I.R.I.S.

INSTITUT DE RECHERCHES INTERNATIONALES SERVIER

Document title	**STATISTICAL ANALYSIS PLAN**
Study title	**An open-label, randomised, non-comparative phase 2 study evaluating S 95005 (TAS-102) plus bevacizumab and capecitabine plus bevacizumab in patients with previously untreated metastatic COlorectal cancer who are non-eligible for intensive therapy (TASCO1 study)**
Test drug code	**S 95005**
Indication	**First-line treatment of metastatic colorectal cancer in patients non-eligible for intensive therapy**
Development phase	**Phase II**
Protocol code	**CL2-95005-002**
EudraCT Number	**2015-004544-18**
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AE	:	Adverse Event
ALT	:	ALanine (Amino)Transferase
ALP	:	ALkaline Phosphatase
AST	:	ASpartate (Amino)Transferase
ATC	:	Anatomical Therapeutic Chemical
b.i.d.	:	bis in die (twice a day)
BUN	:	Blood Urea Nitrogen
BOR	:	Best Overall Response
BP	:	Blood Pressure
bpm	:	beats per minute (heart rate unit)
BSA	:	Body Surface Area
CHMP	:	Committee for Medicinal Products for Human Use
CI	:	Confidence Interval
cm	:	centimetre
CPMP	:	Committee for Proprietary Medicinal Products
CR	:	Complete Response
CRC	:	ColoRectal Cancer
mCRC	:	metastatic ColoRectal Cancer
CRF	:	Case Report Form
e-CRF	:	electronic-Case Report Form
CRO	:	Contract Research Organization
DBP	:	Diastolic Blood Pressure
DLT	:	Dose Limiting Toxicity
DR	:	Duration of response
DCR	:	Disease control rate
EAE	:	Emergent Adverse Event
ECG	:	ElectroCardioGram
ECOG	:	Eastern Cooperative Oncology Group
e.g.	:	exempla gratia (for example)
EMA	:	European Medicines Agency
FAS	:	Full Analysis Set
g	:	gram
G/L	:	Giga (10^9) per litre

GGT	:	Gamma-Glutamyl Transferase (Gamma-Glutamyl Transpeptidase)
h	:	hour
HR	:	Hazard Ratio
ICH	:	International Conference on Harmonization
i.e.	:	id est
IHC	:	ImmunoHistoChemistry
IME	:	Important Medical Event
IMP	:	Investigational Medicinal Product
INR	:	International Normalized Ratio
I.R.I.S.	:	Institut de Recherches Internationales Servier
IRS	:	Interactive Response System
IS	:	Included Set
IU	:	International Unit
IV	:	IntraVenous (route)
IWRS	:	Interactive Web Response System
kg	:	kilogram
L	:	Litre
LDH	:	Lactate DeHydrogenase
LL	:	Lower Limit of normal laboratory reference range
m	:	metre
Max	:	Maximum
MedDRA	:	Medical Dictionary for Regulatory Activities
NCI CTCAE	:	National Cancer Institute Common Toxicity Criteria for Adverse Event
NEAE	:	Non Emergent Adverse Event
NSEAE	:	Non Serious Adverse Event
µmol	:	micromole
mg	:	milligram
min	:	minute
Min	:	Minimum
mL	:	millilitre
mm	:	millimetre
mmHg	:	millimetre of mercury
mmol	:	millimole
NA	:	Not Applicable

NE	:	Not Evaluable
NAE	:	Number of Adverse Events
NEAE	:	Number of Emergent Adverse Events
NLR	:	Neutrophil-Lymphocyte ratio
ng	:	nanogram
NIS	:	Non Included Set
NPD	:	Number of Protocol Deviations
ORR	:	Overall Response Rate
%	:	percentage
PCSA	:	Potentially Clinically Significant Abnormal value
PD	:	Progressive disease
PR	:	Partial Response
PPS	:	Per Protocol Set
PT	:	Preferred Term
PV	:	PharmacoVigilance
QLQ	:	Quality of Life Questionnaire
QLQ-C30	:	Quality of Life Questionnaire - core questionnaire
QLQ-CR29	:	Quality of Life Questionnaire - colorectal cancer specific module
QLS	:	Quality of Life Set
QoL	:	Quality of Life
QTc	:	QT interval corrected for heart rate
RBC	:	Red Blood Cells
RD	:	Recommended Dose
RES	:	Response Evaluable Set
RS	:	Randomised Set
s	:	second
SAE	:	Serious Adverse Event
SAP	:	Statistical Analysis Plan
SBP	:	Systolic Blood Pressure
SD	:	Stable Disease
SEAE	:	Serious Emergent Adverse Event
SERFAS	:	Serum Full Analysis Set
SERTRS	:	Serum Tumour Response Set
SOC	:	System Organ Class

SS	:	Safety Set
TK1	:	Thymidine Kinase
T/L	:	Tera (10^{12}) per litre
TLG	:	Tables, Listings and Graphs
TP	:	Thymidine Phosphorylase
TR	:	Tumour Response
TSH	:	Thyroïd Stimulating Hormone
TU	:	Therapeutic Unit
TUMFAS	:	Archived Tumour Biopsies Full Analysis Set
TUMTR	:	Archived Tumour Biopsies Tumour Response Set
UL	:	Upper Limit of normal laboratory reference range
WBC	:	White Blood Cells
WHO	:	World Health Organisation

1. INTRODUCTION

This Statistical Analysis Plan (SAP) details the planned analyses to be performed, in accordance with the main characteristics of the study protocol.
The templates for Tables, Listings and Graphs (TLG) are described in a separate document.

1.1. Study objectives

The objectives of this study are to evaluate the following endpoints in patients receiving S 95005 + bevacizumab (experimental arm = arm 1) or capecitabine + bevacizumab (control arm = arm 2) as first-line treatment for unresectable metastatic colorectal cancer (mCRC) in patients non-eligible for intensive therapy.

- **The primary objective** is progression-free survival (PFS) based on investigator assessment of radiologic images.
- **The secondary objectives** are:
  - Overall response rate (ORR).
  - Duration of response (DR).
  - Disease control rate (DCR).
  - Overall survival (OS).
  - Safety and tolerability.
  - Quality of Life (QoL) (European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ) core questionnaire (QLQ-C30), colorectal cancer (CRC) specific module (QLQ-CR29)).

- **The exploratory objective** is to evaluate the biomarkers potentially predictive of response and resistance to S 95005 given in combination using blood samples and archived tumour biopsy (if available).

1.2. Study design

The study CL2-95002-002 is a randomised, open-label, phase 2 study evaluating S 95005 plus bevacizumab and capecitabine plus bevacizumab in the first-line treatment of patients with unresectable mCRC who are non-eligible for intensive therapy.

In this phase 2 trial, 100 PFS events are required to describe the difference between the two arms. In order to observe this number of events, approximately 150 patients will be randomised 1:1 to S 95005 plus bevacizumab (experimental arm) or capecitabine plus bevacizumab (control arm).

Patients will be randomised with the minimisation procedure proposed by Pocock and Simon (Pocock SJ *et al*, 1975) The stratification factors will be RAS status (wild-type, mutant type), Eastern Cooperative Oncology Group (ECOG) performance status (0 vs. 1 vs. 2) and country.

1.2.1. Study plan

The study is divided into the following periods:

- Screening period and inclusion (up to 28 days prior to randomisation): to obtain informed consent and to check the eligibility of the patient to be included and randomised in the study.
- Randomisation: Included patients will be randomly assigned to one of the two treatment groups.
- Treatment period: with cycles of 28 days of combination of S 95005 + bevacizumab or cycles of 21 days of combination of capecitabine + bevacizumab except in case of safety concerns. The maximum number of cycles is at the discretion of the investigator.
- Withdrawal visit: up to 4 weeks after the last dose of study drug administration.
- Follow-up period:
  - Tumour assessment follow-up every 8 weeks after the end of the treatment period (for reasons other than radiologic disease progression),
  - Survival follow-up every 8 weeks until patient death or the end of the study (the last visit of the last patient).

Investigational Medicinal Products (IMP) will be administered as follows:

S 95005 + bevacizumab:
- Days 1-5: S 95005 (35 mg/m^2/dose) orally twice daily; bevacizumab 5 mg/kg IntraVenous (IV) infusion on Day 1
- Days 6 -7: Rest
- Days 8-12: S 95005 (35mg/m²/dose) orally twice daily
- Days 13-14: Rest
- Day 15: Bevacizumab 5 mg/kg/IV infusion on Day 15
- Days 16-28: Rest

Capecitabine + bevacizumab:
- Days 1-14: Capecitabine (1000 or 1250 mg/m^2/dose according to local clinical practice) orally twice daily; bevacizumab 7.5 mg/kg IV infusion on Day 1.
- Days 15-21: Rest.

For both treatment arms, treatment with either component of the combination regimen may continue after discontinuation of the other component unless the investigator judges that it is in the interest of the patient to withdraw from the study and to be treated outside of this protocol with a combine modality.

The study plans of both arms are shown in Figure (1.2.1) 1 and Figure (1.2.1) 2.

Figure (1.2.1) 1 - Study plan of S 95005 + bevacizumab arm

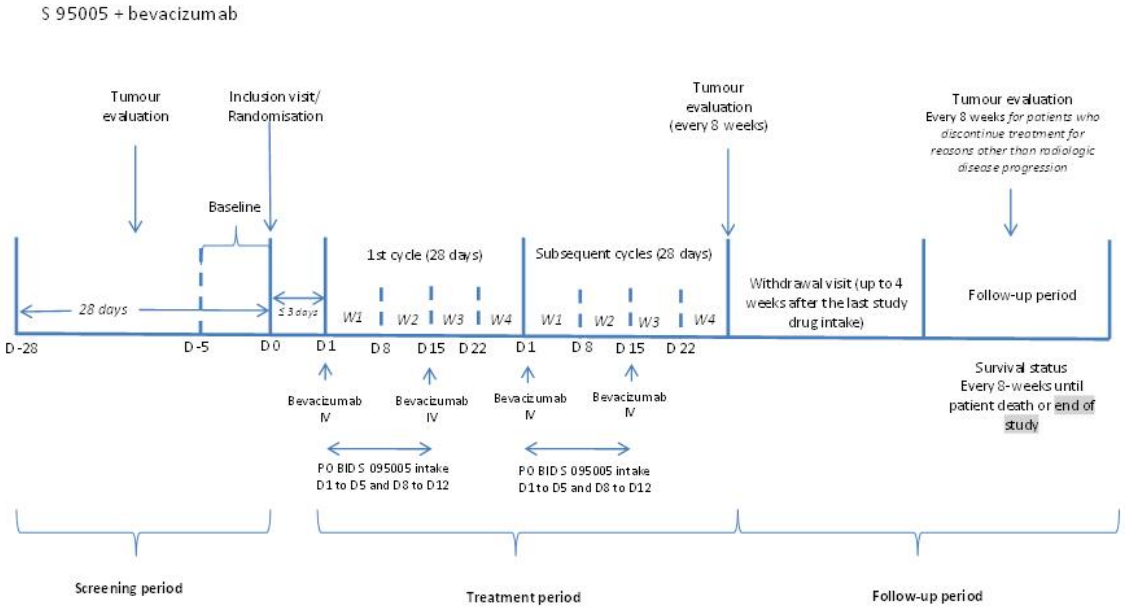
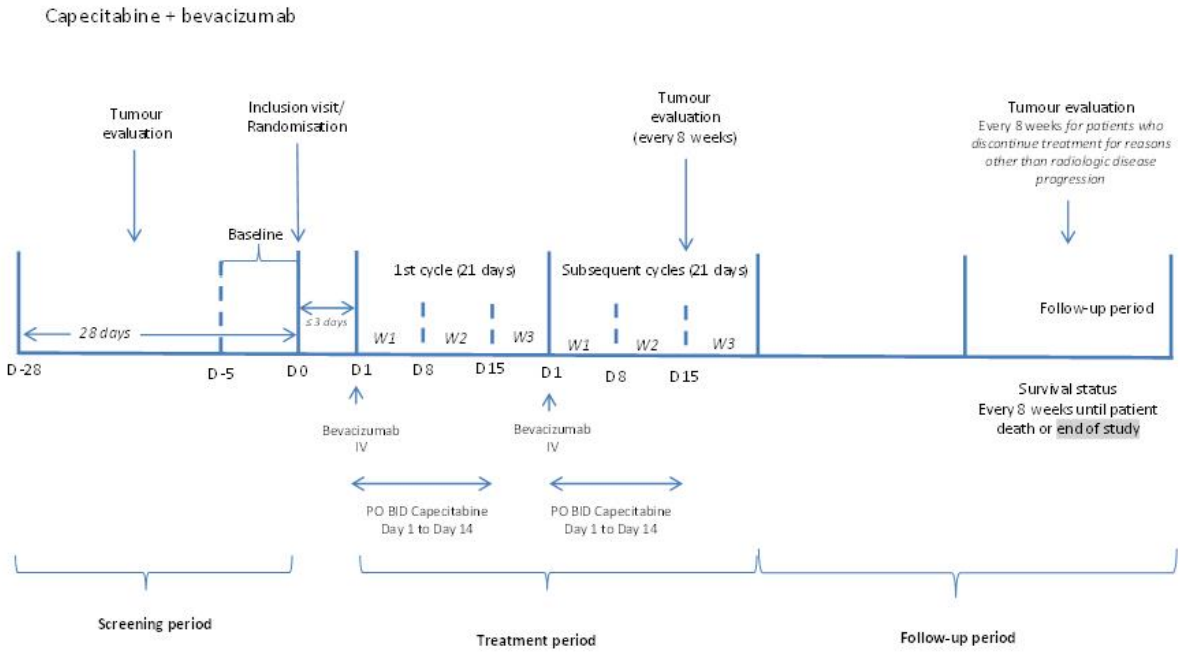


Figure (1.2.1) 2 - Study plan of capecitabine + bevacizumab arm



1.2.2. Type of randomisation

The treatment group will be allocated *via* IWRS using a balanced central randomization (1:1) ratio with the minimisation procedure proposed by Pocock and Simon (Pocock SJ *et al*, 1975). to S 95005 + bevacizumab or capecitabine + bevacizumab with stratification by RAS status (wild-type, mutant type), ECOG performance status (0 vs. 1 vs. 2) and country.

1.2.3. Investigation schedule

The investigation schedules of the 2 arms are described in Table (1.2.3) 1 and Table (1.2.3) 2.

Table (1.2.3) 1 - Investigation schedule of S 95005 + bevacizumab arm

Procedure	Screening period/Inclusion		On-Treatment period						Withdrawal visit	Follow-up period
			CYCLE 1 (28 days)		SUBSEQUENT CYCLES (28 days)					
			Day of Cycle[17]		Day of Cycle[17]					
	≤ 28 days prior randomisation	≤ 5 days prior randomisation	1/Randomisation	15	1	15	Every 8 Weeks	Every 12 Weeks		
Sign ICF	X[1]									
Demography	X									
Medical History	X									
Histological Confirmation	X									
Previous surgery, radiotherapy and treatments	X									
ECG	X								X	
Inclusion/Non-inclusion criteria	X									
Pregnancy Testing		X[2]			X[3]				X[3]	
IWRS[4]										
Patient number	X									
Randomisation[5]			X							
Dispense S 95005[6]			X		X					
Administer IV Bevacizumab[6]			X	X	X	X				
Efficacy measurements										
Tumour Measurements[7]	X[7]						X[7]		X[7]	X[7]
CEA dosage		X					X[8]		X[8]	
Survival Status			→	→	→	→	→	→	→	X[9]
Safety measurements										
Baseline Signs & Symptoms		X								
Physical Examination		X	X[10]		X[11]				X	
ECOG Performance Status[12]		X	X		X				X	
Height		X								
Vital Signs & Weight		X	X[10]	X	X[11]	X			X	
Haematology		X	X[10]	X	X[11]	X			X	
Coagulation		X	X[10]		X[11]				X	
Biochemistry		X	X[10]	X	X[11]				X	
Urinalysis		X	X[10]	X	X[11]				X	
Concomitant treatments	X	→	→	→	→	→	→	→	X	X[13]
AE Assessment[14]	X	→	→	→	→	→	→	→	X	X
Biomarkers assessment										
RAS/BRAF status[15]	X									
Archived tumour biopsy (if available)			X[18]							
Blood samples			X[19]						X	
Quality of Life Assessment		X						X[16]	X[16]	

1. Sign Informed Consent Form (ICF): Written informed consent must be obtained prior to the performance of any study procedure.
2. Pregnancy Testing at screening period: performed within 5 days prior to randomisation only with serum βHCG test.
3. Pregnancy Testing from randomisation: performed from C2, within 48 h prior to Day 1, to withdrawal visit (only if not performed within the previous 4 weeks) with serum βHCG or highly sensitive urine test.
4. IWRS: Once patient has signed ICF, connection to the IWRS for patient's registration and e-CRF patient number (see the IWRS manual for details).
5. Randomisation: Central randomisation via IWRS following confirmation of baseline eligibility criteria. Study medication should begin within 3 days after randomisation.
6. Study Medication: Patients should receive the first dose of S 95005 (Day 1 of Cycle 1) within 3 days of randomisation. A connection to the IWRS should be performed to know the allocated kit number(s) to be dispensed to the patient. Bevacizumab will be provided by the Sponsor. Bevacizumab 5 mg/kg should be administered via IV infusion on Day 1 and Day 15 of each cycle following bevacizumab SmPC. NOTE: treatment with either component of the combination regimen may continue after discontinuation of the other component according to investigator judgment.
7. Tumour Measurements: Obtain imaging based evaluation of the chest, abdomen, and pelvis (as clinically indicated) and clinical examination within 28 days prior to Day 1 of Cycle 1 and every 8 weeks thereafter. Images obtained prior to patient signed ICF may be used if the date of the images is within 28 days of randomisation.
   For patients who discontinue treatment for reasons other than radiologic disease progression, obtain tumour measurements within 8 weeks after the last previous tumour assessment. Every effort should be made to perform the end of treatment tumour assessment prior to the start of new anticancer therapy. Tumour Measurement at withdrawal visit will be performed only if not performed within previous 8 weeks. During the follow-up period, perform tumour measurements every 8 weeks until documentation of radiologic disease progression or initiation of new anticancer therapy (whichever occurs first).
   Tumour assessments should be performed according to RECIST 1.1
8. CEA dosage: This tumour marker will be followed with a dosage every 8 weeks (aligned on tumour assessments) and at withdrawal visit. Note: RECIST 1.1 request normalisation of tumour markers to have a complete response
9. Survival Status: Obtain survival status (alive/dead) at scheduled 8-week intervals until patient death or end of the study
10. Assessments to be performed within 24 hours (for clinical examination and vital signs/weight) or 48 hours (for laboratory assessments) before the first study drug administration on C1D1. If the screening assessments are done within 24/48 hours before C1D1, they do not need to be repeated.
11. Subsequent Cycles ≥2: Obtain within 24 hours (for clinical examination and vital signs/weight) or 48 hours (for laboratory assessments) prior to Day 1 study drug administration. Prior to starting subsequent cycles, verify that patients with toxicities have met resumption criteria prior to administering study drug.
12. ECOG Performance Status: The patient's performance status must remain 0, 1 or 2 during the baseline period and at the time of randomisation for the patient to remain eligible. Collect within 24 hours prior to Day 1 study drug administration for all cycles
13. Concomitant Medications: Collect only anticancer therapies during survival follow-up.
14. AE Assessment: AE will be recorded from the first dose of study medication until the withdrawal visit. Any AE that occur prior to the first dose of study medication should be recorded as Medical History except events associated with any procedure/condition required by the study protocol: procedure (exercise test, MRI, etc.), change or withdrawal of previous/concomitant treatment relating to the conditions of the protocol, or a product other than the test drug, taken as part of the protocol. Up to 100 days after last study drug intake report all ERIN, regardless of the supposed role of the research and all serious adverse event related to the research irrespective of the time of onset after the end of the study.
15. RAS/BRAF status: RAS mutation status should be documented prior to randomisation based on local biological assessment of tumour biopsy. At least the following mutation must be determined: KRAS and NRAS Exon 2: codon 12 and 13. BRAF mutation status will be documented if available.
16. Quality of Life: Patients should complete the EORTC – QLQ-C30 and QLQ-CR29 questionnaires every 12 weeks during study treatment; and at the end of treatment if not performed within the prior 8 weeks.
17. Assessment Windows: A window of +/-3 days is allowable for study procedures (+/-7 days allowable for images), as long as the proper order is maintained.
18. Archived biopsy: the archived biopsy can be provided within 21 days after C1D1
19. Blood sample for genomic and proteomic analysis: To be obtained pre-dose

