contact date, it will be estimated by the 31 December

If only the day is missing,

- If the month/year are the same as the month/year of last contact date, it will be estimated by the last contact date
- If the month/year are prior to the month/year of last contact date, it will be estimated by the last day of the month

If after imputation, the estimated end date is before the start date of the adverse event, it will be replaced by the start date of the adverse event.

- **Missing or incomplete time of onset of adverse event**

In case of completely missing time:

- If the onset date is the same as the date of the first study treatment administration, time will be estimated by the time of the first study treatment administration.

- **Prior and Concomitant medications and Procedures (except antineoplastic)**

Start date:

Missing or incomplete start dates will be imputed using the same rules as for start date of adverse event, except if "taken Prior to the study entry" was ticked "Yes", where the following rules apply:
If the start date is completely missing, it will be estimated by the date of ICF signed - 1 (i.e. the day before)
If the day and the month are missing,

- If the year is the same as the year of ICF signed, it will be estimated by the date of ICF signed - 1
- If the year is prior to the year of ICF signed, it will be estimated by the 31st December

If only the day is missing,

- If the month/year are the same as the month/year of the ICF signed, it will be estimated by the date of ICF signed – 1

- If the month/year are prior to the month/year of the ICF signed, it will be estimated by the 15th day of the month

End date:

Missing or incomplete end dates will be imputed using the same rules as for end date of adverse event.

- **Prior and subsequent antineoplastic therapies (Medications/Surgeries/Radiotherapies)**
  - ***Prior antineoplastic therapies:***

These rules apply to all prior antineoplastic therapies collected, i.e. medications, surgeries and radiotherapies.

Start date:

Missing or incomplete start dates will be imputed using the following rules:

If the start date is completely missing, it will be estimated by the first study treatment administration - 1 (i.e. the day before)

If the day and the month are missing,

- If the year is the same as the first study treatment administration, it will be estimated by the date of first study treatment administration - 1
- If the year is prior to the year of first study treatment administration, it will be estimated by the 31st December

If only the day is missing,

- If the month/year are the same as the month/year of the first study treatment administration, it will be estimated by the date of first study treatment administration – 1
- If the month/year are prior to the month/year of the first study treatment administration, it will be estimated by the 15th day of the month

End date:

Missing or incomplete end dates will be imputed using the same rules as for end date of adverse event.

- ***Subsequent antineoplastic therapies:***

These rules apply to all subsequent antineoplastic therapies collected, i.e. medications (both start and end dates), surgeries (start date only) and radiotherapies (start and end dates).

Start date:

Missing or incomplete start dates of subsequent antineoplastic therapies will be imputed using the following rules:
If the start date is completely missing, it will be estimated by the EOT decision date + 1 (i.e. the day after)
If the day and the month are missing,

- If the year is the same as the EOT decision date, it will be estimated by the EOT decision date + 1
- If the year is posterior to the year of the EOT decision date, it will be estimated by the 1st January

If only the day is missing,

- If the month/year are the same as the month/year of the EOT decision date, it will be estimated by the EOT decision date + 1
- If the month/year are posterior to the month/year of the EOT decision date, it will be estimated by the first day of the month

NB: "EOT decision date" refers to the date collected on the "End-of-treatment" disposition form of the e-CRF.

End date:

Missing or incomplete end dates will be imputed using the same rules as for end date of adverse event.

As radiotherapies cannot be reported as "ongoing", completely missing end date of radiotherapy will be imputed to the cut-off date.

- **Date of death**

Missing or partial dates of death will be imputed as follows:

- If only the day is missing: 1st day of the month and year of death
- If the day and the month are missing: January 1st of the year of death
- If the date is completely missing: it will be estimated by the last contact date

If after imputation: death date < last contact date, then it will be estimated by the last contact date.

- **Date of initial diagnosis of primary site**

Completely missing dates will not be imputed.
Partial dates of initial diagnosis of primary site will be imputed as follows:

- If only the day is missing:
    - If the month/year are the same as the month/year of the first study treatment administration: it will be estimated by the first study treatment administration – 1 (i.e. the day before)
    - If the month/year are before the month/year of the first study treatment administration: it will be estimated by the 15th day of the month
- If the day and the month are missing:
    - If the year is the same as the year of the first study treatment administration: it will be estimated by the first study treatment administration – 1 (i.e. the day before)
    - If the year is before the year of the first study treatment administration: it will be estimated by the 1st of July

- **Date of first metastasis**

Missing or partial dates of first metastasis will be imputed as described for date of initial diagnosis of primary site. If after imputation: date of first metastasis < date of initial diagnosis of primary site, then the date of first metastasis will be considered same as the date of initial diagnosis of primary site.

12. DISPOSITION OF SUBJECTS

The number of screened, assigned to treatment and treated subjects, and main reason for discontinuation or no assignment will be provided on the Screened subjects set.

The number of subjects in each analysis set detailed in section 7 (except the Screened subjects set) will be provided overall, and by country and centre on the Full Analysis Set. The number of subjects in the PK Set will be provided only when Pharmacokinetics parameters described in section 19 are analysed (i.e. End-Of-Study analysis).

The number of subjects by time windows will be also tabulated for the FAS.

The number and percentage of subjects who discontinued the study treatment will be provided by reasons for discontinuation for the FAS.

The number and percentage of patients who discontinued from the 30 days safety follow-up will be provided by reasons for discontinuation for the FAS. The same analysis will be performed for long-term follow-up discontinuation.

13. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Before the first study treatment administration, subject's background, medical and surgical history, prior therapies, demographic data, disease characteristics, BRAF mutation data and ECOG PS will be described on the ES and FAS.

If more than 10.0% subjects of the FAS are excluded from the Per Protocol Set, demographic data, disease characteristics and BRAF mutation data will be repeated on the PP Set.

The table below presents the variables that will be described:

Table 9: Demographics and Baseline Characteristics

Variable	Quantitative parameters	Qualitative parameters	Derived variable	Formula derivation if applicable
Demographic data				
Gender		X		
Age (years)	X			
Age (EudraCT categorization: 18-64, 65-84, ≥ 85 years old)		X		
Age (categorization: 18-64, 65-74, ≥ 75 years old)		X		
Height (cm)	X			
Weight (kg)	X			
BMI (kg/m^2)	X		X	Weight (kg) / [Height (m)]^2 rounded to 1 decimal place
BSA(m^2)	X		X	BSA=W**0.425 x H**0.725 x 0.007184 NB: if calculated, the BSA will be rounded to the first decimal place
Race		X		
Ethnicity		X		
Disease characteristics				
Time since initial diagnosis (days)	X		X	(reference start date - date of initial diagnosis of primary site)
Primary tumor location		X		"Other" modalities reported will be considered into existing category when appropriate. In particular, "caecum" or "cecum" will be considered as "Colon, right" and "sigmoid will be considered as "Colon, left" Rectum location reported as "Other" will be considered as a category.
Time since date of first metastasis (days)	X		X	(reference start date - date of first metastasis)
Number of subjects with metastases at initial diagnosis	X		X	Subjects with Date of initial diagnosis ≤ Date of first metastasis ≤ Date of initial diagnosis + 30 days And no antineoplastic therapy taken between the initial diagnosis and the date of first metastasis
Time from initial diagnosis to first metastasis (days)	X		X	(Date of first metastasis – Date of initial diagnosis)
Stage at study entry		X		
Number of metastatic organs		X		
Metastatic organs		X		
Number of subjects with lung metastases only		X		
MSI Status*		X		
ECOG-Performance Status		X		
BRAF mutation				
Local result		X		
Central result		X		
Other subjects characteristics at baseline				

Variable	Quantitative parameters	Qualitative parameters	Derived variable	Formula derivation if applicable
Baseline CRP level		X		≤ local ULN and >local ULN
Baseline CEA		X		≤ local ULN and >local ULN
Baseline CA19-9		X		≤ local ULN and >local ULN

** Blood sample for MSI testing (control sample) will not be processed on an ongoing basis during the study, but once for all subjects enrolled. MSI Status will thus remain undetermined during the study and will be described when available (cf. Appendix 5).*

In addition, a separate summary will be generated for the subgroup of subjects in Japan.

- **Concomitant diseases and medical and surgical histories**

Number and percentage of subjects with at least one concomitant disease as well as medical and surgical histories (as described in MEDICAL HISTORY / CONCOMITANT DISEASE eCRF page) will be tabulated descriptively using the MedDRA codes of System Organ Classes (SOC) and Preferred Terms (PT).

- **Prior antineoplastic therapy**

Number and percentage of subjects with at least one prior antineoplastic therapy since initial CRC diagnosis (including neo-adjuvant), as described in PRIOR ANTI-NEOPLASTIC THERAPY - MEDICATION eCRF page, will be tabulated descriptively overall and, by setting (adjuvant, neo-adjuvant, metastatic, locally advanced, unknown), and best overall response.

Prior Single agent used from the CRC diagnosis (including neo-adjuvant) will be also provided by type of treatment (chemotherapy, chemoradiotherapy, hormonal biologic targeted therapy, other) and therapeutic area according to the WHO-DRUG dictionary using the "anatomical therapeutic chemical" (ATC) classification, by WHO-DRUG ATC2, ATC4 and Preferred Term.

The number of patients with at least one combination identified in Appendix 1 with start dates within the same month or treatments taken in parallel despite being started within the same one month interval will be tabulated.

- **Other Prior Medications**

Number and percentage of subjects with at least one prior medication used before signature of any informed consent (as described in PRIOR AND CONCOMITANT THERAPY eCRF page) will be tabulated descriptively. They will be classified by therapeutic area according to the WHO-DRUG dictionary using the "anatomical therapeutic chemical" (ATC) classification, by WHO-DRUG ATC2, ATC4 and Preferred Term.

- **Prior procedures**

Number and percentage of subjects with at least one prior therapeutic / diagnostic procedure (as described in MEDICAL AND SURGICAL PROCEDURES eCRF page) will be tabulated by SOC and PT using the MedDRA terminology.

Number and percentage of subjects with at least one prior antineoplastic surgery received prior to study entry (as described in PRIOR ANTI-NEOPLASTIC THERAPY - SURGERY eCRF page) will be tabulated by site, location and treatment intent. Location will be classified as done for primary tumor location (cf. Table 9).

Result of surgery will be described by location (primary site, metastatic site).

Number and percentage of subjects with at least one prior antineoplastic surgery will be also tabulated by SOC and PT using the MedDRA terminology.

The following number and percentage of subjects will be provided:

- with at least one prior antineoplastic surgery associated with an ileostomy or colostomy,
- with at least one prior antineoplastic surgery associated with an ileostomy,
- with at least one prior antineoplastic surgery associated with a colostomy

- with no resection of the primary tumor and with an ileostomy or a colostomy
- with an ileostomy or colostomy ongoing at study entry
- with a permanent ileostomy or colostomy

The time since the creation of the ileostomy or colostomy will be described for stomies that are ongoing at study entry, and the duration of the stomy will be described for stomies that were removed before study entry. The time since the creation of the ileostomy or colostomy will be derived as (reference start date - date of stomy creation).

The number and percentage of subjects with at least one prior antineoplastic therapy (Radiotherapy) used prior to study entry (as described in PRIOR ANTI-NEOPLASTIC THERAPY – RADIOTHERAPY eCRF page) will be tabulated by location, treatment intent (palliative, curative, unknown), treatment setting (adjuvant, neo-adjuvant, metastatic, locally advanced, unknown), procedure linked to Chemotherapy (No/Yes) and Best Overall Response.

14. ANALYSIS OF EFFICACY

Efficacy analyses will be conducted using the ES and FAS. A supportive analysis of the primary outcome will be conducted using the PPS.

14.1. PRIMARY ENDPOINT: CONFIRMED ORR BASED ON INVESTIGATOR-ASSESSED TUMOR EVALUATION

BOCR

The best overall confirmed response (BOCR) will be derived as per RECIST guideline version 1.1[1].

Only tumor assessments performed before the start of any further antineoplastic therapies (i.e. any additional secondary antineoplastic medication or anti-cancer surgery or radiotherapy) and not later than 30 days after last study treatment administration will be considered in the assessment of BOCR. Clinical deterioration or clinical progression noted on the end-of-treatment eCRF will not be considered as documented disease progression.

The BOCR for each subject is determined from the sequence of overall (lesion) responses according to the following rules:

- CR: at least two determinations of CR at least 4 weeks apart before progression
- PR: at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR)
- SD: at least one SD assessment (or better) ≥ 6 weeks after start of treatment (and not qualifying for CR or PR).
- PD: early progression ≤ 9 weeks after first study treatment administration (and not qualifying for CR, PR or SD).
- NE = all other cases (i.e. not qualifying for confirmed CR or PR and without SD ≥6 weeks or early progression ≤ 9 weeks after first study treatment administration)

Best overall confirmed response will be summarized, with reasons for having unknown status in Non-Evaluable patients, including:

- No baseline assessment, no measurable disease at baseline
- No post-baseline assessment
- All post-baseline assessments have overall response of "NE"
- New antineoplastic therapy (i.e. any additional secondary antineoplastic medication or anti-cancer surgery or radiotherapy) started before first post-baseline assessment
- Unconfirmed CR, PR or SD with first adequate assessment < 6 weeks Progression >9 weeks after first study treatment administration

The following table, based on Table 3 from the RECIST 1.1[1] guidelines, summarizes the algorithm describing how Best Overall Confirmed Response (BOCR) is determined from the overall tumor assessments. The order used to determine the BOCR is CR>PR>SD>PD, ignoring visits with missing tumor assessments.

All assessments following an assessment of PD will be excluded from the derivation of BOCR.

Table 10: Best Overall Confirmed Response

Case	Best Overall response		BOCR
	First timepoint	Subsequent timepoint	
1	CR	CR	CR (if assessments at least 4 weeks (28 days) apart). (note: sequence of CR – NE – CR would be considered as confirmed CR)
2	CR	PR	SD, PD or PR • If a CR truly met at first timepoint, any subsequent assessment of PR should make the disease PD at that point. That is, neither a PR nor SD may follow CR • Therefore, SD, if CR assessment ≥ 6 weeks, i.e. 42 days after date of first administration of study treatment, • otherwise PD. However BOCR may be PR if subsequent scans suggests small lesions were still present at first time point (in

Case	Best Overall response		BOCR
	First timepoint	Subsequent timepoint	
			which case first assessment of CR should be changed to PR)*
3	CR	SD	SD or PD • SD, if CR or SD assessment ≥ 6 weeks, i.e. 42 days after date of first administration of study treatment, • otherwise PD
4	CR	PD	SD or PD • SD, if CR assessment ≥ 6 weeks, i.e. 42 days after date of first administration of study treatment, • otherwise PD
5	CR	NE	SD or NE • SD, if CR assessment ≥ 6 weeks, i.e. 42 days after date of first administration of study treatment, • otherwise NE
6	PR	CR	PR (if assessments at least 4 weeks (28 days) apart).
7	PR	PR	PR (if assessments at least 4 weeks (28 days) apart). (note: sequence of PR – NE – PR would be considered as confirmed PR)
8	PR	SD	SD or PD • SD, if PR or SD assessment ≥ 6 weeks, i.e. 42 days after date of first administration of study treatment, • otherwise PD
9	PR	PD	SD or PD or NE • SD, if PR assessment ≥ 6 weeks, i.e. 42 days after date of first administration of study treatment, • otherwise PD if PD assessment ≤ 9 weeks, i.e. 63 days after date of first administration of study treatment, • otherwise NE
10	PR	NE	SD or NE • SD, if PR assessment ≥ 6 weeks, i.e. 42 days after date of first administration of study treatment, • otherwise NE
11	SD	SD	SD
12	SD	PD	SD or PD or NE

Case	Best Overall response		BOCR
	First timepoint	Subsequent timepoint	
			• SD, if SD assessment ≥ 6 weeks, i.e. 42 days after date of first administration of study treatment, • otherwise PD if PD assessment ≤ 9 weeks, i.e. 63 days after date of first administration of study treatment, • otherwise NE
13	SD	NE	SD or NE • SD, if SD assessment ≥ 6 weeks, i.e. 42 days after date of first administration of study treatment, • otherwise NE
14	NE, -	SD	SD or NE • SD, if SD assessment ≥ 6 weeks, i.e. 42 days after date of first administration of study treatment, • otherwise NE
15	CR, PR, SD	-	SD or NE • SD, if assessment ≥ 6 weeks, i.e. 42 days after date of first administration of study treatment • otherwise NE.
16	PD		PD or NE • PD if PD assessment ≤ 9 weeks, i.e. 63 days after date of first administration of study treatment, • otherwise NE Ignore all assessments after initial overall response of PD.
17	NE	NE	NE Where all assessments are Not evaluable

* As per Table 3 from RECIST guideline (version 1.1).

Confirmed objective response rate

The **confirmed objective response rate** will be defined as the sum of confirmed CR and PR rate:

$$\text{cORR} = \frac{\sum(\#CR+\#PR)}{N}$$

with:

- # CR = number of subjects with a best confirmed complete response

- # PR = number of subjects with a best confirmed partial response.

- N = number of subjects in the analysis set.

14.1.1. Primary Analysis

The cORR will be provided with a corresponding Clopper-Pearson (exact) binomial 95% CI (Clopper CJ et al, 1934)[4] for the ES. The two-stage method will be used to test the null hypothesis with the possibility of stopping accrual earlier for futility. If the observed cORR at the end of the first stage is less than 28% (i.e., ≤ 11 confirmed CRs + PRs among 40 treated subjects with a centrally confirmed *BRAF*^{V600E} mutation), then insufficient efficacy will be concluded. Otherwise, at the end of stage 2, if the observed cORR is ≥ 41% (i.e., ≥ 37 confirmed responses among 90 treated subjects with a centrally confirmed *BRAF*^{V600E} mutation), the null hypothesis will be rejected.

In case of N > 90 subjects treated with a centrally confirmed *BRAF*^{V600E} mutation, this analysis will be repeated for the Stage 2 analysis, when excluding the overrunning subjects (i.e. on the 90 first treated subjects with a centrally confirmed *BRAF*^{V600E} mutation).

In addition to the Stage 1 and Stage 2 analyses, the analyses for cORR will also be conducted at the time of the end of study.

14.1.2. Supportive Analyses

The cORR will be provided with a corresponding Clopper-Pearson (exact) binomial 95% CI for the PPS and FAS (see section 7).

In order to assess the impact of the Urgent Safety Measure (USM) implemented during the COVID-19 pandemic (see section 15.1), the cORR will be provided with a corresponding Clopper-Pearson (exact) binomial 95% CI, on the subset of the ES composed of subjects who benefited from the USM.

14.1.3. Exploratory Analyses

Primary analysis of the main criterion will be conducted for ES on the subgroups of subjects defined as:

- Age < 65 and ≥ 65 years old
- Males and Females
- Baseline CRP level (≤ local ULN and >local ULN)
- Baseline CEA (≤ local ULN and >local ULN)
- Baseline CA19-9 (≤ local ULN and >local ULN)
- MSI status at screening (MSI-High and Non MSI-High)[2]
- Primary tumor location (right-sided and left-sided)

  Note: Primary tumor location reported as "COLON, TRANSVERSE" will be considered as right-sided. Primary tumor location "Rectum" (reported as "Other") will be considered as left-sided.

  Patients with primary tumor location reported as "OTHER" (except "Rectum", cf. above, and modalities considered as right-sided or left-sided cf. section 13) will not be included in this subgroup analysis.

- Number of metastatic organs (1, 2 and >2)

  Note: "1", "2-3" and ">3" could be used if relevant (i.e. over-represented category)

- Baseline ECOG PS (0 and 1)

[2] Blood sample for MSI testing (control sample) will not be processed on an ongoing basis during the study, but once for all subjects enrolled. MSI Status will thus remain undetermined during the study and will be described when available (cf. Appendix 5).

The primary endpoint and the corresponding 95% CI will be displayed using a forest plot by subgroups.

At the time of the primary analysis (i.e. Stage 2 or at Stage 1 if study stops for futility), analysis of cORR based on investigator-assessed tumor evaluation will be repeated on the ES, when excluding the patients with no confirmed metastatic disease at inclusion (i.e. Inclusion criterion #3 not filled).

cORR based on investigator-assessed tumor evaluation for the subgroup of subjects in Japan will also be examined separately at the time of the primary analysis (i.e. Stage 2 or at Stage 1 if study stops for futility) on the ES and FAS, and according to MSI status at screening on the ES.

14.2. SECONDARY EFFICACY ENDPOINTS

The statistical analyses for the secondary criteria will be described on the FAS unless otherwise stated.

14.2.1. cORR assessed by central radiologist review

For each tumor assessment performed, central radiologist review is performed by two independent readers ("reader 01" and "reader 02"). When there is a discrepancy between both reviews, a third independent reader (named the "adjudicator") will adjudicate and select one of the two readers.

The data sent by the external vendor include:

- Review of reader 01 and reader 02
- Adjudication, if any ("Agree with reader xx").
    - NB: The adjudicator's choice applies to all tumor assessments performed prior to the adjudication.
    - NB2: At any tumor assessment where an adjudication is performed for a given subject (until the last tumor assessment for this subject), the adjudicator's choice may change, and this will apply to all tumor assessments performed prior to the last adjudication. This

means that for a given subject, the results as per central review may change, until the last tumor assessment reviewed, for this subject.

1) For each subject and each tumor assessment, only one reader will be used for statistical analysis. For a given analysis and a given subject: If no adjudication performed:
    a. For tumor assessments where both readers are in agreement => Reader 01's assessment will be taken into account for analysis
    b. For tumor assessments where both readers disagree => Tumor assessments will not be taken into account for analysis.
2) If at least one adjudication performed:
    a. For all tumor assessments done until the last adjudication performed => Reader xx's assessment (according to the last adjudicator's choice) will be taken into account for analysis.
    b. For tumor assessments done after the last adjudication performed:
        i. For tumor assessments where both readers are in agreement => Reader xx's assessment (according to the last adjudicator's choice) will be taken into account for analysis.
        ii. For tumor assessments where both readers disagree => Tumor assessments will not be taken into account for analysis.

The BOCR assessed by central imaging review will be derived as done for BOCR assessed by local review (see section 14.1).

The cORR assessed by central radiologist review will be provided with a corresponding Clopper-Pearson (exact) binomial 95% CI for the ES and FAS.

The cORR assessed by central radiologist review for the subgroup of subjects in Japan will also be examined separately at the time of the primary analysis (i.e. Stage 2 or at Stage 1 if study stops for futility).

14.2.2. ORR (for confirmed+unconfirmed responses) based on investigator-assessed tumor evaluation

Objective Response Rate, considered for confirmed + unconfirmed responses as per local radiologist/investigator assessment, will be analyzed in the same manner as the primary analysis for the ES and FAS.

The best overall response (BOR) for confirmed + unconfirmed responses will be derived as per RECIST guideline version 1.1[1].

Only tumor assessments performed before the start of any further antineoplastic therapies (i.e. any additional secondary antineoplastic medication or anti-cancer surgery or radiotherapy) and not later than 30 days after last study treatment administration will be considered in the assessment of BOR. Clinical deterioration or clinical progression noted on the end-of-treatment eCRF will not be considered as documented disease progression.

The BOR for each subject is determined from the sequence of overall (lesion) responses according to the rules displayed in section 14.1.