Table (1.2.3) 2 - Investigation schedule of capecitabine + bevacizumab arm

Procedure	Screening period/Inclusion		On-Treatment period					Withdrawal visit	Follow-up period
			CYCLE 1 (21 days)		SUBSEQUENT CYCLES (21 days)				
			Day of Cycle[17]		Day of Cycle[17]				
	≤ 28 days prior randomisation	≤ 5 days prior randomisation	1/Randomisation	15	1	Every 8 Weeks	Every 12 Weeks		
Sign ICF	X[1]								
Demography	X								
Medical History	X								
Histological Confirmation	X								
Previous surgery, radiotherapy and treatments	X								
ECG	X							X	
Inclusion/Non-inclusion criteria	X								
Pregnancy Testing		X[2]			X[3]			X[3]	
IWRS[4]									
Patient number	X								
Randomisation[5]			X						
Dispense capecitabine[6]			X		X				
Administer IV Bevacizumab[6]			X		X				
Efficacy measurements									
Tumour Measurements[7]	X[7]					X[7]		X[7]	X[7]
CEA dosage		X				X[8]		X[8]	
Survival Status			→	→	→	→	→	→	X[9]
Safety measurements									
Baseline Signs & Symptoms		X							
Physical Examination		X	X[10]		X[11]			X	
ECOG Performance Status[12]		X	X		X			X	
Height		X							
Vital Signs & Weight		X	X[10]		X[11]			X	
Haematology		X	X[10]	X	X[11]			X	
Coagulation		X	X[10]		X[11]			X	
Biochemistry		X	X[10]	X	X[11]			X	
Urinalysis		X	X[10]	X	X[11]			X	
Concomitant treatments	X	→	→	→	→	→	→	X	X[13]
AE Assessment[14]	X	→	→	→	→	→	→	X	X
Biomarkers assessment									
RAS/BRAF status[15]	X								
Archived tumour biopsy (if available)			X[18]						
Blood samples			X[19]					X	
Quality of Life Assessment		X					X[16]	X[16]	

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5. Randomisation: Central randomisation via IWRS following confirmation of baseline eligibility criteria. Study medication should begin within 3 days after randomisation.
6. Study Medication: Patients should receive the first dose of capecitabine (Day 1 of Cycle 1) within 3 days of randomisation. A connection to the IWRS should be performed to know the allocated kit number(s) to be dispensed to the patient. Bevacizumab will be provided by the Sponsor. Bevacizumab 7.5 mg/kg should be administered via IV infusion on Day 1 of each cycle following bevacizumab SmPC. NOTE: treatment with either component of the combination regimen may continue after discontinuation of the other component according to investigator judgment.
7. Tumour Measurements: Obtain imaging based evaluation of the chest, abdomen, and pelvis (as clinically indicated) and clinical examination within 28 days prior to Day 1 of Cycle 1 and every 8 weeks thereafter. Images obtained prior to patient signed ICF may be used if the date of the images is within 28 days of randomisation.
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   Tumour assessments should be performed according to RECIST 1.1.
8. CEA dosage: This tumour marker will be followed with a dosage every 8 weeks (aligned on tumour assessments) and at withdrawal visit. Note: RECIST 1.1 request normalisation of tumour markers to have a complete response.
9. Survival Status: Obtain survival status (alive/dead) at scheduled 8-week intervals until patient death or end of the study
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17. Assessment Windows: A window of +/-3 days is allowable for study procedures (+/-7 days allowable for images), as long as the proper order is maintained.
18. Archived biopsy: the archived biopsy can be provided within 21 days after C1D1
19. *Blood sample for genomic and proteomic analysis:* To be obtained pre-dose

1.3. Determination of sample size

A screening design approach has been utilized, where sample size considerations are based on estimating the PFS hazard ratio (HR) with certain precision in order to optimize a future Phase 3 confirmatory design. The primary analysis will be conducted after 100 PFS events (progression of disease or death) are observed in approximately 150 patients randomized in the study, based on 1:1 randomisation. The corresponding upper limit of the 2-sided 80% confidence interval (CI) for an observed PFS HR of 0.77 would just exclude 1. The corresponding HR critical value for a 2-sided 95% CI would be 0.67. Additional CI approximations for varying observed HRs are shown in the table below:

	Approximate confidence limits	
Observed HR	**95% CI**	**80% CI**
0.55	0.37 - 0.81	0.43 - 0.71
0.60	0.41 - 0.89	0.46 - 0.78
0.65	0.44 - 0.96	0.50 - 0.84
0.67	0.45 - 0.99	0.52 - 0.86
0.70	0.47 - 1.04	0.54 - 0.90
0.75	0.51 - 1.11	0.58 - 0.97
0.77	0.52 - 1.14	0.60 - 1.00
0.80	0.54 - 1.18	0.62 - 1.03

An accrual period of approximately 24 months and a 20%/year loss to PFS follow-up rate has been assumed to account for patients that discontinue treatment for reasons other than disease progression and a follow-up scan that confirms progression has not been obtained (*e.g.* patient discontinues study treatment due to toxicity and new therapy is initiated prior to documentation of disease progression). Assuming a median PFS time in the capecitabine + bevacizumab arm of approximately 9 months, if the observed PFS HR is 0.77, the primary PFS analysis target events milestone is projected at approximately 12 months after the last patient is randomized in the study (projected total study duration of 36 months until the PFS primary analysis milestone).

2. STATISTICAL ANALYSIS STRATEGY

The statistical analysis will be descriptive and analytic as this is a phase 2 study.

The main characteristics at baseline (cf Section 5.2.4), the status of patients and protocol deviations will be described in the randomized set (RS) by arm and overall. Populations are defined on Section 4.1.
Additionally, the following characteristics at baseline will be described in patients of the Tumor Sets (TUMFAS and TUMTR): (demography, disease history, medical history).

The extent of exposure and treatment compliance, as well as concomitant medication during the treatment period will be described in the safety set (SS).

Biomarkers will be studied by arm on the Tumor Sets (TUMFAS and TUMTR) for biomarkers measured on biopsies and on the Serum Set (SERFAS) for biomarkers measured on serum samples.

The safety will be analysed in the Safety set (SS) unless otherwise specified.

Efficacy analyses will be carried out on the Full Analysis Set (FAS), unless otherwise specified.

Primary analysis of the PFS:

HR and the corresponding 2-sided 80% and 2-sided 95% CIs for S 95005 + bevacizumab versus capecitabine + bevacizumab will be estimated using a Cox proportional hazard model adjusting for the stratification factors based on IWRS data (except country due to the large number of countries in the study). PFS will be summarized using Kaplan Meier curves and further characterized in terms of the median and survival probabilities at 6, 12, 18, and 24 months along with the corresponding 2-sided 80% and 2-sided 95% CI (Brookmeyer and Crowley CI for median and Kalbfleisch and Prentice CI for survival probabilities).

Secondary analyses of the PFS:

The primary analysis will be repeated in the per protocol set (PPS) and another sensitivity analysis taking into account the further anti-cancer therapy as an event will be carried out both in the FAS and the PPS, the analysed parameter will be noted PFSs1. In addition, a sensitivity analysis of PFS taking into account clinical progression (*i.e.* not only based on radiological assessment) will be performed in the FAS and will be noted PFSs2.

Additional exploratory analyses for PFS will investigate the effect of specific factors either in a stepwise multivariate analysis setting (Cox regression model) or as the marginal effect in specific subgroups including a Forest plot. These factors will include, but are not limited to, region, ECOG performance status, gender, age (≤ 65 years,]65-75], > 75 years), prior adjuvant treatment, location of primary disease (including left/right colon…), surgical resection, number of metastatic sites (1, ≥ 2), presence of liver metastasis, RAS/BRAF status, Neutrophil-Lymphocyte ratio 3 (NLR) (< 3, ≥ 3) and NLR5 (< 5, ≥ 5), (cf NLR definitions in Section 7.2.2.1).

Analyses of secondary endpoints:

Analysis of OS will use the same population and analytical methods as described for PFS in the primary analysis.

Analysis of DR will also use similar analytical methods but based on the tumor response (TR) population.

DCR and ORR based on the TR population will be evaluated in each arm with their 2-sided 95% Clopper-Pearson CIs.

Potential predictive biomarkers will be investigated by performing the PFS analysis described above (as well as DCR and ORR) according to the biomarker measured at baseline (TK1, TP, TS and MSI) analyzed at different cut-offs.

The safety will be assessed with a description of adverse events (AEs) (serious and emergent), death, clinical laboratory evaluation (biochemistry, haematology, coagulation and urinalysis) using the National Cancer Institute Common Toxicity Criteria for Adverse Event (NCI CTCAE) classification, vital signs and clinical examination (including blood pressure, heart rate, temperature, body weight, respiratory rate and ECOG performance status) and ECG parameters on the SS; results will be presented by arm and overall.

EORTC QLQ-C30 and QLQ-CR29 questionnaire responses will be described separately in each arm using descriptive statistics in the QLS30 and QLS29.

The global Heath status as well as the Functional Scales in Physical, Role, Emotional, Cognitive and Social dimensions as well as the 9 symptom scales: Fatigue, Nausea and vomiting, Pain, Dyspnoea, Insomnia, Appetite loss, Constipation, Diarrhoea, Financial difficulties scores of the QLQ-C30 will be described at each timepoint.

Functional scales (Body image, Anxiety, Sexual function men, Sexual function women) and symptom scales (Urinary frequency, Blood and mucus in stool, Stool frequency, Urinary incontinence, Dysuria, Abdominal pain, Buttock pain, Bloated feeling, Dry mouth, Hair loss, Trouble with taste, Weight, Flatulence, Faecal incontinence, Sore skin, Embarrassed by bowel movement, Stoma care problems, Impotence, Dyspareunia) scores will be described at each timepoint for EORTC QLQ-CR29.

Only evaluable questionnaires will be used (more than 2/3 of the questions answered).

The quality of life of a patient at the time of a scheduled assessment will be based on the answers provided by the patient in the last questionnaire completed before the 1st administration of the following cycle. The determination of the timing of a QoL assessment (week 12, week24…) will be based on the corresponding cycle number:

Arm A: End of cycle 3 = week 12 / end of cycle 6 = week 24
Arm B: End of cycle 4 = week12 / end of cycle 8 = week 24…

At baseline, only the questionnaires completed within the 14 days prior to the first drug administration will be considered (including questionnaires filled the day of first administration). If more than one questionnaire are available within this period, the last non-missing questionnaire will be used.

Any questionnaire that would be completed after the date of last administration plus 35 days will not be analysed.

3. ENDPOINTS

Calculation rules for endpoints and for their expressions are provided in Appendix 7.1 and Appendix 7.2, respectively

3.1. Efficacy endpoints

The detailed calculation rules for efficacy endpoints are provided in Appendix Section 7.2.2

The efficacy endpoints are:

- BOR (CR / PR / SD / PD / NE): Best response is defined as the best response across all time points.
- PFS (months): defined as the time from the date of randomisation until the date of the investigator-assessed radiological disease progression or death due to any cause. Patients who are alive with no disease progression as of the analysis cut-off date will be censored at the date of the last evaluable tumor assessment, or at the cut-off date, whichever is earlier. Patients who receive non-study cancer treatment before disease progression will be censored at the date of the last evaluable tumor assessment before the non-study cancer treatment is initiated. The PFS cut-off date used for the primary analysis will be based on the observation of the 100th event (radiological PD or death) in the study.
- DCR (Yes / No): Proportion of patients with objective evidence of confirmed CR or PR, or SD as BOR. The assessment of DCR will be based on Investigator review of the images.
- ORR (Yes / No): Proportion of patients with objective evidence of confirmed CR or PR as BOR according to RECIST criteria in the population of interest.
- The assessment of ORR will be based on Investigator review of the images.
- DR (months): calculated among the responders (*i.e.* with BOR equal to CR or PR) as the time from the first documentation of response (CR or PR) to the first documentation of objective tumor progression or death due to any cause, whichever occurs first. Patients alive and progression free as of the analysis cut-off date are censored at their last evaluable tumor response assessment, or at the cut-off date, whichever is earlier, prior to initiation of any non-study cancer treatment.
- OS (months): Time from the date of randomisation to the date of death. In the absence of death confirmation or for patients alive as of the OS cut-off date, survival time will be censored at the date of last study follow-up, or the cut-off date, whichever is earlier. Patients will be followed for OS until end of the study (last visit of the last patient).
- Relative change of the sum of the lesions diameters (%).
- Best relative change of the sum of the lesions diameters (%).

3.2. Safety endpoints

The safety endpoints are:

AEs:

- Serious adverse events (SAEs) during the study, according to the investigator or sponsor opinion.
- Emergent adverse event (EAE) under treatment:
  - All EAE
  - Serious EAE (SEAE), according to the investigator or sponsor opinion
  - Severe EAE
  - Non serious EAE (NSEAE), according to the investigator and sponsor opinion
- EAE of interest
  - Haematological toxicities: Febrile neutropenia, neutropenia, thrombocytopenia and anaemia

Deaths:

- Death (Yes / No)
- Reason of death (Progressive disease, toxicity caused by this protocol, other)

Clinical laboratory evaluation:

- Biochemistry, haematology and coagulation parameters expressed in terms of:
  - For gradable parameters: Albumin (g/L), Alkaline Phosphatase (IU/L), Total Bilirubin (µmol/L), Calcium (mmol/L), GGT (IU/L), Glucose (mmol/L), Potassium (mmol/L), Magnesium (mmol/L), Phosphate (mmol/L), Sodium (mmol/L), AST (IU/L), ALT(IU/L), Hemoglobin (g/L), White Blood Cells (WBC) (10^9/L), Platelets (10^9/L), Lymphocytes (10^9/L), Low Neutrophils (10^9/L), Serum creatinine (mmol/L), Activated Partial Thromboplastin Time (APTT) (seconds) and International normalized ration (INR).
    - Value and grade at baseline (and at each planned post-baseline visit under treatment).
    - Worst grade on treatment according to the grade at baseline.

  - For non-gradable parameters: Chloride (mmol/L), LDH (IU/L), Total Protein (g/L) Basophils (10^9/L), Eosinophils (10^9/L), Hematocrit (%), Monocytes (10^9/L), Red Blood Cells (RBC) (10^{12}/L), Bicarbonate (mmol/L), Blood urea nitrogen (BUN) (mmol/L) and Creatinine clearance (mL/min) (Cockcroft formula).
    - Value and reference ranges at baseline.
    - Worst value on treatment according to baseline, by classes (< LL / [LL-UL] / > UL) or (normal, mild, moderate, severe) for creatinine clearance.

- For parameters of special interest (Haemoglobin, neutrophils, platelets, low WBC, bilirubin ASAT, ALAT, creatinine clearance, serum creatinine and proteinuria):
  For hemoglobin, neutrophils, platelets, low WBC, ASAT, ALAT, bilirubin and serum creatinine:
    - Days to Most Extreme Value and Magnitude of Nadir for Laboratory Parameters of Interest With Grade 3 or 4 Abnormalities that Worsened from Baseline by at Least One Grade.
    - Recovery from the Most Extreme Value for Laboratory Parameters of Interest With Grade 3 or 4 Abnormalities that Worsened from Baseline by at Least One Grade.

For creatinine clearance:
- Days to Most Extreme Value and Magnitude of Nadir for Laboratory Parameters of Interest with moderate or severe renal impairment that Worsened from Baseline by at Least One level of impairment(cf Section 7.2.4.4 for definition of levels of impairment).
- Recovery from the Most Extreme Value for Laboratory Parameters of Interest With moderate or severe renal impairment that Worsened from Baseline by at Least One level of impairment

- For urinalysis parameters: Proteinuria, Glucosuria, Urobilinogen, Haematuria, Leucocyturia:
  - Value at baseline, by classes (negative, trace, positive (+, ++, +++)).
  - Worst value on treatment according to baseline, by classes (negative, trace, positive (+, ++, +++)).

- For tumour marker level given by CarcinoEmbryonic Antigen (CEA):
  - Quantitative value and value by classes (normal, abnormal) at baseline.
  - Worst value on treatment according to baseline and worst value by classes (normal, abnormal).

Vital signs and clinical examination:
- ECOG PS (0, 1, 2, 3, 4)
- Weight (kg)
- Temperature (°C)
- Respiratory rate (breaths/min)
- Body Surface Area (BSA) (m²)
- Supine systolic blood pressure (SBP) (mmHg)
- Supine diastolic blood pressure (DBP) (mmHg)
- Supine heart rate (bpm).

They will be expressed as:
- Value at baseline and worst post-baseline value under treatment.
- Change from baseline to worst post-baseline value under treatment, for weight, temperature, BSA, respiratory frequency, SBP, DBP and heart rate.

ECG:
- Presence of clinically significant ECG abnormalities (yes/no)
- QT interval (msec)
- RR interval (msec)

QT and RR interval will be expressed as:
- Value at baseline and at withdrawal visit.

QT interval (msec) will be expressed as:
- Absolute prolongation at withdrawal visit.
- Change from baseline at withdrawal visit.

3.3. QoL endpoints

For QLQ-C30:

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

For QLQ-CR29:

- **Functional scales**
  - Body image: (1 - (((Q45+Q46+Q47)/3)-1)/3) * 100
  - Anxiety: (1 - (Q43-1)/3) * 100
  - Sexual function men: ((Q56-1) /3) * 100
  - Sexual function women: ((Q58-1) /3) * 100
  - Weight: (1-(Q44-1) /3) * 100
- **Symptom scales**
  - Urinary frequency (((Q31+Q32)/2) -1) /3 * 100
  - Blood and mucus in stool (((Q38+Q39)/2) -1) /3 * 100
  - Stool frequency (((Q52+Q53)/2) -1) /3 * 100
  - Urinary incontinence (Q33-1) /3 * 100
  - Dysuria (Q34-1) /3 * 100
  - Abdominal pain (Q35-1) /3 * 100
  - Buttock pain (Q36-1) /3 * 100
  - Bloated feeling (Q37-1) /3 * 100
  - Dry mouth (Q40-1) /3 * 100
  - Hair loss (Q41-1) /3 * 100
  - Trouble with taste (Q42-1) /3 * 100
  - Flatulence (Q49-1) /3 * 100
  - Faecal incontinence (Q50-1) /3 * 100
  - Sore skin (Q51-1) /3 * 100
  - Embarrassed by bowel movement (Q54-1) /3 * 100
  - Stoma care problems (Q55-1) /3 * 100
  - Impotence (Q57-1) /3 * 100
  - Dyspareunia (Q59-1) /3 * 100

3.4. Biomarkers endpoints

The following markers have been measured on both the experimental arm (S 95005+bevacizumab, arm 1) and the control arm (capecitabine+bevacizumab, arm 2):

Archived tumor biopsies analysis

The markers described in this subsection will be based on archived tumor biopsies, which can be provided within 21 days after C1D1 and will be considered as baseline value.

a)

The following criteria are available for each protein marker measured by IHC (TP, TK1, TS):

i. H-score
ii. Occupancy (defined in Section 7.2.3.1.1).

In case of several subcellular staining localizations for one marker, analyses will be performed separately for each localization.

For markers of interest, localizations of interest are the following:

- TP: tumor cytoplasm
- TK1: tumor cytoplasm and tumor nucleus
- TS: tumor cytoplasm and tumor nucleus.

Based on 5 genes, the number of repetitions of DNA sequences is studied and the following summary information is provided:

i. MSI status group: MSS/MSI-L and MSI-H.

Blood analysis

b) Protein-expression by ELISA

The following criterion is available at baseline (C1D1 pre-dose) for each marker measured (TP):

i. Concentration

c) Mutations by Polymerase Chain Reaction (PCR)

The following criterion is available at baseline (C1D1 pre-dose) for each marker measured (KRAS, NRAS, BRAF):

i. Mutation status.

4. ANALYSIS SETS AND SUBGROUPS / TREATMENT GROUPS

4.1. Analysis sets and subgroups

- **Screened Set**: All screened patients.

- **Included Set**: All included patients.

- **Non-Included Set (NIS)**: All enrolled patients not included.

- **Randomized Set (RS)**: All patients to whom a therapeutic unit (TU) was randomly assigned using IWRS.

- **Full Analysis Set (FAS):** All randomized patients who have taken at least one dose of IMP will be included in the FAS. Based on the intention-to-treat principle, patients in the FAS will be analysed in the arm they were assigned by randomisation.

- **Per Protocol Set (PPS):** All patients of the FAS without relevant deviation(s), which could affect the evaluation of the IMP effect on the primary efficacy endpoint.

- **Tumor Response Population (TR Population):** All patients in the PPS with measurable disease (at least one target lesion) at baseline and with at least one tumor evaluation while on treatment (with the same method of measurement on the same target lesion as baseline). Patients who have a cancer-related death prior to their first tumor evaluation will also be considered evaluable with PD as best overall response (BOR).

- **Safety Set (SS):** This set will correspond to patients who received at least one dose of IMP. Patients will be analyzed according to the treatment actually received. Each patient will be classified into and analyzed consistently within one (and only one) treatment group.

- **Quality of Life Set 30 (QLS30):** All patients of the FAS who have completed at least two third (*i.e.* at least 20 questions) of the questions of the baseline QLQ-C30 questionnaire, and at least two third of the questions of at least one QLQ-C30 questionnaire during the study period.

- **Quality of Life Set 29 (QLS29):** All patients of the FAS who have completed at least two third (*i.e.* 26/27 questions=at least 18 questions) of the questions of the baseline QLQ-C29 questionnaire, and at least two third of the questions of at least one QLQ-C29 questionnaire during the study period.

- **Subgroups** such as region, ECOG performance status, gender, age (≤ 65 years,]65-75], > 75 years), prior adjuvant treatment, location of primary disease (colon (right/left..) / rectal), surgical resection, number of metastatic sites (1, ≥ 2), presence of liver metastasis, RAS and BRAF status, NLR3 (< 3, ≥ 3), NLR5 (< 5, ≥ 5) could be used in the analysis.

- **Archived tumor biopsies Full Analysis Set** (TUMFAS): All FAS patients with an analyzable value based on archived tumor biopsy.

- **Archived tumor biopsies Tumor Response Set** (TUMTR): All TR patients with an analyzable value based on archived tumor biopsy.

- **Serum Full Analysis Set** (SERFAS): All FAS patients with an analyzable value at baseline based on serum sample.

4.2. Treatment groups

Two treatment groups:

Arm 1: S 95005 + Bevacizumab
Arm 2: Capecitabine + Bevacizumab

will be administrated.

Two subgroups in the Arm 2 Capecitabine + Bevacizumab by theoretical starting dose:

Subgroup 1: Capecitabine 1000 mg/m^2
Subgroup 2: Capecitabine 1250 mg/m^2

5. STATISTICAL METHODS

5.1. General considerations

5.1.1. Multiplicity issues

Not applicable.

5.1.2. Handling of missing data

Not applicable.

5.1.3. Statistical elements

5.1.3.1. Descriptive statistics

Descriptive statistics depending on the nature of the criteria and the number of patients by arm:
For **qualitative data**, number of observed values, number and percentage of patients per class will be presented. Unless otherwise specified in the TLG, no class "Missing" is considered.

For **quantitative data**, number of observed values, mean, standard deviation, minimum and maximum, median, first and third quartiles.

For **Event:**

- Number of patients (or cycles) having experienced the event (n).
- Number of events that occurred (for AE analyses only) (NAE).
- Number of patients (or cycles) at risk for the event (N).
- Global incidence rate (%).

(Calculated as the ratio between the number of patients (or cycles) having experienced the event (n) and the number of patients (or cycles) at risk at the beginning of the study (N)).

5.1.3.2. Estimation and statistical test

Difference within an arm will be calculated as "visit of cycle" minus "baseline".

- Fisher's exact test will be used to assess the difference between the 2 arms in terms of DCR and ORR.
- The 95% Clopper-Pearson CI for rates will be computed by inverting the equal-tailed test based on the binomial distribution.
- Median duration and survival probability at 3, 6, 9, 12 and 24 months and 80% and 95% CI for time-dependent parameters will be estimated using Kaplan-Meier method Confidence intervals for median are based upon the methods of Brookmeyer and Crowley. Confidence intervals are calculated using the log-log transformation. A Cox proportional hazard model will be used to estimate HR and the corresponding 2-sided 80% and 2-sided 95% CIs
- Cox regression model to study impact of some factors.

5.2. Study patients: Disposition, baseline characteristics and follow-up

Description of disposition of patients (status, protocol deviations and analysis set), initial tumour assessment as well as treatment duration and extent of exposure and all other baseline characteristics will be performed by arm and overall.

Specific definitions on disposition of patients, baseline characteristics and patient follow-up are provided in Appendix 7.2.

5.2.1. Disposition of patients

Disposition of patients will be described on RS by arm and overall.

5.2.2. Protocol deviations

Protocol deviations before or at inclusion, as well as after inclusion, will be described in the RS, by category of deviations by arm and overall.

5.2.3. Analysis sets and subgroups

The size of each analysis set and reasons for exclusion will be described.
Listings of patients with their membership, or not, of each analysis set and subgroup and of excluded patients with reasons for exclusion will be provided.

5.2.4. Demographic data and other baseline characteristics

Demographic data and other baseline characteristics such as pregnancy test, disease history including smoking status, previous therapies, signs and symptoms, clinical laboratory evaluation, medical history and surgical or medical procedures history, mutation, vital signs and physical examination, ECG parameters and initial tumour assessment will be described on the RS.
Previous chemotherapy will be detailed with regards to intent (neo-adjuvant/adjuvant).

It is of note that previous therapies for CRC will also be described as combination (No previous therapy, Surgery only, Radiotherapy only, drug treatment only, Surgery + radiotherapy, Surgery + drug treatment, Radiotherapy + drug treatment, Surgery + radiotherapy + drug treatment, any previous therapy).

The following continuous data will be described in classes:
- Age (≤ 65 years,]65-75], > 75 years)
- Disease duration (≤ 1 year,]1; 2 years] ,]2; 4 years] , > 4 years)
- Time from diagnosis of first metastases to randomization (in months)
- Progression free interval (≤ 1 Months,]1;6 Months], > 6 Months)
- Disease stage
- Details and number of organs involved
- Biomarkers (KRAS, NRAF, BRAF, RAS IWRS and RAS_CRF defined as follows:
  - **RAS_CRF = mutant type** IF KRAS = mutant OR NRAS = mutant
  - **RAS_CRF = wild type** IF KRAS = wild AND NRAS = wild
  - **RAS_CRF = NE** IF (KRAS = wild AND NRAS = missing) OR (KRAS = missing AND NRAS=wild) OR (KRAS=missing AND NRAS=missing))
- PS (CRF value/IVRS value)
- NLR3 (< 3 vs. ≥ 3)
- NLR5 (< 5 vs. ≥ 5)
- N of patients with measurable disease
- N of patients with non-measurable disease only
- Supine SBP (< 90, [90, 140[, ≥ 140)
- Supine DBP (< 60, [60, 90[, ≥ 90)
- Supine heart rate (< 60, [60, 100[, ≥ 100)

Moreover all previous treatments for CRC will be described by anatomical therapeutic chemical (ATC) code; as well as signs and symptoms related to CRC**,** medical history and surgical or medical procedure other than for CRC, by primary system organ class (SOC) and preferred term (PT). Previous surgery for CRC will be described by PT.

5.2.5. Extent of exposure and treatment compliance

Extent of exposure (number of cycles, number of patients per cycle, treatment duration (weeks)) will be described in the Safety Set for S 95005 and Capecitabine. Treatment compliance (Cumulative dose (mg/m^2), Dose intensity (mg/m^2/week) and Relative Dose Intensity (%)) will be described by arm, by patient and by cycle.

Cumulative dose (mg/kg), Dose intensity (mg/kg/week) and Relative Dose Intensity (%) for the associated agent will be presented by arm, by patient and by cycle.

Cumulative dose (mg/kg), Dose intensity (mg/kg/week) and Relative Dose Intensity (%) will be presented by patient and by cycle in subgroups 1000 mg/m^2 and 1250 mg/m^2 of the Capecitabine + Bevacizumab arm.

For S 95005,
Number of patients with full dose administered (Yes/No), number of patients with at least one cycle delayed (Yes/No), number of cycles delayed, reason for cycle delayed (Medical reason, non-medical reason), number of patients with at least one cycle reduced (Yes/No), number of cycles reduced, number of patients with at least one miss intake, number of miss intake, number of 15 mg tablets given to patient, number of 15 mg tablets returned, number of 20 mg tablets given to patient and number of 20 mg tablets returned will be described in the Safety Set.

For Capecitabine,
Number of patients with full dose administered (Yes/No), number of patients with at least one cycle delayed (Yes/No), number of cycles delayed, reason for cycle delayed (Medical reason, non-medical reason), number of patients with at least one cycle reduced (Yes/No), number of cycles reduced, number of patients with at least one miss intake, number of miss intake, number of 150 mg tablets given to patient, number of 150 mg tablets returned, number of 500 mg tablets given to patient and number of 500 mg tablets returned will be described in the Safety Set.

For Bevacizumab,
Number of patients with full dose administered (Yes/No), number of patients with at least one cycle delayed (Yes/No), number of cycles delayed, reason for cycle delayed (Medical reason, non-medical reason), number of patients with at least one cycle reduced (Yes/No), number of cycles reduced, number of patients with at least one miss intake, number of miss intake, will be described in the Safety Set.

It is of note that number of cycles (1 cycle / 2 cycles /…/>6 cycles), treatment duration (≤ 8 weeks /]8; 24] weeks /]24-36] weeks /]36-48] / > 48 weeks), Relative Dose Intensity (RDI) (≤ 60,]60-80],]80-100],]100- 110], and > 110%), number of cycles delayed (1 cycle / 2 cycles /…/> 3 cycles), number of cycles reduced (1 cycle / 2 cycles /…/> 3 cycles) will also be described in classes.

5.2.6. Concomitant treatments

All concomitant treatments taken at inclusion and during the treatment period will be described in the Safety Set by ATC code.

5.2.7. Other observations related to patient follow-up

Not applicable.

5.3. Efficacy analysis

Calculation rules for expressions of efficacy endpoints, as well as general definitions (such as value prior to treatment / under treatment, analysable value, first and last IMP intake dates…), are provided in Section 7.1.

Calculation rules for efficacy endpoints and other specific definitions are provided in Appendix 7.2.

Fisher's exact test

To assess the difference between the 2 arms in terms of DCR and ORR.

Cox proportional hazard model adjusting on the stratification factors

HR and the corresponding 2-sided 80% and 2-sided 95% CIs for S 95005 + Bevacizumab versus capecitabine + bevacizumab will be estimated using a Cox proportional hazard model adjusting for the stratification factors based on IWRS data (except country due to the large number of countries in the study).

Clopper-Pearson CI

To provide CI for estimates of ORR and DCR, Clopper-Pearson CI will be used. The exact or Clopper-Pearson confidence limits for the binomial proportion are constructed by inverting the equal-tailed test based on the binomial distribution. This method is attributed to Clopper and Pearson (1934).

The Clopper-Pearson interval can be written as follows for n1 = 1, 2, 3, …, n-1 :

$$\left(\left(1+\frac{n-n1+1}{n1\,F\left(1-\alpha/2,2n1,2(n-n1+1)\right)}\right)^{-1},\left(1+\frac{n-n1}{(n1+1)F\left(\alpha/2,2(n1+1),2(n-n1)\right)}\right)^{-1}\right)$$

Where F(α,b,c) is the α^{th} percentile of the F distribution with b and c degrees of freedom.

Where $z^2_{\alpha/2}$ is the $100(1-\alpha/2)^{th}$ percentile of the standard normal distribution, α is the confidence level, $\hat{p}=\frac{n1}{n}$ is the proportion of observations and n is the size of sample.

Kalbfleisch and Prentice

Kalbfleisch and Prentice (2002) got around the problem of having confidence intervals of >1 or <0. The transformation is done by adopting:

The estimated variance of log(-log($\hat{S}(t)$)) is:

$$\tau 2(t) = \sigma 2[\hat{S}(t)] \,/\, [\hat{S}(t) log(\hat{S}(t))]^2$$

The 100(1-α)% confidence interval for S(t) is given by :

$$[\hat{S}(t)]^{\exp(z\propto/2\sigma(t))} \leq S(t) \leq [\hat{S}(t)]^{\exp(-z\propto/2\sigma(t))}$$

Kaplan Meier survival analysis

Kaplan Meier survival analysis will be used for PFS, DR and OS. The objective is to describe time-to-event variables, without covariates, taking into account censored observations (for which the event was not experienced during the observation period)

Event probabilities depend only on time. All subjects are assumed to behave similarly and computed survival functions are assumed to describe all subjects. Censored and uncensored observations behave the same.

The survival function *S*(t) is the probability that a patient survives (has no event) at least up to and including time t.

- $S(t) = Pr(T > t)$ where $S(t)$ denotes the survival distribution function and T is the time to the event of a selected patient.
- The median time to event is the time t so that $Pr(T > t) = 0.5$

The Kaplan-Meier method is based on conditional probabilities calculations and enables to compute nonparametric estimates of the survival function.

The survival function is estimated at each time-point as

$$\frac{\text{The number of patients with no event at that time}}{\text{The total amount of patients who can have the event}}$$

taking into account censored observations.

The Kaplan-Meier estimate of $S(t)$ is

$$\hat{S}(t) = \prod_{t_{(i)} \leq t} \frac{n_{(i-)} - d_{(i)}}{n_{(i-)}}$$

- $t_{(i)}$ is the i^{th} ordered event time
- $d_{(i)}$ is the number of events at $t_{(i)}$
- $n_{(i-)}$ is the number of observations without event an instant before $t_{(i)}$

It is a non-parametric analysis; there is no hypothesis to check on distribution.
In case of the censored and uncensored observations are different, results may be biased. In the same way, if covariates other than time are thought to be important in determining duration to outcome, results reported may not show important differences in groups formed by the covariates (ex., men vs. women).
Cox regression models can then be used to study the impact of covariates.

Multivariate analysis (stepwise procedure)

Multivariate analysis will be performed using the Cox Proportional Hazard (CPH) model, including the two stratification factors (RAS status and ECOG) and the following set of potential prognostic/predictive factors (cf Section 2). A stepwise selection process will be applied to identify a final subset of prognostic/predictive factors in the model.

Once the subset has been established (retaining factors significant at the 10% level), treatment will be added to the final model to assess its effect.

5.4. Biomarkers

Calculation rules for expressions of efficacy endpoints, as well as general definitions (such as value prior to treatment / under-treatment, analyzable value, first and last study drug intake dates…), are provided in Section 7.1. Calculation rules for efficacy endpoints and other specific definitions are provided in Appendix 7.2.

All biomarkers analyses will be done separately for each arm unless specified otherwise.

5.4.1. Archived tumor biopsies analysis

As mentioned in Section 2, the archived tumor biopsies sets (TUMFAS and TUMTR) will be described and the same analyses as in the clinical part of the SAP will be realized on the TUMFAS (PFS/OS, median survival and the corresponding 80%CI and 95%CI).

5.4.1.1. Analysis of protein-expression by IHC

Qualitative description:
The percentage of patients presenting an occupancy (resp. H-score) >0 will be described, using all TUMFAS patients.

Quantitative description:
This will be done only on IHC biomarkers where at least 3 patients present an occupancy greater than 0.

For all biomarkers of interest measured (TP, TK1, TS), the following elements will be provided in a summary table, for each arm (and for each localization in case of multiple localizations for a marker):

- Descriptive statistics at baseline, using all TUMFAS patients
- Boxplot
- Histogram

All of the above will be done for H-score and occupancy separately.

5.4.1.2. Predictive objective: Analysis of protein-expression by IHC according to response

5.4.1.2.1. Qualitative analysis of protein-expression by IHC

- The cutoffs used to define bmk+/bmk- classes are indicated in Section 7.2.3.1. Additional cutoffs of interest could also be studied.

5.4.1.2.1.1. Analysis of protein-expression by IHC according to DCR/ORR

- Biomarker classes (bmk+/ bmk -) will be described according to response groups (defined by ORR but also DCR) using value available at baseline (from archived biopsies) in the TUMTR and TUMFAS.
- Clopper-Pearson CIs will be used for response rates CIs.
- P-value comparing experimental arm vs. control arm will be based on a Fisher's exact test.

In each arm, for each biomarker, cutoff points will be defined as eligible if there are at least 5 pts both in the bmk + and bmk - groups.

- For each biomarker and each cutoff point, the following elements will be provided in each arm:
  - Number of patients in bmk+/ bmk- groups
  - Within bmk+ pts
    - Contingency table comparing response (DCR/ORR) to treatment arm
  - Within bmk- pts
    - Contingency table comparing response (DCR/ORR) to treatment arm;

Additionally, to compare the experimental arm to the control arm, the following elements will be provided for each biomarker (only on eligible cutoff points):

- Within bmk+ pts:
  - Response rate (and its 95% CI) in each arm as well as p-value of experimental arm vs. control arm.
- Within bmk- pts:
  - Response rate (and its 95% CI) in each arm as well as p-value of experimental arm vs. control arm

These analyses will be done on all biomarkers of interest: TP, TK1 and TS.
All of the above will be done for each localization in case of multiple localizations for a marker.
All of the above will be done for H-score and occupancy separately.

5.4.1.2.1.2. Analysis of protein-expression by IHC according to PFS

Biomarkers classes will be described according to PFS using value available at baseline in the TUMFAS.

Cutoff points will be defined as eligible if in each arm there are at least 10 pts both in the bmk+ and bmk- groups.

In each arm, for each biomarker, for all cutoff points, the following elements will be provided:

- Number of patients in each biomarker class.
- Median duration and 80% CI and 95% CI, estimated using Kaplan-Meier method.

Additionally, for each biomarker, for eligible cutoff points, to compare the experimental arm to the control arm, the following elements will be provided:

- Hazard ratio, of experimental arm versus control arm, for bmk+ patients (as well as bmk- patients) and the corresponding 2-sided 80% and 2-sided 95% CIs and Wald Chi-square test p-value; HR will be estimated via a Cox model comparing duration with biomarker class, with no adjustment on randomization factors.
- Forest plot of Hazard Ratios and their corresponding 95% CI for PFS for bmk+ pts (as well as bmk- pts) by each eligible cutoff point.

For each biomarker, based on the analyses described above, the best cutoff point will be defined. The following elements will then be provided using the best cutoff point as well as using the median as a cutoff point:

- Within control arm, Kaplan-Meier curve using bmk+ pts versus bmk- pts.
- Within experimental arm, Kaplan-Meier curve using bmk+ pts versus bmk- pts.
- Hazard ratio, of bmk+ versus bmk-, for control arm (as well as experimental patients) and the corresponding 2-sided 80% and 2-sided 95% CIs and Wald chi-square test p-value.
- Cox Model comparing duration with treatment, biomarker class and treatment*biomarker class interaction, with no adjustment on randomization factors ; following HRs will be provided: HR treatment arm vs experimental arm, independently of BMK class as well as HR BMK+ vs. BMK-, independently of treatment arm.
- Two-sided non-adjusted interaction test p-value.

These analyses will be done for PFS on all biomarkers of interest: TP, TK1 and TS. All of the above will be done for each localization in case of multiple localizations for a marker.

All of the above will be done for H-score and occupancy separately.

5.4.1.3. Analysis of microsatellites

- Microsatellites will be described using MSI status group (MSS/MSI-L versus MSI-H) value available at baseline in the TUMFAS.
- Clopper-Pearson CIs will be used for Odds-Ratios CIs.
- Based on MSI status group, the following element will be provided.
- Number of patients per MSI status group at baseline.