- CR: at least one determination of CR before progression
- PR: at least one determination of PR before progression
- SD: at least one SD assessment (or better) ≥ 6 weeks after start of treatment (and not qualifying for CR or PR).
- PD: early progression ≤ 9 weeks after first study treatment administration (and not qualifying for CR, PR or SD).
- NE = all other cases (i.e. not qualifying for confirmed CR or PR and without SD ≥6 weeks or early progression ≤ 9 weeks after first study treatment administration)

Best overall response (confirmed+unconfirmed) will be summarized, with reasons for having unknown status in Non-Evaluable patients, including:

- No baseline assessment, no measurable disease at baseline

- No adequate post-baseline assessment
- All post-baseline assessments have overall response of "NE"
- New antineoplastic therapy (i.e. any additional secondary antineoplastic medication or anti-cancer surgery or radiotherapy) started before first post-baseline assessment
- SD occurred <6 weeks after first study treatment administration
- Progression >9 weeks after first study treatment administration

The following table, based on Table 3 from the RECIST 1.1[1] guidelines, summarizes the algorithm describing how Best Overall Response (BOR) for confirmed and unconfirmed response is determined from the overall tumor assessments. The order used to determine the BOR is CR>PR>SD>PD, ignoring visits with missing tumor assessments.

All assessments following an assessment of PD will be excluded from the derivation of BOR.

Table 11: Best Overall Response (confirmed+unconfirmed)

Case	Timepoint (Best response with CR>PR>SD>PD>NE)	Best Overall Response (confirmed+unconfirmed)
1	CR	CR
2	PR	PR
3	SD	SD or PD or NE • SD, if SD assessment ≥ 6 weeks, i.e. 42 days after date of first administration of study treatment, • otherwise PD if subsequent PD assessment ≤ 9 weeks, i.e. 63 days after date of first administration of study treatment, • otherwise NE
4	PD	PD or NE • PD if PD assessment ≤ 9 weeks, i.e. 63 days after date of first administration of study treatment, • otherwise NE Ignore all assessments after initial overall response of PD.
5	NE	NE Where all assessments are Not evaluable.

* As per Table 3 from RECIST guideline (version 1.1).

Objective Response Rate

The **Objective Response Rate** will be defined as the sum of CR and PR (confirmed+unconfirmed) rate:

$$ORR = \frac{\sum(\#CR + \#PR)}{N}$$

with:

- # CR = number of subjects with a best complete response (confirmed + unconfirmed)

- # PR = number of subjects with a best partial response (confirmed + unconfirmed)

- N = number of subjects in the analysis set.

14.2.3. ORR (for confirmed+unconfirmed responses) assessed by central radiologist review

The BOR assessed by central imaging review will be derived as done for BOR assessed by local review (see section 14.2.2). See section 14.2.1 for handling of central review data.

Objective Response Rate, considered for confirmed + unconfirmed responses assessed by central radiologist review, will be analyzed in the same manner as the primary analysis for the ES and FAS.

14.2.4. PFS based on investigator assessment

PFS based on local review will be calculated and summarized using the KM method. The corresponding median PFS with 95% CI, 25th and 75th percentiles (Brookmeyer and Crowley 1982, Klein and Moeschberger 1997)[5], as well as PFS estimated probabilities at selected time points (every 2 months up to 14 months) will be provided with 95% CI (Kalbfleisch and Prentice 2002) for the FAS and ES.

Progressive disease and death from any cause will be considered as events. If death or PD is not observed, the PFS will be censored at the date of last adequate tumor assessment prior to the cutoff date or new anti-tumoral treatment intake. However, if a PFS event is observed after more than 1 missing or inadequate tumor assessment, it will be censored at the last adequate tumor assessment. If a PFS event is observed after a single missing or non-adequate tumor assessment, the actual date of event will be used.

Censoring rules to be applied to the PFS endpoint are described in detail in

Table 12. Censor status will be summarized.

Table 12: Censoring rules for PFS

In the below table, "new antineoplastic therapy" refers to any additional secondary antineoplastic medication or anti-cancer surgery or radiotherapy.

	Situation	Event Date	Outcome
No baseline tumor assessments			
A1	No baseline assessment and death after the second scheduled post-baseline tumor assessment, or no death	Date of first study treatment administration	Censored
A2	No baseline assessment and death on or before the second scheduled post-baseline tumor assessment	Date of death	Event
No post-baseline tumor assessments (without new antineoplastic therapy given)			
B1	Death on or before the second scheduled post-baseline tumor assessment	Date of death	Event
B2	Death after the second scheduled post-baseline tumor assessment or no death	Date of first study treatment administration	Censored
With baseline and post-baseline tumor assessments (without new antineoplastic therapy given prior progression or death without progression observed)			
C1	Progression with zero or one missed/inadequate tumor assessment prior to progression	Date of progression	Event
C2	Death but no progression, with zero or one missed/inadequate tumor assessment prior to death	Date of death	Event
D1	Progression but two or more consecutively missed/inadequate tumor assessments prior to progression	Date of last adequate tumor assessment*	Censored
D2	Death without progression, but two or more consecutively missed/inadequate tumor assessments prior to death	Date of last adequate tumor assessment*	Censored
E	No progression, no death	Date of last adequate tumor assessment*	Censored
F	Treatment discontinuation due to 'Disease progression' without documented progression, i.e. clinical progression based on investigator claim	N/A (not considered as an event, patient without documented PD should be followed for progression after discontinuation of treatment)	Information ignored
Initiation of new antineoplastic therapy given prior progression or death without progression observed			
G	New antineoplastic therapy started before progression or death	Date of last adequate tumor assessment prior to initiation of new antineoplastic therapy*	Censored
H	No post-baseline tumor assessment and new antineoplastic therapy started prior to a death	Date of first study treatment administration	Censored

* tumor assessment with non-missing and non-unknown overall lesion response, as defined in section 9.3.

The terms ‘adequate Tumor Assessments (TA)’ and ‘missing adequate TA’ are defined in section 9.3, together with rules to determine whether there is one or two missing/inadequate TAs (Table 8).

As sensitivity analyses, the analyses for PFS will be repeated with a censoring rule that includes a PFS event even if the event is recorded after 2 or more missing tumor assessments

Table 13: Censoring rules for PFS (sensitivity analysis)

In the below table, “new antineoplastic therapy” refers to any additional secondary antineoplastic medication or anti-cancer surgery or radiotherapy.

	Situation	Event Date	Outcome
No baseline tumor assessments			
A1	No baseline assessment and no death	Date of first study treatment administration	Censored
A2	No baseline assessment and death	Date of death	Event
No post-baseline tumor assessments (without new antineoplastic therapy given)			
B1	Death	Date of death	Event
B2	No death	Date of first study treatment administration	Censored
With baseline and post-baseline tumor assessments (without new antineoplastic therapy given prior progression or death without progression observed)			
C1	Progression	Date of progression	Event
C2	Death but no progression	Date of death	Event
E	No progression, no death	Date of last adequate tumor assessment*	Censored
F	Treatment discontinuation due to ‘Disease progression’ without documented progression, i.e. clinical progression based on investigator claim	N/A (not considered as an event, patient without documented PD should be followed for progression after discontinuation of treatment)	Information ignored
Initiation of new antineoplastic therapy given prior progression or death without progression observed			
G	New antineoplastic therapy started before progression or death	Date of last adequate tumor assessment prior to initiation of new antineoplastic therapy*	Censored
H	No post-baseline tumor assessment and new antineoplastic therapy started prior to a death	Date of first study treatment administration	Censored

* tumor assessment with non-missing and non-unknown overall lesion response, as defined in section 9.3.

In addition to the primary analysis (i.e. Stage 2 or at Stage 1 if study stops for futility), the analyses for PFS will also be conducted at the time of the end of study.

PFS based on investigator assessment in the subgroup of subjects in Japan will be examined separately at the time of the primary analysis (i.e. Stage 2 or at Stage 1 if study stops for futility).

14.2.5. PFS assessed by central radiologist review

Analysis of PFS assessed by central radiologist review will be analyzed in a similar way of PFS based on local review for the FAS and ES.

PFS assessed by central radiologist review in the subgroup of subjects in Japan will be examined separately at the time of the primary analysis (i.e. Stage 2 or at Stage 1 if study stops for futility).

14.2.6. Overall survival (OS)

OS will be described using survival curves according to the Kaplan Meier method and reporting estimated median (in months) with 95% CI, 25th and 75th percentiles (Brookmeyer and Crowley 1982, Klein and Moeschberger 1997)[5] and KM estimated probabilities with corresponding 95% CIs (Kalbfleisch and Prentice 2002) at several time points (every 2 months up to 14 months).

In addition to the Stage 1 and Stage 2 analyses, the analyses for OS will also be conducted at the time of the end of study.

OS in the subgroup of subjects in Japan will be examined separately at the time of the primary analysis (i.e. Stage 2 or at Stage 1 if study stops for futility).

14.2.7. DOR based on investigator-assessed tumor evaluation

Duration of response according to investigator will be calculated among the confirmed responders (i.e. CR and PR) from the time that measurement criteria are first met for complete or partial response (whichever status is recorded first) after first study treatment administration until the earliest date of progression or death due to underlying disease.

- Patients who are lost to follow-up, or reach the time point of analysis without a known record of progression or death will have the duration of response censored at the date of last adequate tumor assessment.

- Patients who received a new anti-tumoral treatment (chemotherapy, hormonotherapy, radiotherapy, surgery or other anti-tumoral treatment), whatever the type of treatment before their disease progression will be censored at their last adequate radiological assessment (i.e., at the date of last tumor assessment of CR, PR or SD).
- If an event is observed after a single missing or non-adequate tumor assessment, the actual date of progression will be used.
- If an event is observed after two or more missing or non-adequate tumor assessment, the duration of response will be censored at the date of last adequate tumor assessment.

Table 14: Censoring rules for DOR

In the below table, "new antineoplastic therapy" refers to any additional secondary antineoplastic medication or anti-cancer surgery or radiotherapy.

	Situation	Event Date	Outcome
With baseline and post-baseline tumor assessments (without new antineoplastic therapy given prior progression or death without progression observed)			
A1	Progression with zero or one missed tumor assessment prior to progression	Date of progression	Event
A2	Death (due to underlying disease) but no progression, with zero or one missed tumor assessment prior to death	Date of death	Event
B	Death (not due to underlying disease) but no progression, with zero or one missed tumor assessment prior to death	Date of last adequate tumor assessment*	Censored
C1	Progression but two or more consecutively missed tumor assessments prior to progression	Date of last adequate tumor assessment*	Censored
C2	Death without progression, but two or more consecutively missed tumor assessments prior to death	Date of last adequate tumor assessment*	Censored
D	No progression, no death	Date of last adequate tumor assessment*	Censored
E	Treatment discontinuation due to 'Disease progression' without documented progression, i.e. clinical progression based on investigator claim	N/A (not considered as an event, patient without documented PD should be followed for progression after discontinuation of treatment)	Information ignored
Initiation of new antineoplastic therapy given prior progression or death without progression observed			
F	New antineoplastic therapy started before progression or death	Date of last adequate tumor assessment prior to initiation of new antineoplastic therapy*	Censored

* tumor assessment with non-missing and non-unknown overall lesion response, as defined in section 9.3.

Analysis of DOR will be described using survival curves according to the Kaplan Meier method and reporting estimated median (in months) with 95% CI, 25th and 75th percentiles (Brookmeyer and Crowley 1982, Klein and Moeschberger 1997)[5] and KM estimated probabilities with corresponding 95% CIs (Kalbfleisch and Prentice 2002) at several time points (every 2 months up to 14 months).

DOR in the subgroup of subjects in Japan will be examined separately at the time of the primary analysis (i.e. Stage 2 or at Stage 1 if study stops for futility).

14.2.8. DOR assessed by central radiologist review

Analysis of DOR based on central review will be analyzed in a similar way of DOR based on local review.

DOR in the subgroup of subjects in Japan will be examined separately at the time of the primary analysis (i.e. Stage 2 or at Stage 1 if study stops for futility).

14.2.9. TTR based on investigator-assessed tumor evaluation

Time to first response will be calculated from the date of first study treatment administration up to the date of first documented CR or PR. The CR and PR does not need to be confirmed. Patients who do not achieve a PR or CR will be censored as follows (described in

Table 15):

- if they do not have a PFS event, they will be censored at the last adequate tumor assessment date. In this case patients have not yet progressed, so they theoretically still have a chance of responding;
- if they have a PFS event (i.e. progressed or died due to any cause), they will be censored at maximum follow-up (i.e., FPFV to LPLV used for the analysis, as defined in section 9.1.2). In this case, the PFS event is the worst possible outcome as it means the patient cannot subsequently respond. Since the statistical analysis makes use of the ranking of times to response it is sufficient to assign the worst possible censoring time which could be observed in the study which is equal to the maximum follow-up time (i.e., time from FPFV to LPLV).