5.4.1.3.1. Predictive objective: analysis of microsatellites according to DCR/ORR

MSI status groups (MSS/MSI-L versus MSI-H) will be described according to response groups (defined by ORR but also DCR) using value available at baseline in the TUMTR and TUMFAS.

For both arms, the following elements will be provided:
- Contingency table comparing response (DCR/ORR) to treatment arm, within each MSI status group (MSS/MSI-L *versus* MSI-H).
- Barplot by ORR (respectively DCR), within each MSI status group.

The analyses described below will only be carried out if there are at least 10 MSI-H patients and at least 5 responding patients in the experimental arm.

Additionally, to compare the experimental arm to the control arm, the following elements will be provided:
- Response rate (and its 95% CI) in each arm as well as p-value of experimental arm vs. control arm for MSS/MSI-L patients (resp. MSI-H pts).

5.4.2. Blood analysis

5.4.2.1. Analysis of Protein-expression by ELISA based on serum

Biomarkers will be described using value available at baseline in the SERFAS.

Qualitative description:
The percentage of patients in each class (Below Lower Limit, In Range, Above Upper Limit) will be described.

Quantitative description:
This will be done only on ELISA biomarkers where the proportion of values in range is > 30%.

The following elements will be provided in a summary table, for each arm:
- Descriptive statistics at baseline.
- Boxplot.

This will be done on biomarker of interest: TP.

5.4.2.2. Consistency of mutation results obtained centrally from blood samples and locally (from either blood or biopsy sample)

Biomarkers will be described using value available at baseline in the SERFAS, restricted to patients with local (based on PCR) and central (based on eCRF) value available.

- For each biomarker the following elements will be provided in each arm:
  - Contingency table comparing mutation status obtained with PCR and mutation status obtained based on the eCRF:
    - At the gene level
    - At the exon level

This will be done for each biomarker of interest: KRAS, NRAS and BRAF.

5.5. Safety analysis

All safety analyses will be performed in the SS by arm.

Calculation rules for expressions of safety endpoints, as well as general definitions (such as value prior to treatment / under treatment, analysable value, first and last IMP intake dates…), are provided in Section 7.1.
Calculation rules for safety endpoints and other specific definitions are provided in Appendix 7.2.

5.5.1. Dose limitant toxicity

Not applicable.

5.5.2. Adverse events

Number of events, number and percentage of patients reporting at least one event, presented by primary SOC, high level group term (HLGT), high level term (HLT) and/or PT (depending on the analysis), will be provided for SAE and EAE over the study and treatment periods, respectively.

EAE will be described according to the seriousness, the worst grade, the severity, the relationship, the action taken regarding the IMP, the requirement of added therapy and the outcome.

Of note, the seriousness and the relationship to the IMP of the AE correspond to the investigator opinion or, in case of events upgraded by the sponsor for seriousness or for causality in case of SAE, to the sponsor opinion.

5.5.3. Death

Number of death will be described on each period (during the treatment and follow-up period / during the treatment period / during the follow-up period). Reason of death on each period will be provided. During treatment period, reason will be presented by SOC and PT.

5.5.4. Clinical laboratory evaluation

For all gradable parameters:
Descriptive statistics on quantitative value and value by grade at baseline, worst grade on treatment according to the grade at baseline, change from baseline to the worst value.

For all non-gradable parameters:
Descriptive statistics on quantitative value and value by reference ranges at baseline, worst value on treatment according to baseline, by classes (<LL / [LL-UL] / >UL) or (normal, mild, moderate, severe) for creatinine clearance and change from baseline to worst value under treatment.

For parameters of special interest:
Days to most extreme value.
Time to recovery from most extreme value.
Scatter plot of highest/lowest (worst) post-baseline values on treatment according to baseline.

For urinalysis parameters:
Descriptive statistics on value at baseline, worst value during the treatment period according to baseline, by classes (negative, trace, positive (+, ++, +++)) and change from baseline to worst value under treatment.

For CEA:
Descriptive statistics on quantitative value and value by classes at baseline, quantitative worst value during the treatment period according to baseline and by classes and relative change from baseline to the worst value under treatment.

5.5.5. Vital signs, clinical exam and other observations related to safety

5.5.5.1. Vital signs and clinical examination

- Vital signs and clinical examination will be described, in terms of quantitative value and value by classes (SBP (< 90, [90, 140[, ≥ 140), DBP (< 60, [60, 90[, ≥ 90) and heart rate (< 60, [60, 100[, ≥ 100)) at baseline; as well as in terms of worst value under treatment, change from baseline to worst value under treatment for weight, temperature, BSA, respiratory frequency, SBP, DBP and heart rate and worst value according to baseline by classes for weight, SBP, DBP, heart rate and ECOG.

5.5.5.2. Electrocardiogram

Moreover values and changes from baseline of corrected QT interval will be described in classes, considering thresholds defined in ICH E14 (*i.e.* ≤ 450,]450; 480],]480; 500] and > 500 ms for values, and ≤ 30,]30; 60] and > 60 ms for changes).

Values for RR interval will also be described in the same classes as QT interval.

Clinically significant ECG abnormalities at withdrawal visit will be described, with number of patient and overall.

5.5.5.3. LVEF

Not applicable.

5.6. QoL analysis

Patients of the QLS29 and QLS30 will be analysed for QoL in the arm they were assigned by randomisation.

EORTC QLQ-C30 and QLQ-CR29 questionnaire responses will be described separately in each arm using descriptive statistics.

Compliance for each questionnaire will be displayed per evaluation (baseline, week 12, week 24…). Compliance is defined as the number of forms actually received as a proportion of those expected. The number of QoL questionnaires completed and evaluable per evaluation will also be given, for each questionnaire.

As per protocol, the quality of life will be assessed every 12 weeks and at the withdrawal visit (if not performed within the prior 8 weeks.). The variation of the timing of questionnaire will be provided.

Each parameter will be described at baseline. Changes of the scores from baseline (mean) will be provided at each timepoint (week 12, 24…). Figures will be displayed in order to show the evolution of each scale/item.

6. INTERIM ANALYSIS

One interim analysis for efficacy is planned on October 2017 or after 80 PFS events are observed (disease progression or death), whichever occurs first, to guide the preparation of the phase III study in the same indication.

The interim analysis will be carried out on the Full Analysis Set (FAS). The main characteristics at baseline and the status of patients will be described. For the tumour response evaluation, patients Best Overall Response (BOR) will be described. DCR (Disease Control Rate) and ORR (Overall Response Rate) will be also evaluated in each arm with their 2-sided 95% Clopper-Pearson CIs.

PFS for each arm will be summarized using Kaplan Meier curves and further characterized in terms of the median and survival probabilities at 2, 4, 6, 8 and 10 months along with the corresponding 2-sided 80% and 2-sided 95% CI for the estimates. The analysis of OS (Overall Survival) will use the same approach.

Additional exploratory analyses for PFS will investigate the marginal effect of specific subgroups including a Forest plot. These factors will include, but are not limited to, region, ECOG performance status, gender, age ($\leq$ 65 years,]65-75], $>$ 75 years), prior adjuvant treatment, location of primary disease (including left/right colon…), surgical resection, number of metastatic sites (1-2, $\geq$ 3), time since 1st metastasis diagnosis ($\leq$ 4, $>$ 4), presence of liver metastasis, RAS/BRAF status and Neutrophil-Lymphocyte ratio ($<$ 3, $\geq$ 3).

7. APPENDICES

7.1. General analytic definitions

Definitions below correspond to calculation rules for expressions defined in Section 3, as well as definition of value prior to treatment / under treatment, analysable value, first and last IMP intake dates and other general definitions.

7.1.1. Expressions

Calculation rules for expressions defined in Section 3 are as follows.

Reliable value

For biological samplings:
Identified in SUPPLB with flag biofg_*name of the parameter*.

For other panels: Non-missing result
For biomarkers: last analysable value

Value at baseline is defined as the last reliable value prior to treatment.

Note: In case of patient included and/or randomised but not treated (*i.e.* patients with treatment duration equal to 0): value at baseline is defined as the last analysable value prior to first cycle (i.e "Visit<C001").

Baseline value of cycle n is defined as the last reliable (*i.e.* last non-missing) value prior to first study treatment intake of cycle n.

Value at the Cycle n Day n is defined as the first reliable (*i.e.* first non-missing) value at the visit.

Post-baseline value is defined as available value after the first study drug intake or in case of missing first intake date visit superior (>) to C000.

END value is defined as the last reliable post-baseline value of the criteria of interest during the period of interest.

WORST value is defined as the worst reliable post-baseline value of the criteria of interest during the period of interest.

LOWEST value is defined as the lowest value during the treatment period.

HIGHEST value is defined as the highest value during the treatment period.

Change from baseline to each Cycle n Day n is calculated as:
Value at the $Cycle_n$ Day_n - Value at baseline.

Change from baseline to end value is calculated as:
End value - Value at baseline.

Change from baseline to WORST value is calculated as:
Worst value - Value at baseline.

7.1.2. Value prior to treatment / under treatment

Table (7.1.2) 1 - Time frame

Criteria	**Value prior to treatment if measured between (D1 =) days before and (D2 =) days after the first study drug intake** (D1 and D2 included)		**Post-baseline value during treatment if measured between (D1 =) days after the first study drug intake and until (D2 =) days after the last study drug intake** (D1 and D2 included)	
Tumour assessment	D1 = 60	D2 = Xsup	D1 = Xinf	D2 = Xsupf
Biochemistry / haematology / Coagulation/Urinalysis	D1 = *14*	D2 = Xsup	D1 = Xinf	D2 = Xsupf
Vital signs	D1 = *14*	D2 = Xsup	D1 = Xinf	D2 = Xsupf
BSA	D1 = *14*	D2 = Xsup	D1 = Xinf	D2 = Xsupf
ECG	D1 = *60*	D2 = Xsup		
Mutation status	D1 = *60*	D2 = Xsup	D1 = Xinf	D2 = Xsupf
ECOG performance status	D1 = *14*	D2 = Xsup	D1 = Xinf	D2 = Xsupf
Quality of life	D1 = *14*	D2 = Xsup	D1 = Xinf	D2 = Xsupf
BMK	D1 =	D2 = Xsup	D1 = Xinf	D2 = Xsupf

- Xsup: 0
- Xinf: 1
- Xsupf = 35 for S 95005 + Bevacizumab arm and Capecitabine + Bevacizumab arm

Table (7.1.2) 2 - Time frame of cycle n

Notations	**Definitions**
Cycle n	<u>*Start date:*</u> First study drug intake date of cycle n <u>*End date:*</u> The minute before the 1st study drug intake of cycle (n+1) ⇨ It means that assessments planned the same day but before the 1st study drug intake in cycle (n+1) are part of cycle n. • For the last cycle, End date = min ((*), date of death) (*) max(first intake date of last cycle + 21 days of capecitabine, first intake date of last cycle + 21 days of bevacizumab) (*) max(first intake date of last cycle + 28 days of S 95005, first intake date of last cycle + 28 days of bevacizumab) The Data Management variable VISIT in patient EXdataset will be used to determine the start date of each cycle.

- General duration derivation and conversion :
  - In instances where duration or times-to-event are calculated, the convention to be used unless otherwise specified is [later date] – [earlier date] + 1 day.
  - When converting a number of days to other units, the following conversion factors will be used: 1 year = 365.25 days; 1 month = 30.44 days.

7.1.3. Analysable value

Table (7.1.3) 1 - Definition of analysable value

General definition	
Non missing value	
Specific definitions	
Laboratory parameters	Only reliable values are considered for analyses. Unreliable values are flagged into the database.
Biomarkers	
- Archived tumor biopsies	
ddPCR	Only values with PFSTAT ≠ Not Done and PFSPCCND=OK.
ELISA	Only values with LBSPCCND=OK.
- Blood samples	
IHC	Only values with LBSPCCND=ACCEPTABLE, GOOD or EXCELLENT and % cells tumor content (LBSCAT) >=10%.
MSI	Only values with % cells tumor content of IHC data (TP marker) >= 10% & LBSTRESC not equal to 'Unknown/ Not interpretable'.

7.1.4. First and last study IMP intake dates

The dates of first and last IMP intake on the analysis period will be defined as follows:

- The date substituted by the Data Management Department, if not missing.
- The date mentioned in the CRF, otherwise.

After selection of the dates of first and last IMP intake as defined above, if these dates are missing or incomplete, the following substitution rules will be applied:

Table (7.1.4) 1 - Substitution rules of IMP intake dates

Date to substitute		Substituted date
First IMP intake	../mmm/yyyy	Randomisation date if complete with same month and year *Otherwise:* **01/mmm/yyyy**
	../…/yyyy	if complete with same year *Otherwise:* **01/JAN/yyyy**
	../.../….	Randomisation date if complete
Last IMP intake	../mmm/yyyy	**Last available date*** if same month and year *Otherwise:* **last day of the month/mmm/yyyy**
	../…/yyyy	**Last available date*** if same year *Otherwise:* **31/DEC/yyyy**
	../.../….	**Last available date***

Notes:
- Missing dates will be substituted only for patients having taken at least one dose of study treatment
  ../mmm/yyyy = missing day
  ../.../ yyyy = missing day and month
  ../.../.... = totally missing date
- * Last available date (only for patients included) is defined as date of death if patient died, and as maximum date among completed dates relative to patient's information otherwise.

7.2. Specific analytic definitions and data handling conventions

7.2.1. Study patients: Disposition, baseline characteristics and follow-up

7.2.1.1. Disposition of patients

All withdrawal reasons occurring in the study will be taken into account.

7.2.1.2. Protocol deviations

For the description of protocol deviations, the 6 following categories are considered in accordance with ICH E3 guideline and ICH E3 Q&A:
- Selection/inclusion criteria not fulfilled.
- Patient having withdrawal criteria but not withdrawn.
- Incorrect treatment or dose received.
- Forbidden concomitant treatment.
- Endpoint assessment possibly affected.
- Safety possibly affected.

7.2.1.3. Demographic data and other baseline characteristics

7.2.1.3.1. Demographic data

Age is calculated as difference between year of informed consent and year of date of birth.

7.2.1.3.2. History of CRC

- Disease duration

Disease duration (years) is defined as (Randomisation date – date of the first diagnosis)/365.25

- The progression free interval

Progression free interval (months) is defined as (Date of relapse – date of end of last prior therapy)/30.44

Of note, this progression free interval of patients relapsing or progressing during the last line of treatment is estimated to last one day

Missing diagnosis date		Substituted diagnosis date
../mm/yyyy	⇨	Diagnosis date=**01**/mm/yyyy
../…/yyyy	⇨	Diagnosis date=**01/01**/yyyy
Missing start of the last prior therapy		**Substituted startdate of the last prior therapy**
../mm/yyyy	⇨	start date of the last prior therapy =**01**/mm/yyyy
../…/yyyy	⇨	startdate of the last prior therapy =**01/01**/yyyy
Missing end of the last prior therapy		**Substituted end date of the last prior therapy**
../mm/yyyy	⇨	end date of the last prior therapy = start date of the last prior therapy + 1day if same month and year Otherwise: end date of the last prior therapy=01/mm/yyyy
../…/yyyy	⇨	end date of the last prior therapy=start date of the last prior therapy + 1day if same year Otherwise: end date of the last prior therapy=01/01/yyyy
../…/…	⇨	end date of the last prior therapy=start date of the last prior therapy + 1day

Note: ../mm/yyyy = missing day
../.../ yyyy = missing day and month

7.2.1.3.3. Medical history and surgical or medical procedures history other than CRC

The existence of a history (Yes/No) is defined from the presence, or not, of a Primary SOC and/or PT.

7.2.1.3.4. Previous therapies for CRC

The ATC classification (ATC code = 5 digits) is composed of 4 levels:
- The first (1 digit) represents the anatomo-physiological class.
- The second (2 digits) represents the pharmacological class.
- The third (1 digit) represents the pharmacological sub-class.
- The last (1 digit) represents the therapeutic class.

The existence of a previous surgery (Yes/No) is defined from the presence, or not of a SOC and/or a "preferred name" for previous surgery at inclusion visit.

The existence of a previous radiotherapy (Yes/No) is defined from the presence or not of a verbatim for the previous radiotherapy involved site at inclusion visit.

The existence of a previous drug treatment (Yes/No) is defined from the presence, or not of an "ATC classification" and/or a "preferred name" for the previous drug treatment at inclusion visit.

The existence of a previous treatment (Yes/No) is defined from the presence of a surgery, radiotherapy and/or a drug treatment.

7.2.1.3.5. Initial tumour assessment

Patients with measurable disease are defined as patients with at least one target lesion.
Patients with non-measurable disease are defined as patients without target lesion and with at least one non-target lesion.

7.2.1.4. Extent of exposure and treatment compliance

Treatment duration for S 95005

Treatment duration (weeks) for S 95005 is defined as [(min (first intake date of the last cycle + 27 days, death date) - first IMP intake)+1] / 7

In case of missing or incomplete first intake date of the last cycle, the last intake date of the last cycle will be considered.

Treatment duration for Capecitabine

Treatment duration (weeks) for capecitabine is defined as [(min (first intake date of the last cycle + 20 days, death date) - first IMP intake)+1] / 7

Treatment duration for Bevacizumab in S 95005 + Bevacizumab arm

Treatment duration (weeks) for bevacizumab in S 95005 + Bevacizumab arm is defined as [(min (first intake date of the last cycle + 27days, death date) - first intake)+1] / 7

Treatment duration for Bevacizumab in Capecitabine + Bevacizumab arm

Treatment duration (weeks) for bevacizumab in Capecitabine + Bevacizumab arm is defined as [(min (first intake date of the last cycle + 20 days, death date) - first intake)+1] / 7

Cycle duration

Duration of cycle *i* (weeks) is defined as [[first IMP intake of cycle (*i+1*)] – [first IMP intake of cycle *i*]] / 7

Of note, the duration of the last cycle for S 95005 (respectively Capecitabine) will be estimated to be 4 weeks (respectively 3 weeks) for the calculation of DI and RDI for S 95005 (respectively Capecitabine). By the way the total treatment duration for S 95005 (respectively Capecitabine) will correspond to the sum of all cycle durations.

Numbers of cycles

The number of cycles with study drug intake will be defined based on patient *EX* data. A patient is considered to enter in a cycle if there is at least one intake date.

Planned dose intensity (PDI) (mg/m²/week for S 95005 and Capecitabine, mg/kg/week for Bevacizumab**)**

	S 95005
	10 days of intake per cycle
Dose : 35 mg/m^2 (bid) (70 mg/m²/day)	$\frac{\mathbf{70}(\mathrm{mg/m^2/day}) * \mathbf{10}}{4(wk)}$

	Capecitabine
	14 days of intake per cycle
Dose : 1000 mg/m^2 (bid) (2000 mg/m²/day)	$\frac{\mathbf{2000}(\mathrm{mg/m^2/day}) * \mathbf{14}}{3(wk)}$
Dose : 1250 mg/m^2 (bid) (2500 mg/m²/day)	$\frac{\mathbf{2500}(\mathrm{mg/m^2/day}) * \mathbf{14}}{3(wk)}$

	Bevacizumab in S 95005 + Bevacizumab arm
	2 days of intake per cycle
Dose : 5 mg/kg/day	$\frac{\mathbf{5}(\mathrm{mg/kg/day}) * \mathbf{2}}{4(wk)}$

	Bevacizumab in Capecitabine + Bevacizumab arm
	1 day of intake per cycle
Dose : 7,5 mg/kg/day	$\frac{\mathbf{7.5}(\mathrm{mg/kg/day})}{3(wk)}$

Cumulative dose

The cumulative dose (mg/m²) for S 95005 and Capecitabine per patient in a time period (during the treatment period or per cycle) is the sum of the total dose that the patient received within that period according to the compliance.

$$Cumulative\ dose\ (mg/m^2) = \sum_{timeperiod} \left(\frac{Real\ Administrated\ dose\ (mg)}{BSA\ (m^2)} \right)$$

The cumulative dose (mg/kg) for Bevacizumab per patient in a time period (during the treatment period or per cycle) is the sum of the total dose that the patient received within that period according to the compliance.

$$Cumulative\ dose\ (mg/kg) = \sum_{timeperiod} \left(\frac{Real\ Administrated\ dose\ (mg)}{weight\ (kg)} \right)$$

For S 95005 real administrated dose = number of tablets of 15 mg taken * 15 + number of tablets of 20 mg taken * 20
For Capecitabine real administrated dose = number of tablets of 150 mg taken *150 + number of tablets of 500 mg taken * 500

Number of tablets taken = number of tablets dispensed – number of tablets returned

If number of tablets returned is missing, number of tablets taken = estimated number of tablets
These information are collected in the compliance CRF pages.

For Bevacizumab:
If the question "Was full dose administred" is answered by "Yes", real dose administred = total planned dose administred.
If the answer is "No" , real administred dose = actual volume administred.

DI

The DI (mg/m²/week) for S 95005 and Capecitabine per patient is defined as the cumulative dose (mg/m²*)* received during the whole treatment period divided by the total treatment duration in weeks.

$$DI\ (mg/m^2/wk)\ per\ patient\ = \frac{Cumulative\ dose\ (mg/m^2)}{Treatment\ duration\ (weeks)}$$

The DI (mg/kg/week) for Bevacizumab per patient is defined as the cumulative dose (mg/kg*)* received during the whole treatment period divided by the total treatment duration in weeks.

$$DI\ (mg/kg/wk)\ per\ patient\ = \frac{Cumulative\ dose\ (mg/kg)}{Treatment\ duration\ (weeks)}$$

The duration of the last cycle will be estimated to be 4 weeks for S 95005 and Bevacizumab in S 95005 + Bevacizumab arm and 3 weeks for Capecitabine and Bevacizumab in Capecitabine + Bevacizumab arm.

RDI

The RDI (%) per patient is defined as the ratio of the DI to the initial PDI (mg/m²/week).

$$RDI\ (\%)\ per\ patient\ = \frac{DI}{Planned\ dose\ intensity} * 100$$

Cycle delay

A cycle delay is defined according to the Study medication dispensed CRF page (dispensation postponed (Yes/No)). Moreover a cycle delay of cycle i will be also considered if the duration of the cycle i is higher than 28 days for S 95005 and 21 days for capecitabine. No reason will be fulfilled if not retrieved.

The delay in days will be derived, based on the dates of administration.

For S 95005:
Delay (days) of cycle $_i$ = (administration date of cycle $_i$) – (administration of cycle $_{i-1}$ *+28 days*)

For Capecitabine:

Delay (days) of cycle $_i$ = (administration date of cycle $_i$) – (administration of cycle $_{i-1}$ *+21 days*)

Cycle reduction

A cycle reduction is defined according to the Study medication dispensed CRF page (dose modified compared to previous cycle (Yes/No)).

7.2.1.5. Concomitant treatments

The ATC classification (ATC code = 5 digits) is composed of 4 levels:

- The first (1 digit) represents the anatomo-physiological class.
- The second (2 digits) represents the pharmacological class.
- The third (1 digit) represents the pharmacological sub-class.
- The last (1 digit) represents the therapeutic class.

The existence of a concomitant treatment (Yes/No) is defined from the presence, or not, of an Anatomical therapeutic chemical classification and/or Preferred name.

The **periods** considered **for the analysis** are:

- At inclusion for which treatments:
  - With start date ≤ inclusion date and stop date ≥ inclusion date or missing are taken into account. Inclusion date is equal to the date of inclusion visit, *i.e.* A000/D000 visit date.
- Before treatment period for which treatments:
  - With start date < first IMP or associated agent intake date are taken into account.
- During the treatment period for which treatments:
  - With start date ≥ first IMP or associated agent intake date and < first IMP or associated agent intake date in the last cycle + *28* days for S 95005 (+ 21 days for Capecitabine), or
  - With start date ≤ first IMP or associated agent intake date and stop date ≥ first IMP or associated agent intake date or missing are taken into account.

Concomitant treatments could be considered in one or several of the possible analysis periods.

In case of missing or incomplete first *IMP* or associated agent intake date in the last cycle, the last **completed** *IMP* or associated agent intake date will be considered.

The following **rules for substitution** of missing or incomplete start and stop dates are so that the concomitance period is maximised:

Table (7.2.1.5) 1 - Substitution rules of concomitant treatments intake dates

Date to substitute		Substituted date
Start date	../mmm/yyyy	If the year and the month are the same as the year and the month of inclusion then Start date= **Inclusion date,** otherwise Start date=**01/mm/yyyy**
	../…/yyyy	If the year is the same as the year of inclusion then Start date= **Inclusion date,** otherwise Start date=**01/01/yyyy**
	../.../….	**Inclusion date**

Stop date	../mmm/yyyy	If patient died same month and year then
		Date of death
		Else
		Last day of the month/mmm/yyyy

	../…/yyyy	If patient died same year then
		Date of death
		Else
		31/DEC/yyyy

	../.../….	If patient died then
		Date of death
		Else
		No substitution
		(*i.e.* treatment considered as still ongoing)

Note: ../mm/yyyy = missing day
../.../ yyyy = missing day and month
../.../.... = missing date

The following rules for substitution of totally or partially missing start and stop dates are used for concomitant treatments (only further anti-tumour therapy):

Table (7.2.1.5) 2- Substitution rules of further anti-tumour therapy intake dates

Date to substitute		Substituted date
Start date	../mmm/yyyy	If the year and the month are the same as the year and the month of the last *study drug/IMP* intake date then **Last *study drug/IMP* intake date** otherwise **01/mm/yyyy**
	../…/yyyy	If the year is the same as the year of the last *study drug/IMP* intake date then **Last *study drug/IMP* intake date**, otherwise **01/01/yyyy**
	../.../….	**Last *study drug/IMP* intake date**

Stop date	../mmm/yyyy	If patient died same month and year then
		Date of death
		Else
		Last day of the month/mmm/yyyy ,

	../…/yyyy	If patient died same year then
		Date of death
		Else
		31/DEC/yyyy

	../.../….	If patient died then
		Date of death
		Else
		No substitution
		(*i.e.* treatment considered as still ongoing)

Note: ../mm/yyyy = missing day
../.../ yyyy = missing day and month
../.../.... = completely missing date

7.2.2. Efficacy

7.2.2.1. Antitumoral activity

Tumour response is evaluated according to the "New Response Evaluation Criteria in Solid Tumours: Revised RECIST guideline (version 1.1), Eisenhauer *et al*, 2009".

Overall response is evaluated by the investigator and is not recalculated by the statistical team (see the protocol *paragraph 7.2.1.3.2* for more details about the overall response evaluation).

Overall response date
For each tumor evaluation, if the overall response is PD, the first examination date among target lesion, non-target lesion and new lesion showing a PD will be considered. For all other responses (CR, PR or SD), the last examination date will be taken into account.

Best overall response

Best overall response is defined as the best overall response across all time points.

When SD or Non CR/Non PD is believed to be best overall response, it needs to be assessed a minimum of 6 weeks after study randomisation. Otherwise, the best overall response will be NE, unless any PD was further documented, in which case BOR will be PD.

A patient dead because of progression before the first assessment planned per protocol (cycle 2) will be considered as 'early death'. If a patient progressed before this first assessment, he will be considered as 'early progressive'. If any of these two events occur, the overall response of the patient will be resumed as progression.

In case of best overall response missing under the studied period, this one will be considered as Non Evaluable (NE).

Confirmation of CR and PR (assessed a minimum of *4* weeks after the first assessment of CR or PR) is needed to deem either one the BOR.

The first response assessed during the follow-up period could be used to confirm a previous response observed during the treatment period. However, if a patient received a new anti-tumoral treatment, only the tumor evaluations performed until the date of a new therapy (included) will be used for the calculation of the best overall response.

Table (7.2.2.1) 1 - BOR when confirmation of CR and PR required

Overall response First time point (i)	Overall response • next time point (i+1)	BOR
CR	CR	• CR (if the time length between the two assessment is ≥ *4*weeks) otherwise PR
CR	PR	• -if the CR is truly met (disease reappearance after complete response) then we put PD • - if the CR is not truly met (subsequent scans show small lesions were likely still present) then we consider the first CR time point as a PR so we have 2 cases: • * PR (if the time length between the two assessment is ≥ *4* weeks) • * otherwise SD (the time length between the study randomisation and the first CR ("considered as PR") is not required)
CR	SD or Non CR/Non PD	• SD (if the duration between CR and the study randomisation ≥ 6 weeks) otherwise PD
CR	PD	• SD (if the time length between the study randomisation and the CR is ≥ *6* weeks), otherwise, PD
CR	NE or missing	• SD (if the time length between the study randomisation and the CR is ≥ *6* weeks), otherwise NE
PR	CR	• PR even if the time length between the two assessment is less than *4* weeks
PR	PR	• PR (if the time length between the two assessment is ≥ *4*weeks) otherwise SD (the time length between the study randomisation and the first PR is not required) • If successive PR (PR- PR-PR) then the duration could be calculated with respect to the first PR assessment date (if the interval between two consecutive assessment is less than *4* weeks)
PR	SD or Non CR/Non PD	• SD
PR	PD	• SD (if the time length between the study randomisation and the PR is ≥ *6* weeks), otherwise, PD
PR	NE or missing (*)	• SD (if the time length between the study randomisation and the PR is ≥ *6* weeks), otherwise NE
SD or Non CR/Non PD	PD	• SD or non CR/non PD (if the time length between the study randomisation and the SD is ≥ *6* weeks), otherwise, PD
SD or Non CR/Non PD	SD or Non CR/Non PD	• SD or non CR/non PD (if the time length between the study randomisation and one of the SD is ≥ *6* weeks), otherwise, NE unless any PD was further documented
SD or Non CR/Non PD	NE or missing	• SD or non CR/non PD (if the time length between the study randomisation and the SD is ≥ *6* weeks), otherwise, NE unless any PD was further documented
PD	Whatever the overall response	• PD
NE	PD	• PD
NE	NE	• NE

(*) In addition, we will consider a patient with time point responses of PR-NE-PR as a confirmed partial response.

The Relative change and the best relative change of the sum of lesions diameters will be only calculated if the overall response for the target lesions is not equal to 'Non Evaluable'.

Baseline value will be the sum of all target lesions measurements assessed before the first IMP intake

Relative change of the sum of the lesions diameters (%)

Relative change from baseline of the sum of the lesions diameters (%) is defined at cycle i (Ci) as follows:

$$\left(\frac{\text{sum of the lesions diameters at the cycle i} - \text{sum of the lesions diameters (baseline)}}{\text{sum of the lesions diameters (baseline)}}\right) * 100$$

Relative change from SMALLEST of the sum of the lesions diameters (%) is defined at cycle i (Ci) as follows:

$$\left(\frac{\text{sum of the lesions diameters at the cycle i} - \text{sum of the lesions diameters (SMALLEST) at baseline or cycle< i}}{\text{sum of the lesions diameters (SMALLEST) at baseline or cycle< i}}\right) * 100$$

Best relative change of the sum of the lesions diameters (%)

The best relative change from baseline of the sum of the lesions diameters (%) is defined as the greatest decrease of the sum of the lesions diameters recorded. It can be calculated as follows:

$$\min_{\substack{i \\ i>0}} \left(\frac{\text{sum of the lesions diameters at the cycle i (Ci)} - \text{sum of the lesions diameters (baseline)}}{\text{sum of the lesions diameters (baseline)}}\right) * 100$$

For:

- DR: Among responders (BOR= CR or PR); from date of first response
- PFS, PFSs1 (PFS with further anti-cancer treatment as an event): Overall; from randomisation date

Until:

Situation	End date	Censor
Documented radiological PD	- Date of the first assessment of the series of the tests that determined PD* in tumour assessments form	No
Death during the study before radiological PD	- Date of death	No
Subjects still followed without radiologic PD as of cut-off date	- Date of last adequate (non-NE) tumor assessment or cut-off date whichever is earlier	Yes
Non-study anti-tumor treatment initiated before radiologic PD	- Date of last adequate (non-NE) tumor assessment prior to initiation of non-study antitumor treatment for PFS - Date of initiation of non-study antitumor treatment for PFSs1	Yes for PFS and DR No for PFSs1
No baseline or no post baseline tumor assessment	- Date of randomisation	Yes

For:

- PFSs2 (PFS including clinical progression): Overall; from randomisation date

Until:

Situation	End date	Censor
Documented radiological or clinical PD	- Date of the first assessment of the series of the tests that determined PD* (including AE form & discontinuation form)	No
Death during the study before PD	- Date of death	No
Subjects still followed without radiologic or clinical PD as of cut-off date	- Date of last adequate tumor (non-NE) assessment or cut-off date whichever is earlier	Yes
Non-study anti-tumor treatment initiated before radiologic / clinical PD	- Date of last adequate (non-NE) tumor assessment prior to initiation of non-study antitumor treatment	Yes
No baseline or no post baseline tumor assessment	- Date of randomisation	Yes

For:

- OS: Overall; from date of randomisation

Until:

Event/Censor	Decision	Date of event or censor to consider for analysis
Death	Not censored	- Date of death from AE CRF page - Date of death from follow-up/status of the patient CRF page
Patient alive without documented death	Censored	- Date of last contact

A codelist based on all investigational drugs (number=1533, corresponding to ATC Code=V03AX in CONCMED database) and the pharmacological class coded as 'L02' (Endocrine therapy) will be reviewed by ITP to identify all new anti-tumoral treatment (as hormonotherapy, immunotherapy, targeted agent…). The list 1533 reviewed by the medical coding is the list 3594.0 in WHODD 2016.1.

* The date of first progression during the treatment period is defined as the date of PD at the first cycle where the overall response is PD. The date of PD at cycle *i* is defined as the earliest date among the following dates:

- Date of PD for target lesions: If the response for target lesions is PD at the cycle *i*, the date of PD for target lesions corresponds to the **earliest** date of examination among the target lesions at cycle *i*.
- Date of PD for non-target lesions: If the response for non-target lesions is PD at the cycle i, the date of PD for non-target lesions corresponds to the earliest date of examination among the non-target lesions showing a PD at the cycle i. A non-target lesion showing a PD is defined as a lesion where the status is "Unequivocal progression (UPD)" or the appearance of at least one new lesion. The appearance of a new lesion is defined as a lesion where the status at cycle i is new (TRSPID = NEW and TRORRES = Y)

Neutrophil-Lymphocyte ratio (NLR) = Absolute neutrophil count (10^9/L) / absolute lymphocyte count(10^9/L)/

7.2.3. Biomarkers

7.2.3.1. Protein-expression by IHC

7.2.3.1.1. Protein-expression by IHC occupancy

Occupancy will be defined as:
Occupancy = % cells marked 2+ + % cells marked 3+

7.2.3.1.2. Protein-expression by IHC H-score

H-score will be defined as:
H-score = 1*% cells marked 1 + 2*% cells marked 2 + 3*% cells marked 3+

7.2.3.1.3. Biomarker classes based on protein-expression by IHC

For occupancy, for each biomarker, the following biomarker classes will be defined:
- bmk+: Occupancy ≥ x%;
- bmk-: Occupancy < x%.

x belonging to (5;10;15;20;25;30;35; median(Occupancy).

For H-score, for each biomarker, the following biomarker classes will be defined:
- bmk+: H-score ≥ median(H-score);
- bmk-: H-score < median(H-score).

7.2.3.2. Values out of limits of detection

For quantitative description of protein-expression by ELISA, missing values with a result flag not equal to "In ranges" will be substituted as follows:

Table (7.2.3.2) 1 - Substitution rules for protein-expression by ELISA biomarkers

Value	Substituted by
Below detection limit or Below fit curve limit (based on the result flag)	LLOD / $\sqrt{2}$
Above detection limit or Above fit curve limit (based on the result flag)	ULOD

If the lower (respectively upper) limit of detection is missing then it is replaced by the lower (respectively upper) limit of quantification in the substitution rules.

7.2.4. Safety

7.2.4.1. Dose Limitant Toxicity (DLT)

Not applicable.

7.2.4.2. AEs

Of note: + *x days* = + *35 days for S 95005*
+ *x days* = + *35 days for Capecitabine*

Only AEs with a "primary SOC", a "HLGT", a "HLT" and a "PT" are considered.

Each **medical concept of AEs coded according to the internal "multiple medical concept" process** is taken into account as a single AE in the statistical analysis.
The modalities of the AE (onset and end dates, severity, seriousness, action taken, additional therapy, relationship, outcome...) replicated by default to each medical concept are also taken into account in the statistical analyses of AEs by category.

EAEs on treatment are defined as all AEs:

- which occur between the first IMP or associated agent intake date (included) and the last IMP intake date *"+ 35 days"* (included),

or

- which occur before the first IMP or associated agent intake date and which worsen (in terms of severity) or become serious according to the investigator opinion between the first IMP or associated agent intake date (included) and the last IMP or associated agent intake date *"+ 35 days"* (included),

or

- with an emergence forced by the sponsor during the Important Medical Event (IME) process (upgrade of seriousness) and at least one episode occurring between the first IMP or associated agent intake date (included) and the last IMP or associated agent intake date *"+ 35 days"* (included).

-

  In case of multiple episodes of the same event before the first IMP or associated agent intake date, the episode nearest to the first IMP or associated agent intake date is taken into account.

Note: AEs occurring or worsening or becoming serious on the day of the first IMP intake (if any) is considered as emergent.

SAEs are defined as all AEs upgraded by the sponsor during the IME or PharmacoVigilance (PV) process (upgrade of seriousness) or considered as "serious" from investigator assessment.

SAEs from investigator assessment are defined as all AEs fulfilling at least one of the following seriousness criteria for immediate notification: death, hospitalisation or prolongation of hospitalisation, medically important, life-threatening, disability/incapacity or congenital anomaly.

A fatal AE corresponds to an adverse event with “Death” as PT or “Fatal” as outcome or Severity = Grade 5.

AEs related to IMP correspond to AEs with relationship forced by the sponsor during the PV process (upgrade of relationship for SAEs according to investigator or sponsor opinion) or considered as "related" from investigator assessment. In other cases, the AEs are considered as "not related to IMP".

AEs related to IMP or associated agent from investigator assessment correspond to AEs associated with the answer "Related" to the "Is this event related to test drug?" or “Is this event related to the associated agent questions.

Severity, action taken regarding the IMP, additional therapy requirement and seriousness are recorded for each episode of an AE, whereas only the last relationship with the IMP and the last outcome reported by the investigator are retained in the ClinTrial database. The following information will be taken into account:

- For the analyses where the relationship with MP and the outcome are considered, the information retained in the ClinTrial database will be taken into account.
- For the analyses where the severity of the AE is considered, the worst severity from the day of emergence and during the studied period will be taken into account.
- The number of patient by worst grade: for each patient, SOC and PT, we analyze the worst grade of events.
- The number of event by worst grade: for each patient, SOC and PT, we analyze the worst grade of each event. The percentage will be calculated as the number of events of the PT concerned at grade X divided by the total number of events of the PT concerned.
- For the analyses where the action taken regarding the IMP and the additional therapy requirement are considered, all the actions taken and additional therapy requirements recorded from the day of emergence and on the studied period will be taken into account.
- However, in case of an episode of an EAE leading to studied treatment withdrawal reported after the last IMP intake date "+ *35 days*", the AE will be considered as leading to studied treatment withdrawal during the studied period.
- Seriousness is judged by event: if one episode is serious (whatever the time it occurs), the whole event will be considered as serious.
- A severe adverse event corresponds to an AE with NCI CTCAE grade 3, 4 or 5.
- Any grade corresponds to an AE with NCI CTCAE grade 1, 2, 3, 4 or 5.
- All multicoded events will be taken into account in the analyses.
- The existence of an AE (Yes / No) will be defined from the presence, or not, of a “primary SOC” and/or a “PT”.

For the description of **EAE recovered on treatment / after treatment**:

- All EAE with "recovered", "recovered with sequelae" or "recovering/improving" as outcome will be taken into account.
- An EAE is considered as recovered "on treatment" ("after treatment", respectively) if the outcome occurs between the first IMP or associated agent intake date and the last IMP or associated agent intake date "+ *35 days*" (included) (strictly after the last IMP or associated agent intake date "+ *35 days*", respectively).