Table 15: Censoring rules for TTR

In the below table, "new antineoplastic therapy" refers to any additional secondary antineoplastic medication or anti-cancer surgery or radiotherapy.

	Situation	Event Date	Outcome
A	Documented Response (CR or PR)	Date of first documented response	Event
B	Progression or death	Censoring time assigned to maximum follow-up time: - Time to Event Origin Date = date of first study treatment administration - event date = date of first study treatment administration + (LPLV – FPFV)	Censored
C1	No adequate post-baseline tumor assessment* and no death	Date of first study treatment administration	Censored
C2	No progression, no death	Date of last adequate tumor assessment*	Censored
D1	No adequate post-baseline tumor assessment* and new antineoplastic therapy started before death	Date of first study treatment administration	Censored
D2	New antineoplastic therapy started before progression or death	Date of last adequate tumor assessment prior to initiation of new antineoplastic therapy*	Censored

* tumor assessment with non-missing and non-unknown overall lesion response, as defined in section 9.3.

TTR will be described using survival curves according to the Kaplan Meier method and reporting estimated median (in months) with 95% CI, 25th and 75th percentiles and KM estimated probabilities with corresponding 95% CIs at several time points (every 2 months up to 14 months).

TTR will be also analysed for confirmed responders only.

14.2.10. TTR assessed by central radiologist review

Analysis of TTR based on central review will be analyzed in a similar way of TTR based on local review.

14.2.11. Percentage change in tumor measurement from baseline

The best percentage change in tumor measurement from baseline (according to local assessments) will be displayed using a waterfall plot for ES.

The best percentage change in tumor measurement from baseline in the subgroup of subjects in Japan will be examined separately at the time of the primary analysis (i.e. Stage 2 or at Stage 1 if study stops for futility).

14.2.12. Duration of Follow-Up

A summary of duration between first study treatment administration and cut-off date, and follow-up times for PFS/OS will be generated, which are defined as follows:

• Duration between first study treatment administration and cut-off date = (Cut-off date – Date of first study treatment administration + 1) / 30.4375 (months). This item will be summarized in months overall.

• Follow-up time = (Date of event or censoring – Date of first study treatment administration + 1) / 30.4375 (months) regardless of censoring. This item will be summarized in months overall.

The analysis will be performed for PFS based on local review and PFS assessed by central radiologist review. Date of censoring is the same as defined for main analysis of the PFS and OS.

Separate summaries will be generated for the subgroup of subjects in Japan.

In addition, a reverse Kaplan-Meier analysis will be performed for both PFS and OS to estimate the median duration of potential follow-up as described by Schemper and Smith (1996)[6]. Patients who were censored (e.g. lost to follow-up, withdrew consent, ongoing, etc) in the PFS (or OS) analysis will be considered as events for the purposes of estimating duration of potential follow-up. Patients who had a PFS (or OS) event for the purposes of the PFS (or OS) analysis will be censored at the date of the event. The same duration of time values used in the PFS (or OS) analysis will be used in this analysis. Kaplan-Meier estimated probabilities with corresponding 95% CIs (Kalbfleisch and Prentice 2002) [7] will be presented at the same time points as in the PFS (or OS) analysis.

15. SAFETY ANALYSIS

All safety analyses will be presented on the FAS.

15.1. TREATMENT EXPOSURE

Duration of study drug exposure to any dose (in weeks), actual and relative dose intensity will be summarized.

The number of subjects with at least one dose reduction will be presented, along with reasons for the dose reduction. The same table will be provided for dose interruptions, and for dose reductions or interruptions. The number of subjects with at least one definitive dose reduction (i.e. subjects with a dose reduction and who did not re-escalate to the protocol-planned dose) will be described.

The actual daily doses and reasons for dose reductions/interruptions will be listed in an individual basis for subjects with dose reductions/interruptions.

A dose interruption will be indicated in the eCRF by a dosing record with a total daily dose of 0 mg for one or more days.

To avoid over-counting interruptions, dosing records with 0 mg entered as last dosing record will not be counted as interruptions (those represent the reason for permanent discontinuation and will therefore be presented in the reason for treatment discontinuation analysis).

A dose reduction is defined as a decrease in dose from the protocol-planned dose and a decrease from the previous non-zero dose, even if this decrease has been directly preceded by an interruption. For example, for encorafenib, in the sequence of total daily dose 300 mg – 0 mg – 200 mg, the 200 mg dose will be counted as a reduction.

These analyses will apply for each study drug (encorafenib, binimetinib and cetuximab) individually on the FAS.

- **Duration of study drug exposure** (weeks)

This is the duration that the patient was exposed to the study drug and is defined as ([Date of last (non-zero) dose of study drug] – [date of first dose of study drug] + [days until next dose])/7.

For encorafenib/binimetinib, [days until next dose] = 1.

For Cetuximab,

- before switch to a biweekly infusion: [days until next dose] = 7
- from switch to a biweekly infusion: [days until next dose] = 14

NB: In the initial version of the study protocol, patients were planned to switch to cetuximab infusions at dosage of 500 mg/m^2 administered every 2 weeks (i.e. D1 and D15) at C8D1, instead of weekly infusions at dosage of 250 mg/m^2 (except first administration with dosage of 400 mg/m^2). Following the COVID-19 pandemic outbreak, an Urgent Safety Measure (USM) was implemented to allow the investigators to perform Cetuximab infusions at dosage of 500 mg/m^2 administered every 2 weeks (i.e. D1 and D15) instead of weekly, whatever the cycle (even if the subject has not reached yet C8D1), after having evaluated the benefit/risk for the subject and in order to reduce the number of visit at hospital.

For subjects who benefited from this USM, records post-decision to switch to an administration every 2 weeks will be derived as follows:

1) First step: Among the subjects having received at least one dose of study treatment (complete or partial): only the subjects who didn't have their C8D1 before the 01MAR2020 and who didn't discontinue treatment before 01MAR2020 and who didn't discontinue cetuximab before 01MAR2020 are to be considered
2) Among the subjects selected from first step, subjects with an administrated dose > 400 mg/m^2 before C8D1 will be considered as having benefited from the USM.
3) This subset of subjects will be cross-checked with reason mentioned for dose modification. Dose modifications for reasons not related to COVID-19 pandemic will be excluded

The date of switch to a biweekly infusion for a given subject will be derived as the first date among selected records for this subject.

NB: any infusion after this date at dosage < 500 mg/m^2 will be considered as a dose reduction, even if occurring before C8D1.

Duration of study drug exposure will also be described as a discrete variable, with modalities t to < t+4 weeks (t being the duration of exposure, in weeks), such as: < 4 weeks / 4 - < 8 weeks / 8 - < 12 weeks / etc.

- **Relative dose intensity (RDI) (%)**
  - **Cumulative actual dose (mg or mg/m²)** is the total dose given during the study treatment exposure. The cumulative actual dose for a given patient is the sum of the actual dose received (mg or mg/m²). The actual dose received for Cetuximab (mg/m²) at cycle i is equal to the actual dose received (mg) at cycle i divided by the body surface area at the beginning of cycle i
    - NB: If needed, the BSA at a given timepoint will be derived according to formula displayed in section **Erreur ! Source du renvoi introuvable.** (with same rouding convention)

For encorafenib and binimetinib (daily dosing):

- Duration of planned exposure (this is not summarized in any exposure table) = [Date of EOT or data cut-off (the earliest one)] – [date of first dose of study drug] + 1
- Dose intensity (mg/day) = [Cumulative actual dose]/[duration of planned exposure]
- Cumulative planned dose (mg) = sum(protocol specified dose across each day of planned exposure)
- Planned dose intensity (mg/day) = [Cumulative planned dose]/[duration of planned exposure].
  For encorafenib, PDI = 300 mg/day. For binimetinib, PDI =90 mg/day.
- Relative dose intensity (%) = 100 x [Dose intensity]/[Planned dose intensity]

For Cetuximab (intermittent dosing):

- Duration of planned exposure (this is not summarized in any exposure table) = [Date of EOT or data cut-off (the earliest one)] – [date of first dose of study drug] + 1
- Duration of planned exposure after switch to a biweekly infusion (this is not summarized in any exposure table) = [Date of EOT or data cut-off (the earliest one)] – [date of first dose of study drug] - [number of days with weekly infusion] + 1

- planned day of the first visit when switch occurred is the theoretical day (based on C1D1) of the first visit where the subject was under weekly regimen. It represents the duration subject was under weekly regimen.
    - For instance, for subjects who did not benefit from the USM and switched to biweekly infusions starting from C8D1, as initially planned in the protocol: planned day of the first visit when switch occurred = 197, meaning 196 (28*7) planned days under weekly regimen.
    - For subjects who benefited from the USM, number of days with weekly infusion can be derived using the visit of switch to a biweekly infusion (as derived above) and the theoretical day of visits
- This is calculated only if date of EOT or data cut-off (the earliest one) is after the switch to a biweekly infusion (28 weeks in the initial protocol (i.e. Duration of planned exposure > 196 (28*7) days) or USM)

Let xx be the planned day of the first visit under biweekly regimen (197 in the initial protocol, where dosed bi-weekly from week 29/C8D1 or planned day of the first visit when switch occurred for subjects with USM):

- Number of planned doses = number of non-zero doses plus the number of interrupted doses.
    - if date of EOT or data cut-off (the earliest one) is within the first xx-1 days (i.e. Duration of planned exposure ≤ xx-1 days): Number of planned doses = floor([duration of planned exposure – 1]/[days between doses]) + 1
      with days between doses = 7 (dosed weekly for the first xx-1 days)
    - if date of EOT or data cut-off (the earliest one) is after xx-1 days (i.e. Duration of planned exposure > xx-1 days: Number of planned doses = (xx-1)/7 + floor([duration of planned exposure after xx-1 days – 1]/[days between doses]) + 1
      with days between doses=14 (dosed bi-weekly from day xx)

- Dose intensity (mg/m²/dose) = [Cumulative actual dose]/[number of planned doses]
- Cumulative planned dose (mg/m²) = sum(protocol specified dose across each planned day of dosing)
- Planned dose intensity(mg/m²/dose) = [Cumulative planned dose]/[number of planned doses].

  For Cetuximab, PDI (mg/m^2/week) = Cumulative planned dose (mg/m^2)/ duration of planned exposure (week), *taking into account the Cetuximab administration scheme (400 mg/m^2 intravenous (IV) at Cycle 1 day 1 then 250 mg/m^2 IV every week (QW) for the first xx days. Then, 500mg/m^2 IV every two weeks (Q2W)*
- Relative dose intensity (%)= 100*[Dose intensity]/ [Planned dose intensity]

Separate summaries will be generated for the subgroup of subjects in Japan.

15.2. ADVERSE EVENTS

Any adverse event having been reported during the study for a given subject will be classified by Preferred Term and corresponding System Organ Class using the MedDRA terminology.

The **occurrence** of an adverse event is defined by the appearance of a new single event, the reappearance of a previously recovered event or the worsening of a continuous event in severity or seriousness relative to its previous status (see Appendix 2).

An adverse event will be classified as:

- Pre-Treatment adverse event if it occurs or worsens strictly before the first study treatment administration
- Treatment emergent adverse event (TEAE) if it occurs during the treatment period (i.e. from first treatment administration date up to last administration date + 30 days included) or that worsens during the treatment period. Any new serious event that starts > 30 days after treatment discontinuation and is assessed by the Investigator as related to study treatment will be also considered as TEAE.

A Related TEAE (to a specific study drug) is defined as a TEAE with relationship to the study treatment assessed by the investigator as "Suspected" for this drug.
A Related TEAE (to any drug) is defined as a TEAE with relationship to the study treatment assessed by the investigator as "Suspected" for ENCORAFENIB or BINIMETINIB or CETUXIMAB.

An adverse event leading to study drug discontinuation (for a specific study drug) is defined as an adverse event with Action Taken with Study Treatment reported as "DRUG WITHDRAWN" for this drug.
An adverse event leading to study treatment discontinuation is defined as an adverse event with Action Taken with Study Treatment reported as "DRUG WITHDRAWN" for ENCORAFENIB or BINIMETINIB or CETUXIMAB.

An adverse Event leading to dose reduction or study drug interruption (for a specific study drug) is defined as an adverse event with Action Taken with Study Treatment reported as "DOSE REDUCED" or "DRUG INTERRUPTED" for this drug.
An adverse Event leading to dose reduction or study treatment interruption is defined as an adverse event with Action Taken with Study Treatment reported as "DOSE REDUCED" or "DRUG INTERRUPTED" for ENCORAFENIB or BINIMETINIB or CETUXIMAB.

An adverse event requiring a corrective treatment or procedure is defined as an adverse event with the box "yes" ticked for either Corrective Treatment or Corrective procedure.

Missing severity or relationship to the study treatment will not be substituted.
Missing or incomplete dates will be imputed for the calculation of TEAE as described in section 11.2.4, but will be presented as reported in the CRF in the data listings.
A summary table will be produced giving the number of:

- Subjects with at least one AE
- Subjects with at least one TEAE
- Subjects with at least one related TEAE

- Subjects with at least one AE leading to study treatment discontinuation (at least one study drug)
- Subjects with at least one AE leading to study drug discontinuation (respectively: binimetinib, encorafenib, cetuximab)
- Subjects with at least one related AE leading to study treatment discontinuation (at least one study drug)
- Subjects with at least one AE leading to discontinuation of binimetinib and encorafenib
- Subjects with at least one related AE leading to discontinuation of binimetinib and encorafenib
- Subjects with at least one AE leading to discontinuation of all study drugs
- Subjects with at least one related AE leading to discontinuation of all study drugs
- Subjects with at least one AE leading to dose reduction or study treatment interruption (at least one study drug)
- Subjects with at least one related AE leading to dose reduction or study treatment interruption (at least one study drug)
- Subjects with at least one AE requiring a corrective treatment or procedure
- Subjects with at least one related AE requiring a corrective treatment or procedure
- Subjects with at least one Serious Adverse Event (SAE)
- Subjects with at least one Treatment Emergent Serious Adverse Event (TESAE)
- Subjects with at least one related TESAE
- Subjects with at least one Adverse Event leading to death

Associated number of occurrences will be provided for each case listed above.
The number and percentage of subjects with at least one AE having occurred before first study treatment administration (Pre-Treatment AEs) will be tabulated by MedDRA System Organ Class (SOC) and Preferred Term (PT).

Treatment Emergent Adverse Events

Numbers and percentages of subjects with at least one reported TEAE will be tabulated:

- By MedDRA System Organ Class (SOC) and Preferred Term (PT), overall and maximum Grade 3 or higher

- By MedDRA System Organ Class (SOC), Preferred Term (PT), and maximum grade (Grade 1 to Grade 5)
- And by MedDRA System Organ Class (SOC), Preferred Term (PT), and worst outcome (from "Recovered" to "Fatal" as following: Recovered/Resolved, Recovered/Resolved with sequelae, Recovering/Resolving, Unknown, Not Recovered/Not Resolved, Fatal)

A subject with multiple occurrences of the same AE will only be counted under the maximum NCI-CTCAE v4.03 grade or worst outcome for this AE, depending on the analysis.

The number and percentage of subjects with at least one TEAE, and the number of occurrences of TEAEs, will be tabulated by MedDRA System Organ Class (SOC), Preferred Term (PT), and seriousness (by descending order of frequency*)*.

The same analyses will be performed for TEAEs assessed as related to study treatment by the investigator, overall and by study drug.

Adverse Events related to COVID-19 pandemic will be listed on an individual basis: subject's code, sex and age, Investigator's reported term, preferred term and LLT, NCI-CTCAE v4.03 grade, seriousness, onset day, date and time of the first study treatment administration, duration, relationship to study treatment, action taken regarding the study treatment administration, use of a corrective treatment, outcome, AE status with respect to treatment emergence (AE/TEAE). AEs related to COVID-19 are reported in the eCRF with a prefix "COVID19" and will be coded using appropriate MedDRA codes. Prefix will not be displayed in the listing.

Onset day of TEAEs

The number and percentage of subjects with at least one TEAE will be presented by MedDRA System Organ Class (SOC) and Preferred Term (PT), and the first onset day presented in classes ([D1-Week4], [week4-week12], [week12-week24], [week24-EOT], Safety Follow-Up, Long term Follow-Up). The onset day is calculated in section 9.1.3.

Serious Adverse Events (SAEs)

The number and percentage of subjects with at least one Treatment Emergent SAE (TESAE) will be presented by MedDRA System Organ Class (SOC) and Preferred Term (PT), overall and

maximum Grade 3 or higher. The same analysis will be performed for related TESAEs, overall and by study drug.

Serious adverse events will also be listed on an individual basis: subject's code, sex and age, Investigator's reported term, preferred term, NCI-CTCAE v4.03 grade, onset day, date and time of the first study treatment administration, duration, action taken regarding the study treatments administration, use of a corrective treatment, outcome and relationship to the study treatments in the Investigator's opinion, SAE status with respect to treatment emergence (SAE/TESAE).

Adverse events leading to study treatment discontinuation or interruption

The number and percentage of subjects with at least one AE leading to study treatment discontinuation will be presented by study drug, MedDRA System Organ Class (SOC) and Preferred Term (PT), overall and maximum Grade 3 or higher.

The same table will be provided for AEs having led to a study treatment interruption.

AEs having led to study treatment discontinuation will be listed, on an individual basis in the same way as serious adverse events previously described, during the study (from the date of the first study treatment administration onwards).

Adverse events leading to dose reduction

The number and percentage of subjects with at least one AE leading to dose reduction will be presented by study drug, MedDRA System Organ Class (SOC) and Preferred Term (PT), overall and maximum Grade 3 or higher.

Adverse events requiring corrective treatment or procedure

The number and percentage of subjects with at least one AE requiring corrective treatment or procedure will be presented by MedDRA System Organ Class (SOC) and Preferred Term (PT), overall and maximum Grade 3 or higher.

Death

The number and percentage of subjects with adverse event leading to death will be presented by MedDRA System Organ Class (SOC) and Preferred Term (PT) for:

- on-treatment deaths (occurring during the treatment period, as defined in section 9.1.2)
- deaths occurring > 30 days after the last study treatment administration

In addition, deaths will be also listed on an individual basis for:

- Patients who died within 30 days (included) after the last study treatment administration,
- Patients who died > 30 days after the last study treatment administration

AE analyses will be generated for the subgroup of subjects in Japan.

AEs of special interest (AESI)

AEs of special interest are described in Appendix 3.
The MedDRA terms used to define the AESIs and the list of AESIs may be updated during the trial based on accumulating safety data.

Treatment emergent AESIs (TEAESI) will be presented by AESI grouping and PT, overall and maximum Grade 3 or higher.
The same analysis will be performed for related TEAESIs, overall and by study drug.

The number and percentage of subjects with at least one Serious TEAESI (TESAESI) will be presented by AESI grouping and PT, overall and maximum Grade 3 or higher. The same analysis will be performed for related TESAESIs, overall and by study drug.
TESAESIs will also be listed on an individual basis.

The number and percentage of subjects with at least one AESI leading to study treatment discontinuation will be presented by study drug, AESI grouping and PT, overall and maximum Grade 3 or higher.
The same table will be provided for AESIs having led to study treatment interruption.
AESIs having led to study treatment discontinuation will be listed on an individual basis.

The number and percentage of subjects with at least one AESI leading to the dose reduction will be presented by study drug, AESI grouping and PT, overall and maximum Grade 3 or higher.

The number and percentage of subjects with at least one AESI requiring corrective treatment/procedure will be presented by AESI grouping and PT, overall and maximum Grade 3 or higher.

The number and percentage of subjects dead due to an AESI will be presented by AESI grouping and PT.

Groupings of adverse events

Such groups (see Appendix 3) consist of one or more AEs (MedDRA Preferred Terms) and for which there is a specific clinical interest regarding the study treatment.

Grouping of AEs will be summarized as follows:

- Overall summary of each grouping, including the number of subjects with at least one AESI of the grouping, at least one related AESI, at least one serious AESI, at least one AESI leading to study treatment discontinuation, at least one AESI leading to study treatment interruption, at least one AESI leading to dose reduction, at least one AESI requiring corrective treatment/procedure, and the associated numbers of occurrences.
- Number and percentage of subjects with at least one TEAESI by grouping and PT, and by maximum grade (Grade 1 to Grade 5).
- Number and percentage of subjects with at least one TEAESI by grouping and PT, and worst outcome

The onset day of first occurrence of any TEAESI from the grouping will be described by grouping and Preferred Term (PT), overall and maximum Grade 3 or higher.

For each grouping, the maximum duration of TEAESI occurrences for subjects with at least one TEAESI from the considered grouping will be also described by Preferred Term (PT), overall and maximum Grade 3 or higher. For the calculation of the duration, end date of TEAESI will be imputed according to rules described in section 11.2.4 (AE end dates).

All AEs will be included in the listings of individual data.

15.3. LABORATORY DATA

The following laboratory parameters will be analyzed:

Table 16: Summary of Clinical Laboratory Tests

Hematology	Chemistry	Urinalysis	Coagulation
Basophils Eosinophils Hematocrit Hemoglobin Lymphocytes Monocytes Neutrophils/ANC Platelets Red blood cells (RBC, Erythrocytes), White blood cells (WBC, Leucocytes)	ALT AST Bilirubin (total and direct) [a] Albumin Alkaline phosphatase Bicarbonate ($_{HCO3}$) BUN Urea Calcium Chloride CK Serum CK isoenzymes (CK BB, CK MM, CK MB) Creatinine Glucose LDH Magnesium Potassium Sodium Total protein Troponin I or T Uric acid (Urate) Lipase Amylase Myoglobin	Blood Glucose Ketones Leukocytes pH Protein Myoglobin	PT or INR aPTT

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CA19-9 = cancer antigen 19-9; CEA = carcinoembryonic antigen; CK = creatine kinase; CRP = C-reactive protein; FSH = follicle-stimulating hormone; INR = International Normalized Ratio; LDH = lactate dehydrogenase; LH = luteinizing hormone; pH = hydrogen ion concentration; PT = prothrombin time; aPPT = activated partial thromboplastin time; RBC = red blood cell(s); WBC = white blood cell(s); HIV = Human Immuno deficiency Virus.

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

For laboratory tests covered by the NCI-CTCAE v4.03, laboratory data will be graded accordingly. For laboratory tests covered by the NCI-CTCAE v4.03, Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

Sponsor specifications for lab toxicity grading will be described in a specific document, separately from the statistical analysis plan. Corrected Calcium will be derived for analyses purposes, as described in these specifications.

Graded hematology, coagulation, urinalysis, and clinical chemistry test results will be summarized by worst grade on study treatment period as well as in shift tables from Baseline to worst grade on study treatment period. For shift tables, the number of patients with missing data at Baseline or on study treatment period will be displayed.

For laboratory parameters that are not gradable by NCI-CTCAE v4.03, shift tables of normal-abnormal will be provided for worst post-baseline value (both directions).

Grade 3 and 4 observations will be listed on an individual basis.

Possible Hy's Law (subjects with any elevated ALT or AST of >3xULN, ALP <2xULN, and associated with an increase in total bilirubin ≥2xULN) and drug-induced liver injury (DILI) cases (AE preferred term) will be summarized. Drug-induced liver injuries will be flagged using the SMQ "Drug related hepatic disorders" (narrow terms). Hy's Law and drug-induced liver injuries will be considered after the first study treatment administration.