- The date used to determine if the outcome occurs on treatment or after treatment is the recovery date for EAE with "recovered" or "recovered with sequelae" as outcome, and the date of AE last information(*) for EAE with "recovering/improving" as outcome.

  (*) Date of AE last information is defined as the maximum between onset date, dates of modification of severity and dates of the six seriousness criteria for this AE.

Time to onset: time between the first study drug intake date and the onset date of the first emergent episode of AE.
The following rules are applied in case of missing severity:

Table (7.2.4.2) 1 - Emergence of adverse events in case of missing severity/grade (if any)

Severity/Grade			AE considered as
Nearest before the first IMP intake date	**During the treatment period**		
Missing	Missing	→	Emergent
Missing	Grade 1	→	Non emergent
Missing	Grade 2, 3, 4 or 5	→	Emergent
Grade 1, 2, 3	Missing	→	Emergent
Grade 4	Missing	→	Non emergent

The rules for substitution of missing or incomplete episode date (onset date, dates of the *six* seriousness criteria and dates of change of severity *and action taken*) are as follows:

Table (7.2.4.2) 2 - Substitution rules of AE dates

Date to substitute	Substituted date (Episode date)
../mmm/yyyy	• If same month and year than first *study drug/IMP* intake date then: • **First *study drug/IMP* intake date** Else: **01/mmm/yyyy**
• ../…/yyyy	• If same year than first *study drug/IMP* intake date then: **First *study drug/IMP* intake date** Else: **01/JAN/yyyy**
• ../.../….	• **First *study drug/IMP*intake date**

Note: ../mm/yyyy = missing day
../.../ yyyy = missing day and month
../.../.... = missing date

The rules for substitution of missing or incomplete recovery dates, in case of AE outcome "recovered" or "recovered with sequelae" are as follows:

Table (7.2.4.2) 3 - Substitution rules of recovery date

Date to substitute	Substituted date
../mmm/yyyy	If same month and year than date of AE last information(*) then: **Date of AE last information** Else: **Last day of the month /mmm/yyyy**
../…/yyyy	If same year than date of AE last information(*) then: **Date of AE last information** Else: **31/DEC/yyyy**
../.../….	**Date of AE last information**(*)

Notes:
- ../mmm/yyyy = missing day,
  ../.../ yyyy = missing day and month,
  ../.../.... = missing date.
- (*) Date of AE last information is defined as the maximum between onset date, dates of change of severity and dates of the six seriousness criteria for this adverse event.

Duration of AE (days) = recovery date (last episode) – onset date of AE + 1

7.2.4.3. Death

Death information are taken on 'Adverse Event' (serious criteria for immediate reporting = Death) and 'Status of the patient at follow-up n° X' (reason for not continuing/completed the follow-up period = Death) CRF pages.

In case of death reported on 'Adverse Event' page, the date of death is compared to the date of last intake + *35 days* to classify occurrence on-study or during follow-up.

7.2.4.4. Clinical laboratory evaluation

Values

Only reliable values are considered for analyses. Unreliable values are flagged into the database.

In case of **multiple samples**:
- For the description of the values at each planned post-baseline visit, only the first analysable one measured under treatment at the visit is taken into account.
- Otherwise, each post-baseline value (test, re-test, planned, unplanned) measured under treatment is taken into account for analyses.

Units

All parameters will be analysed in international units (IU).

Abnormal values

Abnormal values are described according to:
- Reference laboratory ranges for the non-gradable parameters.
- CTCAE grade for gradable parameters.

Laboratory reference limits and CTCAE grades are reported in the database.

Any grade corresponds to a laboratory value with NCI CTCAE grade 0, 1, 2, 3 or 4.

A grade 0 corresponds to a laboratory value within limit or reference range.

The LOWEST value for a patient is defined as the lowest absolute laboratory value during the treatment period.

A Lowest value for a cycle is defined as the lowest laboratory value in that cycle.

The time to LOWEST value is defined from the date of the first drug intake to the sampling date of the LOWEST value.

The time to LOWEST value in a cycle is defined from the first date of drug intake in that cycle to the sampling date of the LOWEST value.

The HIGHEST value for a patient is defined as the highest laboratory value during the treatment period.

A highest value for a cycle is defined as the highest laboratory value in that cycle.

The time to HIGHEST value is defined from the date of the first drug intake to the sampling date of the HIGHEST value.

The time to HIGHEST value in a cycle is defined from the first date of drug intake in that cycle to the sampling date of the HIGHEST value.

The NADIR for a patient is defined as the worst (lowest or highest according to parameter) absolute laboratory value during the treatment period.

A NADIR for a cycle is defined as the worst (lowest or highest according to parameter) laboratory value in that cycle.

Urinary results

The category positive includes results '+', '++' and '+++'.

Creatinine clearance

Creatinine clearance will be categorised in 4 levels of impairment:

- Normal renal function (CLcr ≥ 90 mL/min).
- Mild renal impairment (CLcr 60-89 mL/min).
- Moderate renal impairment (CLcr 30-59 mL/min).
- Severe (< 30mL/mn).

CEA results

CEA is abnormal if its value is out of lower and upper reference range.

Relative change form baseline to worst value under treatment is given by:

$$\left(\frac{\text{Worst value under treatment} - \text{value at baseline}}{\text{value at baseline}}\right) * 100$$

Worst value

Worst value will be analysed as follow:

	Parameter	Worst Highest	Worst lowest
Gradable	**sodium**	hypernatremia	hyponatremia
Gradable	**Potassium**	hyperkalemia	hypokalemia
Gradable	**calcium**	hypercalcemia	hypocalcemia
Gradable	**magnesium**	hypermagnesemia	hypomagnesemia
Gradable	**phosphates**	NA	hypophosphatemia
Gradable	**serum creatinine**	high creatinine	NA
Gradable	**albumin**	NA	Low albumin
Gradable	**glucose**	hyperglycemia	hypoglycemia
Gradable	**GGT**	high GGT	NA
Gradable	**AST**	high AST	NA
Gradable	**ALT**	high ALT	NA
Gradable	**alkaline phosphatase**	high alkaline phosphatase	NA
Gradable	**total bilirubin**	high total bilirubin	NA
Gradable	**haemoglobin**	high haemoglobin	Anemia
Gradable	**white blood cells**	leucocytosis	low WBC
Gradable	**neutrophils**	NA	low Neutrophils
Gradable	**lymphocytes**	high lymphocyte	low lymphocyte
Gradable	**platelets**	NA	Low platelets
Gradable	**INR**	high INR	NA
Gradable	**Activated Partial thromboplastin time**	high aPTT	NA
	Haematocrit	High haematocrit	Low haematocrit
	Red Blood Cell Count	High RBC	Low RBC
	Monocytes	High monocytes	NA
	Eosinophils	High eosinophil	NA
	Basophils	NA	Low Basophil
	Chloride	High chloride	Low chloride
	Bicarbonate	High bicarbonate	Low bicarbonate
	Blood urea nitrogen	NA	High BUN
	Total protein	High Proteins	Low total Proteins
	LDH	High LDH	NA

For the urinalysis parameters, the worst class will correspond to ‘Positive’ class, then ‘Trace’ and finally ‘Negative’ will be considered as normal class.
For creatinine clearance, the worst class will correspond to “severe” category, then “moderate”, then “mild” and finally “normal”.

Worst grade for Hypo and Hyper:
- Hypo: If the lowest result is below lower normal range limit, Hypo =grade (for gradable parameter), Else Hypo=0.
- Hyper: If the highest result is above upper normal range limit, Hyper =grade (for gradable parameter), Else Hyper =0.

Days to most extreme value:
The "most extreme value" recorded, and the corresponding number of days to the most extreme value recorded, are summarized descriptively for Grade 3 or 4 abnormalities (or with moderate or severe renal impairment for creatinine clearance). This is expected to be limited to the selected "parameters of interest". The "most extreme" is defined as the worst value (Nadir) that worsened from baseline by at least one grade (or one level of impairment for creatinine clearance) (or had a missing baseline).
Note: In the event a patient had the same nadir at multiple times for a cycle, the first occurrence was selected.

Days to recovery:
The median number of days to 'recovery' in patients with Grade 3 or 4 abnormalities (or with moderate or severe renal impairment for creatinine clearance) that worsened from baseline is obtained from Kaplan-Meier estimates.

'Recovery' in patients with Grade 3 or 4 laboratory abnormalities (or with moderate or severe renal impairment for creatinine clearance) that worsened from baseline is defined as the presence of a subsequent measurement (after the first occurrence of the most extreme value observed that has a value of Grade 3 or 4 (or has moderate or severe renal impairment for creatinine clearance)) of the parameter that is ≤ Grade 1 or ≤ baseline grade (or that had mild or normal renal impairment for creatinine clearance).

Days to recovery is calculated as:
For patients who recovered: (Date of recovery – date of most extreme value) +1

For patients who did not recover: (Date of last subsequent value for that parameter – date of most extreme value) +1

7.2.4.5. Vital signs, clinical examination and other observations related to safety

7.2.4.5.1. Vital signs and clinical examination

Worst value

For ECOG, weight, *BSA*, SBP, DBP, HR and respiratory rate, the worst (highest) value will be derived.

For weight, *BSA,* SBP, DBP and HR, the worst (lowest) value will be derived.
Body Surface Area

$BSA\ (m^2) = 0.007184 \times Weight\ (kg)^{0.425} \times height\ (cm)^{0.725}$

ECOG performance status

STATUS KARNOFSKY	*GRADE*	*STATUS* ECOG - ZUBROD / WHO
Normal, no disorders	100 0	Normal unrestricted activity
Normal activity. Minor signs or symptoms of the disorder. Activity normal with effort	90 1 80	Arduous physical activity restricted, but patient able to walk unaided and perform light work
Independent but incapable of normal activity or work Requires occasional help, but able to cope with most personal needs.	70 2 60	Able to walk unaided and independent but unable to work more than half-time
Requires frequent help and medical care Requires considerable help and medical care	50 3 40	Much less independent. Spends more than half his / her time in bed or seated.
Bedridden. Hospitalization indicated, even though death not imminent Gravely ill. Hospitalization necessary. Symptomatic treatment necessary	30 4 20	Incapable of looking after him / herself. Completely confined to bed or to a chair

7.2.4.5.2. Electrocardiogram

Unscheduled ECGs are not taken into account in the analysis.

For all other analyses, all analyzable values are taken into account, whether at planned visit or not, initial sample or additional sample.

Absolute prolongation at withdrawal visit = max (Absolute prolongation at withdrawal visit).
Change from baseline = absolute prolongation - Absolute prolongation at baseline.

7.2.4.5.3. LVEF

Not applicable.

7.2.5. QoL

For the QLQ-C30 and QLQ-CR29, raw scores and scores will be calculated as follows :

- For all scales, the Raw Score, RS, is the mean of the component items:

  Raw Score = RS = (I1 + I 2 +...+ In) / n

- For Functional scales:

  Score = {1 - (RS−1) / range} ×100

- For Symptom scales / items and QoL:

  Score = {(RS - 1) / range}×100

7.3. Statistical methods details

Not applicable

7.4. Software and programming codes

Cox proportional hazard model adjusting for the stratification factors

```
PROC PHREG data = work.data;
model TIME* CENSOR(censoredval)= ARM RAS ECOG / RL TIES=efron;
Run;
```

Fisher's exact test

```
PROC FREQ DATA= work.data;
  TABLES ARM * VAR / FISHER;
RUN;
```

Clopper Pearson CI

```
PROC FREQ data=work.data;
        tables RESPONSERATE / binomial (exact);
        by ARM;
        run;
```

Kaplan Meier survival analysis

```
PROC LIFETEST data= work.data alpha=0.05/0.2 alphaqt=0.05/0.2  method=KM;
        TIME TIME *CENSOR(censoredval);
        strata ARM;
        id SUBJID,
        survival out=surv conftype=loglog ; /*Kalbfleisch and Prentice CI*/
        run;
```

8. REFERENCES

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Guidelines

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I.R.I.S.

INSTITUT DE RECHERCHES INTERNATIONALES SERVIER

Document title	**TEMPLATES FOR TABLES, LISTINGS AND GRAPHS (TLG)**
Study title	**An open-label, randomised, non-comparative phase 2 study evaluating S 95005 (TAS-102) plus bevacizumab and capecitabine plus bevacizumab in patients with previously untreated metastatic COlorectal cancer who are non-eligible for intensive therapy (TASCO1 study)**
Test drug code	**S 95005**
Indication	**First-line treatment of metastatic colorectal cancer in patients non-eligible for intensive therapy**
Development phase	**Phase II**
Protocol code	**CL2-95005-002**
EudraCT Number	**2015-004544-18**
Universal Trial Number	**Not applicable**
Sponsor	**Institut de Recherches Internationales Servier (I.R.I.S.)**
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CONFIDENTIAL

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Table of contents

This document presents the templates for Tables, Listings and Graphs (TLG) associated with the analyses planned in the Statistical Analysis Plan (SAP).

The correspondence between the SAP and TLG should be done using sections names (instead of sections numbers).

Templates provided hereafter are produced with all the treatment groups.

For analyses by cycles, refer to the Investigation Scheduled in Section 1.2.3 of the SAP to find details on cycles concerned and, if applicable, to the note providing specific information, associated to the shell considered.

As concerns the decimal places, the following rules will be applied:

- Quantitative analyses:
  - Data precision + 1 decimal place for means, standard deviations, medians, first and third quartiles.
  - Same as data precision for minimums and maximums.
- Qualitative analyses:
  - 1 decimal place for percentages in tables relative to coded data (adverse events, medical history/surgical or medical procedures history, previous/concomitant treatments), analysis sets and protocol deviations.
  - 2 decimal places for percentages otherwise.
- Inferential analyses: 3 decimal places for p-value, displayed as < 0.001 if less than 0.001.

In instances where the percentage calculation is not specified in footnote, the convention to be used is % = (n/Nobs)*100.

SUMMARY OF STATISTICAL ANALYSES

Criterion / Analysis	NIS	IS	RS	FAS	PPS	TR	SS	QLS 29	QLS 30	TUM FAS	TUM TR	SER FAS
Study Patients: Disposition, baseline characteristics and Follow-Up												
Disposition of patients (Section 1.1)	☑	☑										
Protocol deviations (Section 1.2)			☑									
Analysis sets and subgroups (Section 1.3)	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑	
Demographic data (Section 1.4.1)			☑							☑	☑	
Pregnancy test (Section 1.4.2)												
History of studied disease (Section 1.4.3)			☑							☑	☑	
Signs and symptoms (Section 1.4.4)			☑									
Meical history and surgical or medical procedures other than studied disease (Section 1.4.5)			☑									
Clinicalllaboratory evaluation (Section 1.4.6)			☑									
Previous therapies for studied disease (Section 1.4.7)			☑							☑	☑	
Initial tumor assessment (Section 1.4.8)			☑									

Criterion / Analysis	NIS	IS	RS	FAS	PPS	TR	SS	QLS 29	QLS 30	TUM FAS	TUM TR	SER FAS
Vital signs and clinical examination (Section 1.4.9)			☑									
Electrocardiogram (Section 1.4.10)			☑									
Mutation (1.4.11)			☑									
Treatment duration and extent of exposure (Section 1.5)			☑		☑							
Concomitant treatments (Section 1.6)							☑					
Efficacy analysis												
Efficacy analysis (Section 2)				☑	☑	☑				☑	☑	
Biomarker analysis												
Protein-expression by IHC (Section 3.1)										☑		
Protein-expression by IHC according to response (Section 3.2)										☑	☑	
Microsatellites (Section 3.3)										☑	☑	
Protein-expression by ELISA (Section 3.4)												☑
Consistency of mutation results (Section 3.5)												☑

Criterion / Analysis	NIS	IS	RS	FAS	PPS	TR	SS	QLS 29	QLS 30	TUM FAS	TUM TR	SER FAS
Safety analysis												
DLTs (Section 4.1)												
Adverse events (Section 4.2)							☑					
Death (Section 4.3)							☑					
Clinical laboratory evaluation (Section 4.4)							☑					
Vital signs and clinical examination (Section 4.5)							☑					
Electrocardiogram (Section 4.6)							☑					
QOL analysis								☑	☑			

TABLES, LISTINGS AND GRAPHS

1. STUDY PATIENTS: DISPOSITION, BASELINE CHARACTERISTICS AND FOLLOW-UP

1.1. Disposition of patients

Status of patients – Screened Set (N = xx) - Disposition of patients before inclusion

STATUS		ALL
SCREENED	**n (%)**	
Included	n (%)	
Excluded*	n (%)	
Withdrawal by subject	n (%)	
Screen failure	n (%)	
Adverse event	n (%)	

STD table created using macro %_STATUS_

n: number of patients related to the status
*% = (n/N)*100 (N: number of screened patients)*
**NIS*

Status of patients – Included Set (N = xx) - All analytical approaches
Descriptive statistics at and after inclusion

STATUS		Arm 1 (N = xx)	Arm 2 (N = xx)	ALL (N = xx)
INCLUDED	**Nobs**			
In Conformity with the Protocol	n (%)			
With Protocol Deviation(s) Before or at Inclusion	n (%)			
WITHDRAWN DUE TO	**n (%)**			
Adverse event	n (%)			
Protocol deviation	n (%)			
Progressive disease	n (%)			
Non-medical reason	n (%)			
Lost to follow-up	n (%)			
Other, physician decision	n (%)			
Patient's refusal	n (%)			
Death	n (%)			

STD table created using macro %_STATUS_

N: number of patients by arm
n: number of patients related to the status
*% = (n/Nobs)*100 (Nobs: number of included patients by arm)*

1.2. Protocol deviations

For the following tables:

- (*) Before or at inclusion / After inclusion

Protocol deviations – Randomised Set (N = xx) – (*): Number of protocol deviations and number of patients with at least one protocol deviation
Follow-up of patients

Protocol deviations	Arm 1 (N = xx)			Arm2 (N = xx)			All (N = xx)		
	NPD (1)	n (2)	% (3)	NPD (1)	n (2)	% (3)	NPD (1)	n (2)	% (3)
ALL									
Selection/inclusion criteria not fulfilled									
xxxxxxxx									
…									
Patient having withdrawal criteria but not withdrawn									
xxxxxxxx									
…									
Incorrect treatment or dose received									
xxxxxxxx									
…									
Forbidden concomitant treatment									
xxxxxxxx									
…									
Endpoint assessment possibly affected									
xxxxxxxx									
…									
Safety possibly affected									
xxxxxxxx									
…									

STD table created using macro %_DEVIATION_

(1) Number of protocol deviations (*)
(2) Number of patients with at least one protocol deviation (*)
*(3) (n/N)*100 (N : number of patients by arm)*

1.3. Analysis sets and subgroups

Analysis sets – All analysis sets – Value over time
Distribution of patients by analysis set

		Arm 1	Arm 2	All
Randomised Set (N=xx)	n (%) (1)			
Full Analysis Set (N=xx)	n (%) (1)			
Per Protocol Set (N=xx)	n (%) (1)			
Tumor Response pop (N=xx)	n (%) (1)			
Safety Set (N=xx)	n (%) (1)			
Quality of Life Set 29	n (%) (1)			
Quality of Life Set 30	n (%) (1)			
Archived Tumor Biopsies Full Analysis Set	n (%) (1)			
Archived Tumor Biopsies Tumor Response Set	n (%) (1)			

(1) n: Number of patients by arm in a given analysis set
*% : (n/N)*100 (N: Number of patients in a given analysis set)*

STD table created using macro %_TAB_ENS_PAT_

The reference and studied analysis sets are as follows:

Reference set	Studied set
IS	RS
IS	SS
IS	QLS29 QLS30
RS	FAS
FAS	PPS
PPS	TR
FAS	TUMFAS
RS	TUMTR

Analysis sets – All analysis sets – Value over time
Comparison between analysis sets

Arm 1 or Arm 2 or ALL

		RS	FAS	PPS	TR	SS	QLS
IS	% (1)						
RS							
FAS							
PPS							

(1) [Number of patients in the analysis set (notified in column)/Number (notified in row)] x 100