Values outside laboratory normal ranges and Hy's law will be flagged in the individual data listings of laboratory data in appendix 16 of the ICH report.

Laboratory data analyses will be generated for the subgroup of subjects in Japan.

15.4. VITAL SIGNS

The number and percentage of patients with at least one clinically notable abnormality (see Appendix 4) will be tabulated by type of abnormality. Clinically notable abnormality will be also tabulated in an individual data listing.

In addition, blood pressure (systolic, diastolic and both combined) shift table based on NCI-CTCAE v4.03 grade for hypertension at baseline and worst post-baseline values will be produced:

- Systolic BP (SBP) only (mmHg):

- Grade 0: < 120
- Grade 1: 120-139
- Grade 2: 140-159
- Grade 3: ≥ 160
- No Grade 4 or 5

- Diastolic BP (DBP) only (mmHg):
  - Grade 0: < 80
  - Grade 1: 80-89
  - Grade 2: 90-99
  - Grade 3: ≥ 100
- Systolic and diastolic BP combined (mmHg). Maximum grade based on SBP and DBP values will be considered:
  - Grade 0: SBP < 120 and DBP < 80
  - Grade 1: SBP in 120-139 or DBP in 80-89
  - Grade 2: SBP in 140-159 or DBP in 90-99
  - Grade 3: SBP ≥ 160 or DBP ≥ 100
  - No Grade 4 or 5

Clinically notable values will be flagged in the individual data listings of vital signs in appendix 16 of the ICH report.

15.5. ECG

Automatic corrections for QTcF will be used, whenever available. Otherwise QTcF will be calculated as QT / $(60/HR)^{1/3}$ (rounded to the nearest integer).

Values of QTcF will be classified as following:

QTc Categories (ms)
≤450
451-480
481-500
>500

Changes from baseline of QTcF will be classified as following:

QTc change from baseline(ms)
≤30
31-60
>60

The number and percentage of patients with at least one clinically notable ECG abnormalities (see Appendix 4) will be tabulated by type of abnormalities.

Patients with clinically notable QTcF values >500 ms and changes from baseline >60 ms will be listed including the corresponding notable values and abnormality findings.

15.6. MUGA/ECHOCARDIOGRAM

Left Ventricular Ejection Fraction (LVEF) abnormalities will be defined by grade according to NCI-CTCAE version 4.03. Patient will be considered as having a LVEF abnormality if the worst post-baseline value is grade 2, 3 or 4 according to the following classification (as defined in NCI-CTCAE version 4.03):

- Grade 0: Non-missing value below Grade 2
- Grade 2: 40% ≤ LVEF value ≤ 50% or -20% < absolute change from baseline ≤ -10%
- Grade 3: 20% ≤ LVEF value < 40% or absolute change from baseline ≤ -20%
- Grade 4: LVEF value < 20%.

The following summaries will be produced for LVEF:

- Incidence of worst post-baseline LVEF value with NCI-CTCAE version 4.03 grades.
- Shift tables using NCI-CTCAE version 4.03 grades to compare baseline to the worst post-baseline LVEF value with NCI-CTCAE version 4.03 grades.
- Time to LVEF abnormalities will be presented as KM plots if at least 10 patients with abnormality are observed. Patients with no LVEF abnormality will be censored at their last on-treatment LVEF examination date. Patients with no adequate post-baseline LVEF

assessment will be censored at their date of first study treatment administration. Two types of abnormalities will be considered:

- LVEF value < 50%;
- LVEF value < 50% and/or absolute change from baseline ≤ -10% .

Different modalities to assess LVEF might be used for the same patient, change from baseline and shift table will be provided regardless of the modality.

Patients with abnormalities (grade 2 or above NCI-CTCAE version 4.03) will be tabulated in an individual listing.

15.7. ECOG PS

ECOG PS will be summarized descriptively by time windows for each score category. Shift table to compare baseline to the worst post-baseline score will be produced.

15.8. PHYSICAL EXAMINATION

The results on physical examination will not be tabulated as used to detect potential AE. They will be only listed in appendix 16 of the ICH report.

15.9. DERMATOLOGIC EXAMINATION

Number of patients with post-Baseline skin abnormalities will be summarized by type of abnormalities (keratoacanthoma, squamous cell carcinoma, other).

15.10. OPHTHALMIC EXAMINATION

All ophthalmic examinations will be listed:

- Visual assessment performed by the investigator: General inspection, Motility examination, Alignment examination, Visual disturbance
- Full ophthalmic examination: Tonometry, Visual acuity, Fundoscopy, Slit lamp, Optical Coherence Tomography (OCT), Fluorescein Angiography

General inspection, Motility examination, Alignment examination, Visual disturbance:

For each considered category, the number of subjects with at least one newly occurring abnormalities (whatever the clinical significance) will be described, on the subjects at risk of developing the abnormality. Subjects at risk of developing the abnormality will be defined as subjects. with baseline not missing and not being abnormal (whatever the clinical significance) in both eyes, and with at least one post-baseline value).

Same analysis will be performed for the number of subjects with at least one newly occurring clinically significant abnormalities. Subjects at risk of developing the abnormality will be defined as subjects with baseline not missing and not being clinically significantly abnormal in both eyes, and with at least one post-baseline value).

Subjects with newly occurring abnormalities in general inspection, motility examination, alignment examination and visual disturbance respectively will be tabulated in a listing of individual data.

Visual acuity

Visual acuity will be measured using the Snellen visual acuity. This is determined by establishing the smallest optotypes that can be identified correctly by the patient at a given observation distance. Snellen visual acuity will be reported as a Snellen fraction (m/M) in which the numerator (m) indicates the test distance and the denominator (M) indicates the distance at which the gap of the equivalent Landolt ring subtends 1 minute of arc. For each timepoint, the LogMAR score will be calculated as –log(m/M). LogMAR is a notation of visual loss since positive logMAR values indicate reduced vision, while normal vision is indicated by negative logMAR numbers.

Total visual acuity score will also be assessed identifying clinically meaningful deterioration in visual acuity (LogMAR increase). LogMAR results will be summarized in a shift table from Baseline score ($\leq$0, >0 to <0.1, 0.1 to <0.2, 0.2 to <0.3 and $\geq$0.3) to worst post-baseline value ($\leq$0 (no deterioration), >0 to <0.1, 0.1 to <0.2, 0.2 to <0.3 and $\geq$0.3).

Ophthalmic events (AESI from groupings "Retinopathy excluding RVO" and "Retinal vein occlusion") occurring within -15 days to 30 days of the worst logMAR score (<=0, 0 to <0.1, 0.1 to <0.2, 0.2 to <0.3 or ≥0.3) will be presented by preferred term and worst logMAR score.

Patients with ≥ 0.2 LogMAR increase (visual loss) will be listed by patient and timepoint including the Snellen fraction and logMAR score.

All Snellen fraction and logMAR scores will be listed by eye in appendix 16 of the ICH report.

Intraocular pressure

Number and percentage of patients with clinically intraocular pressure above 30 mmHg will be summarized by time windows. For patients with such values, a listing will also be provided.

Optical Coherence Tomography (OCT) and Fluorescein Angiography (FA)

The clinical outcome presented in the listing combine the clinical observation (present, not clinically significant and clinically significant) and the eye involvement (unilateral or bilateral). For each considered category, the number of subjects with at least one newly occurring abnormalities (whatever the clinical significance and clinically significant abnormalities) will be described by type of abnormality, on the subjects at risk of developing the abnormality (*i.e.* with baseline not missing and not being significantly abnormal in both eyes, and with at least one post-baseline value). Patients without baseline assessment will also be considered at risk at baseline of developing a new abnormality.[3] For each considered category in each assessment (OCT and FA), newly occurring abnormalities will be provided.

Fundoscopy and slit lamp

For each considered category (fundoscopy and slit lamp), the number of subjects with at least one newly occurring abnormalities (whatever the clinical significance) will be described by type of abnormality, on the subjects at risk of developing the abnormality. Subjects at risk of developing

the abnormality will be defined as subjects with baseline not missing and not being abnormal (whatever the clinical significance) in both eyes, and with at least one post-baseline value).

Same analysis will be performed for the number of subjects with at least one newly occurring clinically significant abnormalities. Subjects at risk of developing the abnormality will be defined as subjects with baseline not missing and not being clinically significantly abnormal in both eyes, and with at least one post-baseline value).

Subjects with newly occurring abnormalities in fundoscopy and slit lamp respectively will be tabulated in a listing of individual data.

15.11. CONCOMITANT THERAPIES AND THERAPEUTIC / DIAGNOSTIC PROCEDURES

Concomitant therapies (as described in PRIOR AND CONCOMITANT THERAPY eCRF page) prior to and after the start of the study treatment will be tabulated from a descriptive perspective by therapeutic area according to the WHO-DRUG dictionary using the "anatomical therapeutic chemical (ATC) classification (ATC2, ATC4 and Preferred Term) for the FAS and according to the first study treatment administration:

- starting between informed consent signature and start of study treatment, and ending prior to the start of study treatment,
- starting prior to the start of study treatment and continuing after the start of study treatment,
- starting on or after the start of study treatment but no later than 30 days (included) after last dose of study drug.

The number and percentage of subjects with at least one concomitant therapeutic / diagnostic procedure (as described in MEDICAL AND SURGICAL PROCEDURES eCRF pages) will be tabulated by SOC and PT using the MedDRA terminology and according to the first study treatment administration.

The number and percentage of subjects with at least one antineoplastic therapy since study treatment discontinuation (as described in ANTI-NEOPLASTIC THERAPY SINCE STUDY TREATMENT

DISCONTINUATION - MEDICATION eCRF page) will be described by treatment intent (palliative, curative, unknown).

The number and percentage of subjects with at least one single agent since study treatment discontinuation (as described in ANTI-NEOPLASTIC THERAPY SINCE STUDY TREATMENT DISCONTINUATION - MEDICATION eCRF page) will be provided by WHO-DRUG ATC2, ATC4 and Preferred Term.

The number of patients with at least one combination identified in Appendix 1 with start dates within the same month or treatments taken in parallel despite being started within the same one month interval will be tabulated.The number and percentage of subjects with at least one antineoplastic surgery since study treatment discontinuation (as described in ANTI-NEOPLASTIC THERAPY SINCE STUDY TREATMENT DISCONTINUATION - SURGERY eCRF page) will be described by treatment intent, location of surgery and result. Location will be classified as done for primary tumor location (cf. Table 9).

The number and percentage of subjects with at least one antineoplastic surgery since study treatment discontinuation (as described in ANTI-NEOPLASTIC THERAPY SINCE STUDY TREATMENT DISCONTINUATION – SURGERY eCRF page) will be tabulated by SOC and PT using the MedDRA terminology.

The number and percentage of subjects with at least one antineoplastic radiotherapy since study treatment discontinuation (as described in ANTI-NEOPLASTIC THERAPY SINCE STUDY TREATMENT DISCONTINUATION – RADIOTHERAPY eCRF page) will be tabulated by treatment intent (palliative, curative, unknown), best overall response and procedure linked to Chemotherapy (No/Yes).

Time to subsequent therapy (TST) will be defined as the time from the first study treatment administration to the initiation of subsequent antineoplastic therapy or death. TST will be described using survival curves according to the Kaplan Meier method and reporting estimated median (in months) with 95% CI, 25th and 75th percentiles and KM estimated probabilities with corresponding 95% CIs at several time points (every 2 months up to 14 months).

Table 17: Censoring rules for TST

In the below table, "subsequent antineoplastic therapy" refers to any additional secondary antineoplastic medication or anti-cancer surgery or radiotherapy.

	Situation	Event Date	Outcome
A	Initiation of subsequent antineoplastic therapy	Start date of subsequent antineoplastic therapy	Event
B	Death at any time after the first study treatment administration	Date of death	Event
C	Patient alive without starting a subsequent antineoplastic therapy	Date of last contact	Censored

PFS after next line of treatment (PFS2) will be defined as the time from the first study treatment administration to the earlier of death at any time after the first study treatment administration or progression after the start of subsequent anticancer therapy.

PFS2 will be described using survival curves according to the Kaplan Meier method and reporting estimated median (in months) with 95% CI, 25th and 75th percentiles and KM estimated probabilities with corresponding 95% CIs at several time points (every 2 months up to 14 months).

Table 18: Censoring rules for PFS2

In the below table, "subsequent antineoplastic therapy" refers to any additional secondary antineoplastic medication or anti-cancer surgery or radiotherapy.

	Situation	Event Date	Outcome
A	Progression after start of subsequent antineoplastic therapy	Date of progression	Event
B1	Death at any time after the first study treatment administration and before the start of any subsequent antineoplastic therapy, after zero or one missed/inadequate tumor assessment while on the Study	Date of death	Event
B2	Death at any time after the first study treatment administration and before the start of any subsequent antineoplastic therapy, after 2 or more missed/inadequate tumor assessments while on the Study	Date of last contact	Censored
B3	Death after the start of any subsequent antineoplastic therapy	Date of death	Event
C	Patient alive and without progression on their subsequent antineoplastic therapy	Date of last contact	Censored

	Situation	Event Date	Outcome
D	Patient alive, without starting a subsequent antineoplastic therapy	Date of last contact	Censored

Procedures related to COVID-19 pandemic (e.g. quarantine, patient isolation, testing, etc) will be listed on an individual basis, with reported term, MedDRA Preferred Term (PT) and Lowest Level Term (LLT), and dates, day relative to first study treatment administration and status with respect to the study treatment period. Procedures related to COVID-19 are reported in the eCRF with a prefix "COVID19" and will be coded using appropriate MedDRA codes. Prefix will not be displayed in the listing.

16. QUALITY OF LIFE ANALYSIS

Quality of Life will be evaluated through the EORTC QLQ-C30, EQ-5D-5L QoL and PGIC questionnaires on the FAS.

The number of patients completing the questionnaires and the number of missing or incomplete assessments will be summarized for each time window. Compliance for each questionnaire is described in

Table 19.

Table 19: Patient Reported Outcomes Compliance

	Status		
Questionnaire	**Missing**	**Incomplete assessment**	**Complete assessment**
EORTC QLQ-C30	0 question answered	1 to 29 questions answered	30 questions answered
EQ-5D-5L	0 question answered	1 to 5 questions answered	6 questions answered
PGIC	0 question answered	NA	1 question answered

16.1. EORTC QLQ-C30 SCORING

Following the European Organisation for Research and Treatment of Cancer (EORTC) recommendations [12], fifteen scores will be derived from the initial 30 questions of the QLQ-C30 questionnaire:

a global health-related quality of life scale,

five functional scales: physical, role, cognitive, emotional, social,

nine symptom scales: nausea and vomiting, pain, fatigue, dyspnoea, insomnia, appetite loss, constipation, diarrhoea, financial difficulties.

They will be the health-related quality of life parameters of the analysis on QLQ-C30 questionnaire.

Of note, a higher value in functional scales (resp. Global Health Status) will reflect a better level of function (resp. quality of life), but for “symptoms” scales a higher value will reveal a deterioration of the condition.

Each scale in the EORTC QLQ-C30 questionnaire will be scored (0 to 100) according to the EORTC recommendations in the EORTC QLQ-C30 Scoring Manual. The scoring method is summarized below. In this summary Qi refers to the i^{th} question on the EORTC QLQ-C30, and score value correspondence is ["1" = "Not at All", "2" = "A Little", "3" = "Quite a Bit", "4" = "Very Much"] for Q1 to Q28.

Table 20: EORTC QLQ-C30 questionnaire scoring

	Raw score	**Analysed Score**
Functional scales		
Physical functioning:	(Q1+Q2+Q3+Q4+Q5)/5	(1 – (raw score -1) / 3) * 100
Role functioning:	(Q6+Q7)/2	(1 – (raw score -1) / 3) * 100
Emotional functioning:	(Q21+Q22+Q23+Q24)/4	(1 – (raw score -1) / 3) * 100
Cognitive functioning	(Q20+Q25)/2	(1 – (raw score -1) / 3) * 100
Social functioning	(Q26+Q27)/2	(1 – (raw score -1) / 3) * 100
Global health status:		
Global health status/QOL	(Q29+Q30)/2	((raw score -1) / 6) * 100
Symptom scales/Items:		
Fatigue	(Q10+Q12+Q18) / 3	((raw score -1) / 3) * 100
Nausea and vomiting	(Q14+Q15) / 2	((raw score -1) / 3) * 100
Pain	(Q9+Q19) / 2	((raw score -1) / 3) * 100
Dyspnoea	**Q8**	((raw score -1) / 3) * 100
Insomnia	**Q11**	((raw score -1) / 3) * 100
Appetite loss	**Q13**	((raw score -1) / 3) * 100
Constipation	**Q16**	((raw score -1) / 3) * 100
Diarrhoea	**Q17**	((raw score -1) / 3) * 100
Financial difficulties	**Q28**	((raw score -1) / 3) * 100

Descriptive statistics will be used to summarize the 15 scores values and changes from baseline by time windows on the FAS. Figures will be displayed for scores changes by time windows.

16.2. EQ-5D-5L

The EQ-5D-5L[13] contains 1 item for each of 5 dimensions health-related quality of life (mobility, self-care, usual activities, pain or discomfort, and anxiety or depression).

Each dimension has 5 levels: Level 1 indicating no problems, Level 2 indicating slight problems, Level 3 indicating moderate problems, Level 4 indicating severe problems and Level 5 indicating extreme problems.

Descriptive statistics will be used to summarize the scored scales at each time window.

For each dimension, the EQ-5D-5L levels will be also described as dichotomised into 'no problems' (i.e. level 1) and 'problems' (i.e. levels 2 to 5) by time windows.

The EQ-5D-5L VAS records the patient's self-rated health on a vertical visual analogue scale numbered from 0 to 100, where the endpoints are labelled 'The best health you can imagine' (i.e. 100) and 'The worst health you can imagine' (i.e. 0).

Descriptive statistics for EQ-5D-5L VAS values and changes will be tabulated by time windows on the FAS. Figure will be displayed for EQ-5D-5L VAS changes from baseline by time windows.

16.3. PGIC

PGIC score will be summarized using descriptive statistics by time windows on the FAS.

17. BIOMARKERS ANALYSIS

The relationship between protein levels, mutations and clinical outcomes will be explored.

Descriptive statistics for values and changes from baseline in tumor markers blood CEA and CA19-9 will be tabulated by time windows on the FAS.

The primary endpoint and the corresponding 95% CI will be presented by the microsatellite instability (MSI) status subgroups, CEA subgroups and CA19-9 subgroups as described in section 0. Scatter plots highlighting individual results will display baseline CEA vs baseline CA19-9 Levels, each BOCR being identified differently, on the FAS.

The relationship between changes in blood CEA and CA19-9 and radiographic response to treatment will be investigated. Descriptive statistics for percentage change from baseline to nadir in blood CEA and CA19-9 will be tabulated for each type of response (BOCR) on the FAS. The nadir corresponds to the lowest post-baseline blood CEA value recorded for a patient during the study.

All the blood and tissue biomarkers analyses will be exploratory. They will not be part of the CSR, outside the analysis specified above, but summarized in a separate report under the supervision of translational medicine department.

18. HEALTHCARE RESOURCE UTILIZATION

Descriptive statistics of hospitalizations occurring during the treatment period (i.e. from first treatment administration date up to last administration date + 30 days included) will be provided.

The number of patients hospitalized, the number of hospitalizations by patient, the cumulative duration of hospitalization by patient, the total number and duration of hospitalizations, the facility used and hospital discharge disposition will be summarized descriptively on the FAS.
For hospitalization that are “ongoing” at the cut-off date, the end date will be imputed to the last contact date to compute the duration.

19. PHARMACOKINETICS ANALYSIS

Blood samples for encorafenib, binimetinib and the active metabolite of binimetinib (AR00426032) plasma concentration measurements will be performed as follow:

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

Abbreviations: h = hours; PK = pharmacokinetic
PK samples will be collected on Cycle 1 Day 1 postdose (encorafenib/binimetinib) at 2 h (± 10 min) and 6 h (± 30 min). PK samples will be collected on Cycle 2 Day 1 predose (just prior to encorafenib/binimetinib dose) and postdose at 2 h (± 10 min). Blood samples for encorafenib/binimetinib PK will be processed to collect plasma.

Blood samples for serum Cetuximab concentration measurements will be performed as follow:

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

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

The pharmacokinetic set (cf section 7) will be used to perform the PK analysis.

19.1. DESCRIPTIVE STATISTICS

The plasma concentrations of encorafenib, binimetinib and the active metabolite of binimetinib (AR00426032) and the serum concentrations of Cetuximab will be tabulated with their related descriptive statistics.

Individual concentrations tables will be presented by drug-related analyte (i.e encorafenib, binimetinib, AR00426032 and cetuximab), by dose (if applicable) and by nominal time points, with

descriptive statistics as number of available data (N), arithmetic mean, StD, CV, geometric mean, geometric CV, median, [min – max] according to the following rules.

Values reported as 'NS' (no sample) will be set to 'missing'.

Encorafenib, binimetinib and AR00426032 concentrations will be flagged and excluded from the descriptive statistics if a vomiting episode occurs within the first 4 hours post-dosing of during the day of the last dose prior to collection of PK samples.

Concentrations will be flagged and excluded from the descriptive statistics if the actual sampling time is outside the nominal sampling time predefined window (i.e T2h ±10 min and T6h ± 30 min).

For calculated statistics, by time point, if more than (or equal) half of values are not BLQ, statistics will be calculated considering BLQ values as missing data, but Min value will take into account BLQ (i.e Min = BLQ). If more than half of values are BLQ: arithmetic and geometric means, StD, CV geometric CV, median will not be calculated and only Min (BLQ) and Max values will be presented. By time point, if all the concentration values are BLQ, the corresponding statistics will be indicated as not applicable (NA).

19.2. POPULATION PK AND EXPOSURE RESPONSE ANALYSES

PK parameters for encorafenib, binimetinib, AR00426032 and cetuximab may be generated by a compartmental approach such as a population approach, as appropriate. Details of these analyses and of the incorporation of prior information to support the model building will be provided in a specific standalone modeling plan. Results of these analyses will be provided in a separate report.

20. CHANGES TO THE STATISTICAL ANALYSIS PLAN SINCE PROTOCOL WRITING

The following modifications were made to statistical analyses compared to those envisaged in the Version 1 of the protocol dated May 25th, 2018:

In SAP Version 1:

- Addition of analysis of the best percent change in tumor measurements from baseline added
- Addition of analyses on the duration of follow-up added
- Removal of over time analyses for safety data
- Addition of analyses (demographic and disease characteristics, primary and secondary outcomes measures, treatment exposure, AE and laboratory data analyses) for the subgroup of subjects in Japan.
- Addition of analysis of "Time to disease progression under next regimen"

In SAP Version 2:

- Definition of cut-off for Stage 1/Stage 2 analysis was completed with a footnote, to explicitly mention discontinued subjects.
- Study flow-chart updated following protocol amendment V5.
- Following protocol amendment V5: Wording updated for time point for futility analysis, for Stage 2 analysis.
- Following protocol amendment V5: Update of the paragraph on the lack of confirmation of mutation / discordance between local and central (threshold before requirement to perform assessment using central laboratory).
- Following protocol amendment V5: List of labs parameters completed (Myoglobin, Serum CK isoenzymes).