STD table created using macro %_TAB_ENS_PAT_

Reasons for exclusion from the "Studied analysis set" – "Reference analysis set" – Value over time

	Arm 1 (N = xx)		Arm 2 (N = xx)		All (N = xx)	
	n	%	n	n	n	%
Reasons for exclusion	**(1)**	**(2)**	**(1)**	**(1)**	**(1)**	**(2)**
ALL						
DEVIATIONS						
Exclusion class 1						
Reason 1						
…						
Reason n						
…						
OTHER						
Exclusion class 1						
Reason 1						
…						
Reason n						
…						

STD table created using macro % TAB REAS EXCL

(1) Number of patients with at least one reason for exclusion
*(2) (n/N)*100 (N: number of patients by arm)*

Analysis sets – Set 1 (N = xx) – Listing of patients by analysis set

Arm	Patient	Set 1	Set 2	…	Set n
Arm 1					
Arm 2					

STD listing created using macro %_EDIT_ENS_PAT_

Reasons for exclusion from the "Studied analysis set" – "Reference analysis set" – Listing of patients excluded

Arm	Patient	Cycle	Reasons for exclusion class	Reasons for exclusion	Comment
Arm 1					
Arm 2					

STD listing created using macro % EDIT REAS EXCL

1.4. Demographic data and other baseline characteristics

1.4.1. Demographic data

- **<Analysed> Set (RS, TUMFAS, TUMTR)**

Demographic data - <Analysed> Set (N = xx)
Descriptive statistics at baseline

			Arm 1 (N = xx)	Arm 2 (N = xx)	All (N = xx)
Age (years)		Nobs			
		Mean ± SD			
		Median			
		Q1 ; Q3			
		Min ; Max			
Age (years) in classes	Nobs				
	≤ 65 years	n (%)			
	]65;75]	n (%)			
	> 75 years	n (%)			
Gender	Nobs				
	Female	n (%)			
	Male	n (%)			
Race	Nobs				
	Caucasian/White	n (%)			
	Black/African American	n (%)			
	Asian	n (%)			
	Other	n (%)			

- **<Analysed> Set (IS, TUMFAS, TUMTR)**

Demographic data –<Analysed> Set (N = xx) – Value at the visit (EudraCT)
Age (years) in EudraCT classes – Description – baseline

		Arm 1 (N = xx)	Arm 2 (N = xx)	All (N = xx)
Nobs				
In utero	n (%)			
Preterm newborn - gestational age < 37 wk	n (%)			
Newborns (0-27 days)	n (%)			
Infants and toddlers (28 days-23 months)	n (%)			
Children (2-11 years)	n (%)			
Adolescents (12-17 years)	n (%)			
Adults (18-64 years)	n (%)			
From 65 to 84 years	n (%)			
85 years and over	n (%)			

1.4.2. Pregnancy test and contraception

Pregnancy test and Contraception - Randomised Set (N = xx)
Descriptive statistics at baseline

			Arm 1 (N = xx)	**Arm 2 N = xx)**	**All (N = xx)**
PREGNANCY TEST	Nobs				
	YES	n (%)			
	NO	n (%)			
	NOT APPLICABLE	n (%)			
IF YES:POSITIVE PREGNANCY TEST	Nobs				
	YES	n (%)			
	NO	n (%)			

Nobs : Number of patients with available information by parameter

1.4.3. History of studied disease

- **<Analysed> Set (RS, TUMFAS, TUMTR)**

History of the colorectal cancer - <Analysed> **Set (N = xx)**
Descriptive statistics at baseline

			Arm 1 (N = xx)	**Arm 2 (N = xx)**	**All (N = xx)**
PRIMARY DIAGNOSIS	Nobs				
	Level 1	n (%)			
	Level 2	n (%)			
	…	n (%)			
	Level k	n (%)			
DISEASE DURATION (years)		Nobs			
		Mean ± SD			
		Median			
		Q1 ; Q3			
		Min ; Max			
DISEASE DURATION (years)	Nobs				
	≤1 year	n (%)			
	]1; 2 years]	n (%)			
	]2; 4 years]	n (%)			
	>4 years	n (%)			
PROGRESSION FREE INTERVAL (MONTHS)		Nobs			
		Mean ± SD			
		Median			
		Q1 ; Q3			
		Min ; Max			
	Nobs				
	Level 1	n (%)			
	Level 2	n (%)			
	…	n (%)			
	Level k	n (%)			
PRIMARY TUMOUR SITE	Nobs				
	Level 1	n (%)			
	Level 2	n (%)			
	…	n (%)			
	Level k	n (%)			
HYSTOLOGY / CYTOLOGY	Nobs				
	Level 1	n (%)			
	Level 2	n (%)			
	…	n (%)			
	Level k	n (%)			

Nobs : Number of patients with available information by parameter

History of the colorectal cancer - <Analysed> **Set (N = xx)**
Descriptive statistics at baseline (Cont'd)

STAGE AT DIAGNOSIS	Nobs		
	Level 1	n (%)	
	Level 2	n (%)	
	…	n (%)	
	Level k	n (%)	
TUMOUR STATUS : IN RELPASE	Nobs		
	NO	n (%)	
	YES	n (%)	
TUMOUR STATUS : METASTASIS	Nobs		
	NO	n (%)	
	YES	n (%)	
CURRENT SMOKING	Nobs		
	NO	n (%)	
	YES	n (%)	

Nobs : Number of patients with available information by parameter

- **<Analysed> Set (RS, TUMFAS, TUMTR)**

History of of studied disease - <Analysed> Set (N = xx)
Descriptive statistics of TNM at baseline

				Arm 1 (N = xx)	Arm 2 (N = xx)	All (N = xx)
TNM: PRIMARY TUMOUR	TNM: LYMPH NODES	TNM: MESTASTASES	Nobs			
LEVEL 1	LEVEL 1	LEVEL 1	n (%)			
LEVEL 2	LEVEL 2	LEVEL 2	n (%)			
…..	…..	…..	n (%)			
LEVEL k	LEVEL k	LEVEL k	n (%)			

1.4.4. Signs and Symptoms

Signs and symptoms related to colorectal cancer - Randomised Set (N = xx)
Descriptive statistics by primary system organ class and preferred term at baseline

PRIMARY SYSTEM ORGAN CLASS / PREFERRED TERM	Arm 1 (N = xx)		Arm 2 (N = xx)		All (N = xx)	
	n	%	n	%	n	%
ALL						
SOC-a						
PT-aa						
PT-ab						
...						
SOC-b						
PT-ba						
PT-bb						
...						

n: Number of patients with at least one signs or symptoms in a given preferred term or in a given primary system organ class
*%: (n/N)*100 (N: Number of patients by arm)*

Note: Within the table, a descending sorting will be carried out taking into account the number of patients with at least one signs or symptoms of the considered primary system organ class, preferred term

1.4.5. Medical history and surgical or medical procedures other than colorectal cancer

(*)- Randomised Set (N = xx)
Descriptive statistics by primary system organ class and preferred term at baseline

PRIMARY SYSTEM ORGAN CLASS / PREFERRED TERM	Arm 1 (N = xx)		Arm 2 (N = xx)		All (N = xx)	
	n	%	n	%	n	%
ALL						
SOC-a						
PT-aa						
PT-ab						
...						
SOC-b						
PT-ba						
PT-bb						
...						

n: Number of patients with at least one (*) in a given preferred term or in a given primary system organ class
*%: (n/N)*100 (N: Number of patients by arm)*

Macro %_HISTORY_04

Note: (*) Medical history other than colorectal cancer / Surgical or medical procedures history other than for colorectal cancer. Within the table, a descending sorting will be carried out taking into account the number of patients with at least one (*) of the considered primary system organ class, preferred term

1.4.6. Clinical laboratory evaluation

For the following table:

- Gradable parameters
  Albumin (G/L), Sodium (mmol/L), Potassium (mmol/L), Calcium (mmol/L), Magnesium (mmol/L), phosphate (mmol/L), serum creatinine (µmol/L), glucose (mmol/L), ASAT (IU/L), ALAT (IU/L), GGT (IU/L), Alkaline phosphatase (IU/L), total bilirubin (µmol/L), haemoglobin (G/L), White Blood Cell (WBC) count (G/L), neutrophils (G/L), lymphocytes (G/L) and platelets (G/L), APTT and INR.

  - (*) Biochemical parameters / Haematological parameters / Coagulation.
  - (**) Low Albumin, high Alkaline Phosphatase, high Total Bilirubin, hypercalcemia, hypocalcemia, high GGT, hyperglycemia, hypoglycaemia, hyperkalemia, hypokalemia.
  - hypermagnesemia, hypomagnesemia, hypophosphatemia, hyponatremia, hypernatremia, high AST, high ALT, high haemoglobin, anemia, leucocytosis, low WBC, low platelets, high lymphocyte, low lymphocyte, low Neutrophils, high creatinine, aPTT prolonged/high aPTT and high INR.

(*): (**) – Randomised Set (N = xx) – Value at baseline

			Arm 1 (N = xx)	Arm 2 (N = xx)	All (N = xx)
BASELINE		**Nobs**			
		Mean ± SD			
		Median			
		Q1 ; Q3			
		Min ; Max			
	Grade 0	n (%)			
	Grade 1	n (%)			
	Grade 2	n (%)	***STD table created using macro %_LB_TAB1***		
	Grade 3	n (%)			
	Grade 4	n (%)			

For the following table:

- Non-gradable parameters:
  - (*) Biochemical parameters / Haematological parameters.
  - (**) Chloride (mmol/L), bicarbonate (mmol/L), blood urea nitrogen (BUN) (mmol/L), proteins (G/L), lactate dehydrogenase (IU/L), haematocrit (no unit), Erythrocytes (T/L), monocytes (G/L), eosinophils (G/L) and basophils (G/L).

(*): (**) – Randomised Set (N = xx) – Value at baseline

			Arm 1 (N = xx)	Arm 2 (N = xx)	All (N = xx)
BASELINE		**Nobs**			
		Mean ± SD			
		Median			
		Q1 ; Q3			
		Min ; Max			
	<LL	n (%)	***STD table created using macro %_LB_TAB1***		
	[LL-UL[	n (%)			
	>UL	n (%)			

Biochemical parameter: Creatinine clearance – Randomised Set (N = xx) – Value at baseline

			Arm 1 (N = xx)	Arm 2 (N = xx)	All (N = xx)
BASELINE		**Nobs**			
		Mean ± SD			
		Median			
		Q1 ; Q3			
		Min ; Max			
	normal	n (%)			
	mild	n (%)	***STD table created using macro %_LB_TAB1***		
	moderate	n (%)			
	severe	n (%)			

For the following table:

- Urinalysis parameters

  - (**) Proteinuria, Glucosuria, Urobilinogen, Haematuria, Leucocyturia

Urinalysis: (**) – Randomised Set (N = xx) – Value at baseline

				Arm 1 (N = xx)	Arm 2 (N = xx)	All (N = xx)
BASELINE	Nobs					
	Negative		n (%)			
	Trace		n (%)			
	Positive		n (%)			
		+	n (%)	***STD table created using macro %_LB_TAB1***		
		++	n (%)			
		+++	n (%)			

- Neutrophil-Lymphocyte ratio

Neutrophil-Lymphocyte ratio – Randomised Set (N = xx) – Value at baseline

			Arm 1 (N = xx)	Arm 2 (N = xx)	All (N = xx)
BASELINE		**Nobs**			
		Mean ± SD			
		Median			
		Q1 ; Q3			
		Min ; Max			
	NLR < 3	n (%)			
	NLR ≥ 3	n (%)			
	NLR < 5	n (%)			
	NLR ≥ 5				

For the following table:

- Tumor markers
  - (**) CEA

Tumor markers: (**) – Randomised Set (N = xx) – Value at baseline

			Arm 1 (N = xx)	Arm 2 (N = xx)	All (N = xx)
BASELINE	Nobs				
		Mean ± SD			
		Median			
		Q1 ; Q3			
		Min ; Max	***STD table created using macro %_LB_TAB1***		
	Abnormal	n (%)			
	Normal	n (%)			

1.4.7. Previous therapies for colorectal cancer

- **<Analysed> Set (RS, TUMFAS, TUMTR)**

Previous therapies for colorectal cancer - <Analysed> Set (N = xx)
Descriptive statistics at baseline

		Arm 1 (N = xx)	Arm 2 (N = xx)	All (N = xx)
PREVIOUS SURGERY	Nobs			
YES	n (%)			
NO	n (%)			
PREVIOUS RADIOTHERAPY	Nobs			
YES	n (%)			
NO	n (%)			
PREVIOUS DRUG TREATMENT	Nobs			
YES	n (%)			
NO	n (%)			
IF YES				
PREVIOUS NEO-ADJUVANT	Nobs			
YES	n (%)			
NO	n (%)			
PREVIOUS ADJUVANT	Nobs			
YES	n (%)			
NO	n (%)			
PREVIOUS NEO-ADJUVANT/ADJUVANT	Nobs			
YES	n (%)			
NO	n (%)			

n: Number of patients with at least one previous therapy

Combination of previous therapies for colorectal cancer - Randomised Set (N = xx)
Descriptive statistics at baseline

PREVIOUS THERAPIES	Arm 1 (N = xx)		Arm 2 (N = xx)		ALL (N = xx)	
	n	%	n	%	n	%
No previous therapy						
Surgery only						
Radiotherapy only						
Drug treatment only						
Surgery + radiotherapy						
Surgery + drug treatment						
Radiotherapy + drug treatment						
Surgery + radiotherapy + drug treatment						
Any previous therapy						

Previous surgery for colorectal cancer - Randomised Set (N = xx)
Descriptive statistics by surgical procedure preferred term at baseline

PREFERRED TERM	Arm 1 (N = xx)		Arm 2 (N = xx)		ALL (N = xx)	
	n	%	n	%	n	%
ALL						
PT-aa						
PT-ab						
...						

n: Number of patients with at least one previous surgery in a given preferred term
***%:** (n/N)*100 (N: Number of patients by arm)*

Macro %_TRT_04

Note: Within the table, a descending sorting will be carried out taking into account the number of patients with at least one previous surgery of the considered preferred term

Previous drug treatment) for colorectal cancer
- Randomised Set (N = xx)
Descriptive statistics by pharmacological class at baseline

PHARMACOLOGICAL CLASS	Arm 1 (N = xx)		Arm 2 (N = xx)		ALL (N = xx)	
	n	%	n	%	n	%
ALL						
ATC-a level2						
ATC-b level2						
...						

n: Number of patients with at least one previous drug treatment in a given pharmacological class
*%: (n/N)*100 (N: Number of patients by arm)*

Note: Within the table, a descending sorting will be carried out taking into account the number of patients with at least one previous drug treatment of the considered pharmacological class

Macro %_TRT_04

1.4.8. Initial tumor assessment (Metastatic colorectal cancer)

Initial tumour assessment - Randomised Set (N = xx)
Descriptive statistics at baseline

		Arm 1 (N = xx)	Arm 2 (N = xx)	All (N = xx)
Measurable disease	Nobs			
YES	n (%)			
NO	n (%)			
Non measurable disease	Nobs			
YES	n (%)			
NO	n (%)			

1.4.9. Vital signs and clinical examination

Vital signs – Randomised Set (N = xx)
Descriptive statistics at baseline

		Arm 1 (N = xx)	Arm 2 (N = xx)	All (N = xx)
ECOG PERFORMANCE STATUS	Nobs			
0	n (%)			
1	n (%)			
2	n (%)			
3	n (%)			
4	n (%)			
WEIGHT (kg)	Nobs			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
TEMPERATURE (°C)	Nobs			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
Respiratory rate (breaths/min)	Nobs			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
BSA (m²)	Nobs			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
Supine Heart rate (bpm)	Nobs			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
< 60	n (%)			
[60, 100[	n (%)			
>= 100				
Supine SBP (mmHg)	Nobs			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
< 90	n (%)			
[90, 140[	n (%)			
>= 140				

Vital signs – Randomised Set (N = xx)
Descriptive statistics at baseline (Cont'd)

Supine DBP (mmHg)	Nobs			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
< 60	n (%)			
[60, 90[	n (%)			
>= 90				

1.4.10. Electrocardiogram

ECG – Randomised Set (N = xx)
Descriptive statistics at baseline

		Arm 1 (N = xx)	Arm 2 (N = xx)	All (N = xx)
PRESENCE OF CLINICALLY SIGNIFICANT ECG ABNORMALITIES	n (%)			
RR interval (msec)	Nobs			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
≤ 450 ms	n (%)			
]450;480 ms]	n (%)			
] 480;500 ms]	n (%)			
> 500 ms	n (%)			
QT INTERVAL UNCORRECTED (ms)	Nobs			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
≤ 450 ms	n (%)			
]450;480 ms]	n (%)			
] 480;500 ms]	n (%)			
> 500 ms	n (%)			

ECG - Randomised Set (N = xx)
List of clinically significant ECG abnormalities at baseline

Arm	Patient	Cycle	Analysis date	Analysis value	Clinically significant ECG abnormalies?

1.4.11. Mutation

Mutation - Randomised Set (N = xx)
Descriptive statistics at baseline

		Arm 1 (N = xx)	Arm 2 (N = xx)	All (N = xx)
Biopsy performed	Nobs			
YES	n (%)			
NO	n (%)			
Site of biopsy	Nobs			
Primary tumour				
Metastasis				
Lung metastasis	n (%)			
Liver metastasis	n (%)			
Bone metastasis	n (%)			
Brain metastasis	n (%)			
Skin metastasis	n (%)			
Othser soft tissue	n (%)			
Other metastasis	n (%)			
Method of biopsy				
Sequencing/NGS				
PCR				
Unknown				
Other				
BRAF STATUS	Nobs			
WILD TYPE	n (%)			
MUTANT TYPE	n (%)			
NOT DONE	n (%)			
BRAF MUTATION TYPE	Nobs			
VAL600GLU	n (%)			
UNKNOWN	n (%)			
OTHER	n (%)			
NRAS STATUS	Nobs			
WILD TYPE	n (%)			
MUTANT TYPE	n (%)			
NRAS MUTATION TYPE	Nobs			
MUTATION TYPE CODON 12	Nobs			
YES	n (%)			
NO	n (%)			
MUTATION TYPE CODON 13X	Nobs			
YES	n (%)			
NO	n (%)			
MUTATION TYPE CODON 61	Nobs			
YES	n (%)			
NO	n (%)			
MUTATION TYPE CODON 146	Nobs			
YES	n (%)			
NO	n (%)			
OTHER	Nobs			
YES	n (%)			
NO	n (%)			

Mutation - Randomised Set (N = xx)
Descriptive statistics at baseline (Cont'd)

KRAS STATUS	Nobs			
WILD TYPE	n (%)			
MUTANT TYPE	n (%)			
KRAS MUTATION TYPE				
MUTATION TYPE CODON 12	Nobs			
YES	n (%)			
NO	n (%)			
MUTATION TYPE CODON 13	Nobs			
YES	n (%)			
NO	n (%)			
MUTATION TYPE CODON 61	Nobs			
YES	n (%)			
NO	n (%)			
MUTATION TYPE CODON 117	Nobs			
YES	n (%)			
NO	n (%)			
MUTATION TYPE CODON 146	Nobs			
YES	n (%)			
NO	n (%)			
OTHER	Nobs			
YES	n (%)			
NO	n (%)			

1.5. Extent of exposure and treatment compliance

Extent of exposure and treatment compliance – Safety Set (N = xx) – During the treatment period
Description – Value by patient

			Arm 1 (N = xx)	Arm 2 (N = xx)
Number of cycles		Nobs		
		Mean ± SD		
		Median		
		Q1 ; Q3		
		Min ; Max		
Number of cycles in classes	Nobs			
	1 cycle	n (%)		
	2 cycles	n (%)		
	….	n (%)		
	> 6 cycles	n (%)		
Treatment duration (weeks)		Nobs		
		Mean ± SD		
		Median		
		Q1 ; Q3		
		Min ; Max		
Treatment duration (weeks) in classes	Nobs			
	≤ 8 weeks	n (%)		
	]8; 24]	n (%)		
	]24; 36]	n (%)		
	]36; 48]	n (%)		
	> 48	n (%)		