Following protocol amendment V5: Add analysis of new visual assessments performed (General inspection, Motility examination, Alignment examination, Visual disturbance)

In SAP Version 3:

- No change compared to analyses planned in the initial version of the protocol.
    - Clarifications were added to avoid any ambiguity for programming
    - Two variables were added (disease characteristics), following iDSMC recommendations provided after the first iDSMC meeting.
    - Analysis of "Time to disease progression under next regimen" detailed into "Time to subsequent therapy" (TST) and "Progression under next line of treatment" (PFS2)
    - Exploratory analysis of the primary endpoint was added after Steering Committee at Stage 1 (excluding the patients with no metastases at inclusion)

In SAP Version 4:

- Definition of PP set was clarified to explicitly mention that subjects with no central confirmation of the BRAF V600E status will be excluded from the PP set. (It was initially considered that it will be a protocol deviation, but this is).
- Exploratory analysis of the primary endpoint was added to assess impact of the USM implemented during the COVID-19 pandemic
- No change compared to analyses planned in the initial version of the protocol for:
    - Clarifications were added to avoid any ambiguity for programming
    - Some parameters were added in demographics and disease characteristics
    - Additional analyses (protocol deviations, AEs, procedures) to describe impact of COVID-19 pandemic on the study

- Analyses were updated in accordance with USM implemented during COVID-19 pandemic (Protocol V8): take into account in exposure derivations for cetuximab + add an exploratory analysis of the primary endpoint
- Description of additional items collected in the eCRF (prior surgeries, stomies) were added
- A section was added to detail how to handle central imaging data sent by the vendor

21. DATA PROCESSING

Version 9.4 of SAS Software for windows will be used to perform the statistical procedures.

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23. APPENDIX

APPENDIX 1	PRIOR OR SUBSEQUENT ANTINEOPLASTIC THERAPY COMBINATIONS	

The combinations or monotherapies to be described have been identified following a Medical Review on the basis of a database extract at the time of the Data Review Meeting and before the Database Lock. The combination/Monotherapy name will be imported from an external excel file resulting from this medical review. The following terms will be described:

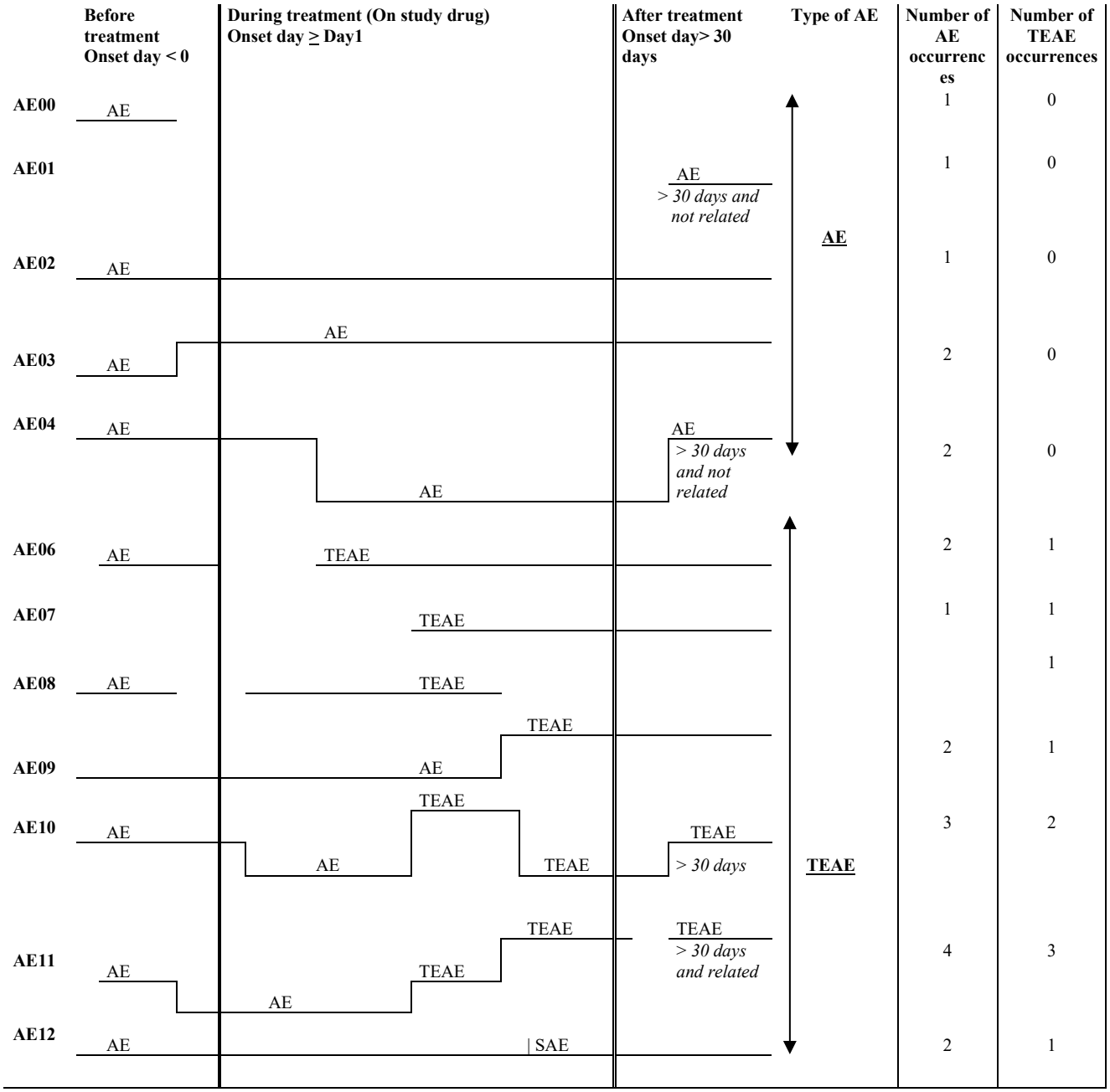
Combination/Monotherapy term to describe	Term used during review
5-Fluorouracil + folinic acid	LV5FU
5-Fluorouracil + folinic acid + Oxaliplatin	FOLFOX
5-Fluorouracil + folinic acid + Oxaliplatin + Bevacizumab	FOLFOX + BEVACIZUMAB
5-Fluorouracil + folinic acid + Irinotecan	FOLFIRI
5-Fluorouracil + folinic acid + Irinotecan + Oxaliplatin	FOLFOXIRI
Oxaliplatin + Capecitabine	CAPEOX
5-Fluorouracil + folinic acid + Oxaliplatin + Cetuximab	FOLFOX + CETUXIMAB
5-Fluorouracil + folinic acid + Irinotecan + Bevacizumab	FOLFIRI + BEVACIZUMAB
5-Fluorouracil + folinic acid + Irinotecan + Cetuximab	FOLFIRI + CETUXIMAB
5-Fluorouracil + folinic acid + Irinotecan + Oxaliplatin + Bevacizumab	FOLFOXIRI + BEVACIZUMAB
5-Fluorouracil + folinic acid + Irinotecan + Oxaliplatin + Cetuximab	FOLFOXIRI + CETUXIMAB
Oxaliplatin + Capecitabine + Bevacizumab	CAPEOX + BEVACIZUMAB
Encorafenib + Binimetinib + Cetuximab	ENCO + BINI + CETUX
Oxaliplatin + Bevacizumab	Oxaliplatin + Bevacizumab
5-Fluorouracil + folinic acid + Irinotecan + Aflibercept	FOLFIRI + Aflibercept
Irinotecan + Bevacizumab	Irinotecan + Bevacizumab
Lonsurf + Immunomodulator	Lonsurf + Immunomodulator
Capecitabine	Capecitabine
Bevacizumab	Bevacizumab
Nivolumab	Nivolumab
Pembrolizumab	PEMBROLIZUMAB
Irinotecan	Irinotecan

APPENDIX 2	CONVENTIONS RELATED TO ADVERSE EVENTS	

2.1) Conventions relative to Treatment Emergent Adverse Events (TEAEs)

Onset Day of AE = Day_[Start date of AE – Date of first administration +1] if start date ≥ Date of first administration
= Day_[Start date of AE – Date of first administration] if start date < Date of first administration

_____ = severity



APPENDIX 3	SPECIFIC GROUPINGS OF ADVERSE EVENTS	

Encorafenib, Binimetinib and Cetuximab Adverse Events of Special Interest are displayed in the excel file: ANCHOR_Statistical_Analysis_Plan_AESI.xls. Last version of this file will be used for analysis.

Note: Any update of this list (e.g. modification of a title) without impact on the statistical analysis described in this plan will not lead to a new version of the statistical analysis plan.

APPENDIX 4	VITAL SIGNS AND ECG CLINICALLY NOTABLE ABNORMALITIES	

Table 1: Vital signs clinically notable values

Parameter	Clinically notable values
SBP	SBP ≥ 160 mmHg and increase from Baseline ≥ 20 mmHg SBP ≤ 90 mmHg and decrease from Baseline ≥ 20 mmHg
DBP	DBP ≥ 100 mmHg and increase from Baseline ≥ 15 mmHg DBP ≤ 50 mmHg and decrease from Baseline ≥ 15 mmHg
HR	HR ≥ 120 bpm and increase from Baseline ≥ 15 bpm HR ≤ 50 bpm and decrease from Baseline ≥ 15 bpm
Weight	Weight increase ≥ 10 % from baseline Weight decrease ≥ 20 % from baseline
Body temperature	Body temperature ≥ 37.5 C Body temperature ≤ 36 C

Table 2: ECG clinically notable values or changes [11]

Parameter	Clinically notable values or changes
QTcF	Value in 451-480 ms Value in 481-500ms Value > 500 ms
	Increase from Baseline in 31-60 ms Increase from Baseline > 60 ms
Heart rate	HR > 100 bpm HR < 60 bpm

APPENDIX 5	TABLES, FIGURES AND LISTINGS	

The list of TFLs to be produced is displayed in the excel file: ANCHOR_SAP_Appendix5_TFL.xls. Last version of this file will be used for analysis.

Note: Any update of this list (e.g. modification of a title) without impact on the statistical analysis described in this plan will not lead to a new version of the statistical analysis plan.

The stage 2 analysis (if considered as primary analysis) will include all analyses listed (except PK and Healthcare resource utilization analyses that will be performed once at the end of study).

Each output name (.rtf) will end with the population reference (including 16.2 listings), for instance:

- Table 11_2_1_1 (Demographics on ES): *T11_2_1_1_demo_ES.RTF*
- Table 12_1_1_1 (Duration of Exposure to Encorafenib on FAS): *T12_1_1_1_enco_expos_FAS.RTF*

Tables, figures and listings that will be performed for the subgroup of subjects in Japan separately at the time of the primary analysis (i.e. Stage 2 or at Stage 1 if study stops for futility), will have RTF reference ended with "[Population]_JAP". For instance:

- Table 11_2_1_1 (Demographics on ES, only Japanese subjects): *T11_2_1_1_demo_ES_JAP.RTF*
- Table 12_1_1_1 (Duration of Exposure to Encorafenib on FAS): *T12_1_1_1_enco_expos_FAS_JAP.RTF*

It should be mentioned in the Titles:

- The analysis (IDSMC, Stage 1, Stage 2 or EOS),
- When analyses are performed on the subgroup of Japanese subjects

For instance, for the description of demographics characteristics performed on the FAS (Title in the TFL list is: *"Demographics [FAS]"*), Title should display:

- IDSMC analysis: *"Demographics [FAS, IDSMC x]"*
- Stage x analysis: *"Demographics [FAS, Stage x]"*

- EOS analysis: *"Demographics [FAS, EOS]"*
- Stage x analysis on the subgroup of Japanese subjects: *"Demographics – Japanese Subjects [FAS, Stage x]"*

APPENDIX 6	SIGNATURE PAGE FROM SAP V4	

Pierre Fabre Médicament
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1. TITLE PAGE

STATISTICAL ANALYSIS PLAN

Reference:	**W00090 GE 2 01**
Author: Name (First & Last name)	PII
Title	**Statistician**
Version n°:	**4**
Date:	**30OCT2020**

2. SIGNATURES

	Title	Name (First & Last name)	Consistency between SAP and study protocol	Date	Signature
Author	**Statistician**	PII			
Reviewer	**Clinical Program Director**	PII			
Approving Officer	**Head of PKPD Department**	PII			
Approving Officer	**Director of Translational Medecine department**	PII			
Approving Officer	**Head of Biometry Department DMPC**	PII			