N: Number of patients by arm

For the following table:
(*) IMP / Associated Agent
(**) Patient / Cycle

Extent of exposure and treatment compliance (*) – Safety Set (N = xx) – During the treatment period
Description by (**)

			Arm 1 (N = xx)	**Arm 2 (N = xx)**
Cumulative dose (1)		Nobs		
		Mean ± SD		
		Median		
		Q1 ; Q3		
		Min ; Max		
Dose Intensity (2)		Nobs		
		Mean ± SD		
		Median		
		Q1 ; Q3		
		Min ; Max		
Relative Dose Intensity (%)		Nobs		
		Mean ± SD		
		Median		
		Q1 ; Q3		
		Min ; Max		
Relative Dose Intensity (%) in classes	Nobs			
	≤ 60	n (%)		
	]60;80]	n (%)		
	]80;100]	n (%)		
	]100; 110]	n (%)		
	>110	n (%)		

(1) (mg/m2) for IMP, (mg/kg) for Associated Agent
(2) (mg/m2/wk) for IMP, (mg/kg/wk) for Associated Agent

For the following table:
(*) Patient / Cycle

Extent of exposure and treatment compliance in Capecitabine + Bevacizumab arm by theoretical starting dose – Safety Set (N=xx) – During the treatment period
Description by Cycle – Value by (*)

			Capecitabine 1000 mg (N = xx)	Capecitabine 1250 mg (N = xx)
Cumulative dose (mg/m2)		Nobs		
		Mean ± SD		
		Median		
		Q1 ; Q3		
		Min ; Max		
Dose Intensity (mg/m2/wk)		Nobs		
		Mean ± SD		
		Median		
		Q1 ; Q3		
		Min ; Max		
Relative Dose Intensity (%)		Nobs		
		Mean ± SD		
		Median		
		Q1 ; Q3		
		Min ; Max		
Relative Dose Intensity (%) in classes	Nobs			
	≤ 60	n (%)		
	]60;80]	n (%)		
	]80;100]	n (%)		
	]100; 110]	n (%)		
	>110	n (%)		

Extent of exposure and treatment compliance – Safety Set (N = xx) – During the treatment period
Description – Value by patient

			Arm 1 (N = xx)	Arm 2 (N = xx)
Cycles	Nobs			
	Cycle 1	n (%)		
	Cycle 1	n (%)		
	….	n (%)		
	Cycle k	n (%)		

n: Number of patients per cycle
*%: (n/N)*100 (N: Number of patients by arm)*

Extent of exposure and treatment compliance – Safety Set (N = xx) – During the treatment period
Description – Dose administration, Cycle delayed, cycle reduced and missed intake of IMP

			Arm 1 (N = xx)	**Arm 2 (N = xx)**
Number of patients with at least one cycle delayed	Nobs			
	Yes	n (%)		
	No	n (%)		
Number of cycles delayed		Nobs		
		Mean ± SD		
		Median		
		Q1 ; Q3		
		Min ; Max		
Dispensiation postponed reason		Nobs		
Medical reason		n (%)		
Non-medical reason		n (%)		
Number of patients with at least one cycle reduced	Nobs			
	Yes	n (%)		
	No	n (%)		
Number of cycles reduced		Nobs		
		Mean ± SD		
		Median		
		Q1 ; Q3		
		Min ; Max		
Number of patients with at least one missed intake		Nobs		
		Mean ± SD		
		Median		
		Q1 ; Q3		
		Min ; Max		
Number of cycles with at least one missed intake		Nobs		
		Mean ± SD		
		Median		
		Q1 ; Q3		
		Min ; Max		
Number of missed intake		Nobs		
		Mean ± SD		
		Median		
		Q1 ; Q3		
		Min ; Max		

Extent of exposure and treatment compliance – Safety Set (N = xx) – During the treatment period
Description – Dose administration, Cycle delayed, cycle reduced and missed intake of associated agent

			Arm 1 (N = xx)	**Arm 2 (N = xx)**
Number of patients with full dose administered	Nobs			
	Yes	n (%)		
	No	n (%)		
Number of cycles reduced		Nobs		
		Mean ± SD		
		Median		
		Q1 ; Q3		
		Min ; Max		
Number of patients with at least one missed infusion		Nobs		
		Mean ± SD		
		Median		
		Q1 ; Q3		
		Min ; Max		
Number of cycles with at least one missed intake		Nobs		
		Mean ± SD		
		Median		
		Q1 ; Q3		
		Min ; Max		
Number of missed intake		Nobs		
		Mean ± SD		
		Median		
		Q1 ; Q3		
		Min ; Max		

For the following listings:
(*) IMP, Associated agent

Extent of exposure and treatment compliance – Safety Set (N = xx) – During the treatment period
Listing of extent of exposure of (*) by patient

Arm	Theoretical starting dose of IMP (mg/m2)	Patient	Number of cycle	Treatment duration (weeks)	Treatment duration in classes	BSA at Baseline (m2)	Cumulative dose (1)	Planned Dose Intensity (2)	Dose intensity (2)	Relative Dose Intensity (%)	Number of cycle delay	Number of cycle reduced
Arm 1												
...												
Arm 2												

(1) (mg/m2) for IMP, (mg/kg) for Associated Agent
(2) (mg/m2/wk) for IMP, (mg/kg/wk) for Associated Agent

Extent of exposure and treatment compliance – Safety Set (N = xx) – During the treatment period
Listing of extent of exposure of (*) by patient by cycle

Arm	Theoretical starting dose of IMP (mg/m2)	Patient	Number of cycle	Cycle	BSA (m2)	Theoretical intake number (mg/day)	Real intake number (mg/day)	Cumulative dose (1)	Planned Dose Intensity (2)	Dose intensity (2)	Relative Dose Intensity (%)	Cycle delay	Cycle reduced
Arm 1				Cycle 1									
				…									
				Cycle X									
...													
Arm 2													

(1) (mg/m2) for IMP, (mg/kg) for Associated Agent
(2) (mg/m2/wk) for IMP, (mg/kg/wk) for Associated Agent

Extent of exposure and treatment compliance – Safety Set (N = xx) – During the treatment period
Listing of tablet distribution by patient – S95005 + Bevacizumab arm

Arm	Patient	Number of cycle	Number of 15 mg tablet given	Number of 15 mg tablet return	Number of 15 mg tablet return (estimated)	Number of 20 mg tablet given	Number of 20 mg tablet return	Number of 20 mg tablet return (estimated)
Arm 1								
...								
Arm 2								

Extent of exposure and treatment compliance – Safety Set (N = xx) – During the treatment period
Listing of tablet distribution by patient by cycle – S95005 + Bevacizumab arm

Arm	Patient	Number of cycle	Cycle	Number of 15 mg tablet given	Number of 15 mg tablet return	Number of 15 mg tablet return (estimated)	Number of 20 mg tablet given	Number of 20 mg tablet return	Number of 20 mg tablet return (estimated)
Arm 1			Cycle 1						
			…						
			Cycle X						
...									
Arm 2									

Extent of exposure and treatment compliance – Safety Set (N = xx) – During the treatment period
Listing of tablet distribution by patient – Capecitabine + Bevacizumab arm

Arm	Patient	Number of cycle	Number of 150 mg tablet given	Number of 150 mg tablet return	Number of 150 mg tablet return (estimated)	Number of 500 mg tablet given	Number of 500 mg tablet return	Number of 500 mg tablet return (estimated)
Arm 1								
...								
Arm 2								

Extent of exposure and treatment compliance – Safety Set (N = xx) – During the treatment period
Listing of tablet distribution by patient by cycle – Capecitabine + Bevacizumab arm

Arm	Patient	Number of cycle	Cycle	Number of 150mg tablet given	Number of 150mg tablet return	Number of 150mg tablet return (estimated)	Number of 500mg tablet given	Number of 500mg tablet return	Number of 500mg tablet return (estimated)
Arm 1			Cycle 1						
			…						
			Cycle X						
...									
Arm 2									

1.6. Concomitant treatments

For the following 2 tables:
- (*) Concomitant treatments
- (**) at inclusion / before treatment period / during treatment period (***) concomitant treatment

(*) - Safety Set (N = xx) – Description (**)
Number of patients having taken at least one (***) by pharmacological class - Description of concomitant treatments

PHARMACOLOGICAL CLASS	Arm 1 (N = xx)		Arm 2 (N = xx)		ALL (N = xx)	
	n (1)	% (2)	n (1)	% (2)	n (1)	% (2)
ALL						
ATC-a level 2						
ATC-b level 2						
…						

STD table created using macro %_TRT_

(1) Number of patients with at least one () (**) in a given pharmacological class
*(2) (n/N)*100 (N: number of patients by arm*

Note: Within the table, a descending sorting will be carried out taking into account the number of patients with at least one concomitant treatment of the considered pharmacological class

(*) - Safety Set (N = xx) – Description (**)
Number of patients having taken at least one (***) by pharmacological class, pharmacological sub-class, therapeutic class and preferred name - Description of concomitant treatments

PHARMACOLOGICAL CLASS/ PHARMACOLOGICAL SUB-CLASS/ THERAPEUTIC CLASS/ PREFERRED NAME	**Arm 1 (N = xx)**		**Arm 2 (N = xx)**		**ALL (N = xx)**	
	n (1)	**% (2)**	**n (1)**	**% (2)**	**n (1)**	**% (2)**
ALL						
ATC-a level 2						
+ ATC-a level 3						
-ATC-a level 4						
PN-aaaa						
PN-aaab						
…						
- ATC-b level 4						
PN-aaba						
PN-aabb						
…						
…						
+ ATC-b level 3						
…						
ATC-b level 2						
…						

STD table created using macro %_TRT_

(1) Number of patients with at least one (***) (**) in a given level
*(2) (n/N)*100 (N: number of patients by arm)*

Note: Within the table, a descending sorting will be carried out taking into account the number of patients with at least one concomitant treatment of the considered pharmacological class, pharmacological sub-class, therapeutic class and preferred name

2. EFFICACY ANALYSIS

For the following table:

- **<Analysed> Set (FAS, PPS, TR, TUMFAS, TUMTR)**

		Arm 1 (N = xx)	**Arm 2 (N = xx)**
Descriptive Statistics			
Best overall response	Nobs	xx	xx
Complete response (CR)	n (%)		
Partial response (PR)	n (%)		
Stable disease (SD)	n (%)		
Non complete response / non progressive disease (NON CR/NON PD) (1)	n (%)		
Progressive disease (PD)	n (%)		
Non evaluable (NE)	n (%)		
Statistical analysis			
Objective response rate (2)	n (%)		
	95% (4)		
	P-value (5)		
Disease control rate (3)	n (%)		
	95% (4)		
	P-value (5)		

(1) For patients with non-measurable disease
(2) Objective Response Rate (Best overall response = CR or PR)
(3) Disease control rate (Best overall response = CR or PR or SD)
(4) 95% Confidence interval of the estimate using Clopper Pearson method
(5) P-value given by Fisher's exact test

For the following table and graph, parameter and the corresponding population are as follows:

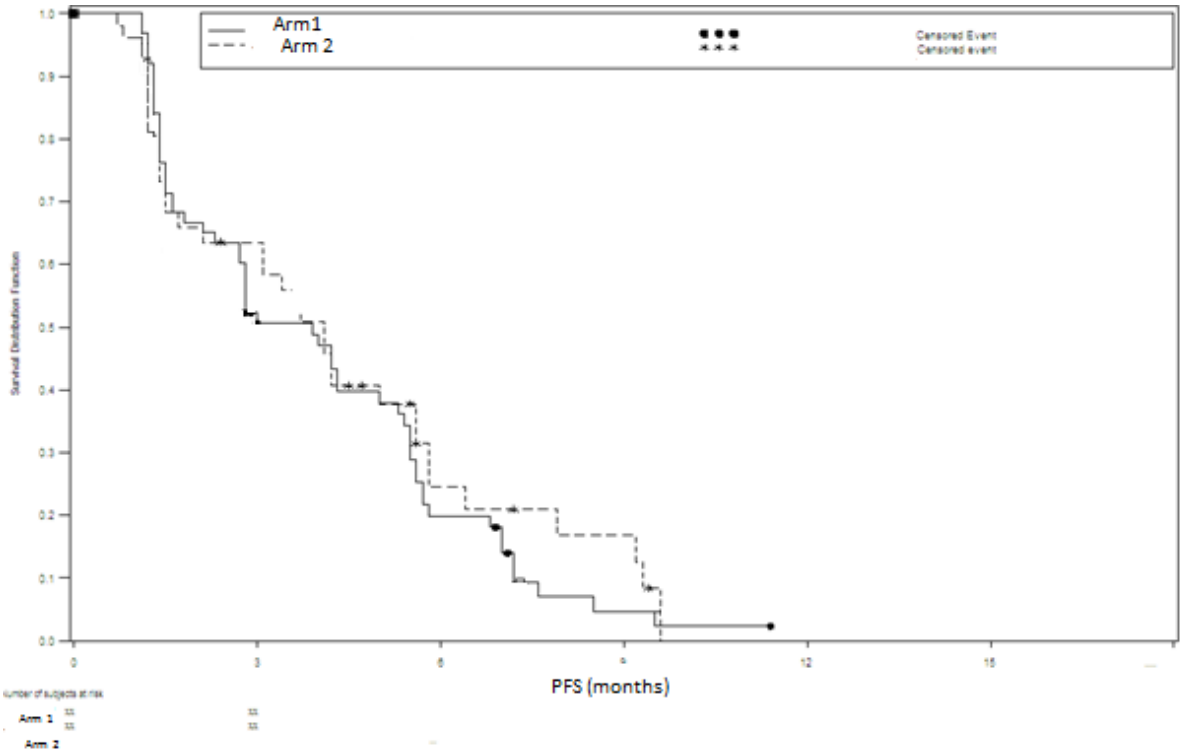
< Parameter>	**PFS**	**PFS**	**PFS**	**OS**	**OS**	**DR among responders**	**PFSs1**	**PFSs1**	**PFSs2**
<Analysed> Set	**FAS**	**PPS**	**TUMFAS**	**FAS**	**TUMFAS**	**TR**	**FAS**	**PPS**	**FAS**

Antitumoral activity - <Analysed> Set (N = xx)
Hazard ratio estimate for < Parameter>

	Arm 1 (N = xx)	Arm 2 (N= xx)
Hazard ratio* (relative to Arm 2)		
95% confidence interval		
80% confidence interval		
P-value		

** Cox proportional hazard model adjusting for the stratification factors*

Antitumoral activity - <Analysed> Set (N = xx)
Kaplan-Meier curves of < Parameter>



For the following table, parameter and the corresponding population are as follows:

< Parameter>	PFS	PFS	PFS	DR among responders
<Analysed> Set	FAS	PPS	TUMFAS	TR

Antitumoral activity - <Analysed> Set (N = xx)
Product-limit of Kaplan-Meier estimates for < Parameter>

		Arm 1 (N = xx)	Arm 2 (N= xx)
< Parameter>			
Number of censors	Nobs		
Lost to follow-up without new treatment nor PD	n (%)		
Start of new anti-cancer therapy	n (%)		
Alive without new treatment nor PD	n (%)		
Number of events	Nobs		
Progression Disease (PD)	n (%)		
Death	n (%)		
Median (months)			
95% confidence interval[a]			
80% confidence interval[a]			
Min ; Max			
Survival probability at 6 months			
95% confidence interval[b]			
80% confidence interval[b]			
Survival probability at 12 months			
95% confidence interval[b]			
80% confidence interval[b]			
Survival probability at 18 months			
95% confidence interval[b]			
80% confidence interval[b]			
Survival probability at 24 months			
95% confidence interval[b]			
80% confidence interval[b]			

[a] Methodology of Brookmeyer and Crowley
[b] Using log-log transformation methodology of Kalbfleisch and Prentice

- For the following table:
- **<Analysed> Set (FAS, PPS)**

Antitumoral activity - <Analysed> Set (N = xx)
Product-limit of Kaplan-Meier estimates for PFSs1

		Arm 1 (N = xx)	Arm 2 (N= xx)
PFSs1			
Number of censors	Nobs		
Lost to follow-up without new treatment nor PD	n (%)		
Alive without new treatment nor PD	n (%)		
Number of events	Nobs		
Start of new anti-cancer therapy	n (%)		
Progression Disease (PD)	n (%)		
Death	n (%)		
Median (months)			
95% confidence interval[a]			
80% confidence interval[a]			
Min ; Max			
Survival probability at 6 months			
95% confidence interval[b]			
80% confidence interval[b]			
Survival probability at 12 months			
95% confidence interval[b]			
80% confidence interval[b]			
Survival probability at 18 months			
95% confidence interval[b]			
80% confidence interval[b]			
Survival probability at 24 months			
95% confidence interval[b]			
80% confidence interval[b]			

[a] Methodology of Brookmeyer and Crowley
[b] Using log-log transformation methodology of Kalbfleisch and Prentice

Antitumoral activity - Full analysis Set (N = xx)
Product-limit of Kaplan-Meier estimates for PFSs2

		Arm 1 (N = xx)	Arm 2 (N= xx)
PFSs2			
Number of censors	Nobs		
Lost to follow-up without new treatment nor PD	n (%)		
Alive without new treatment nor PD	n (%)		
Start of new anti-cancer therapy			
Number of events	Nobs		
Progression Disease (PD)	n (%)		
Death	n (%)		
Median (months)			
95% confidence interval[a]			
80% confidence interval[a]			
Min ; Max			
Survival probability at 6 months			
95% confidence interval[b]			
80% confidence interval[b]			
Survival probability at 12 months			
95% confidence interval[b]			
80% confidence interval[b]			
Survival probability at 18 months			
95% confidence interval[b]			
80% confidence interval[b]			
Survival probability at 24 months			
95% confidence interval[b114]			
80% confidence interval[b]			

[a] Methodology of Brookmeyer and Crowley
[b] Using log-log transformation methodology of Kalbfleisch and Prentice

- **<Analysed> Set (FAS, TUMFAS)**

Antitumoral activity – <Analysed> Set (N = xx)
Product-limit of Kaplan-Meier estimates for overall survival

		Arm 1 (N = xx)	Arm 2 (N= xx)
Overall survival			
Number of censors	Nobs		
Patient alive without documented death	n (%)		
Number of events	Nobs		
Death	n (%)		
Median (months)			
95% confidence interval[a]			
80% confidence interval[a]			
Min ; Max			
Survival probability at 6 months			
95% confidence interval[b]			
80% confidence interval[b]			
Survival probability at 12 months			
95% confidence interval[b]			
80% confidence interval[b]			
Survival probability at 18 months			
95% confidence interval[b]			
80% confidence interval[b]			
Survival probability at 24 months			
95% confidence interval[b]			
80% confidence interval[b]			

[a] Methodology of Brookmeyer and Crowley
[b] Using log-log transformation methodology of Kalbfleisch and Prentice

PFS (Stepwise Model Multivariate Analysis) – FAS population

Factor	Levels[a]	P-Value[b]	Hazard Ratio[c]	95% CI[c] [Low, High]
Stratification Factors (In Base Model):				
RAS Status	Wild Type (vs. Mutant Type)			
ECOG	0 (vs. 1)			
	0 (vs. 2)			
Additional Factors (for Selection):				
Factor 1	Level 1			
	…			
	Level X			
…				
Factor X	Level 1			
	…			
	Level X			

[a] *The level in the numerator for the hazard ratio. Factors with just two levels have just one level for hazard ratio.*
[b] *Wald Chi-Square Test for Factor.*
[c] *From Cox Regression with forward stepwise selection process ("entry" and "stay" alpha =0.1). Factors with more than two levels display each level of the factor and the hazard ratio is relative to all those not in that level.*
N.S. Not selected by stepwise procedure (not significant at alpha=0.1).

PFS (Final Stepwise Model Multivariate Analysis with Factor for Treatment) – FAS population

Factor	Levels	P-Value[a]	Hazard Ratio[b]	95% CI[b] [Low, High]	Interaction P-Value[c]
Treatment	Arm 1, Arm 2				n/a
RAS Status	Wild Type, Mutant Type				
ECOG	0, 1				
	0, 2				
Factor 1	Level1, …, Level X				
…					
Factor X	Level1, …, Level X				

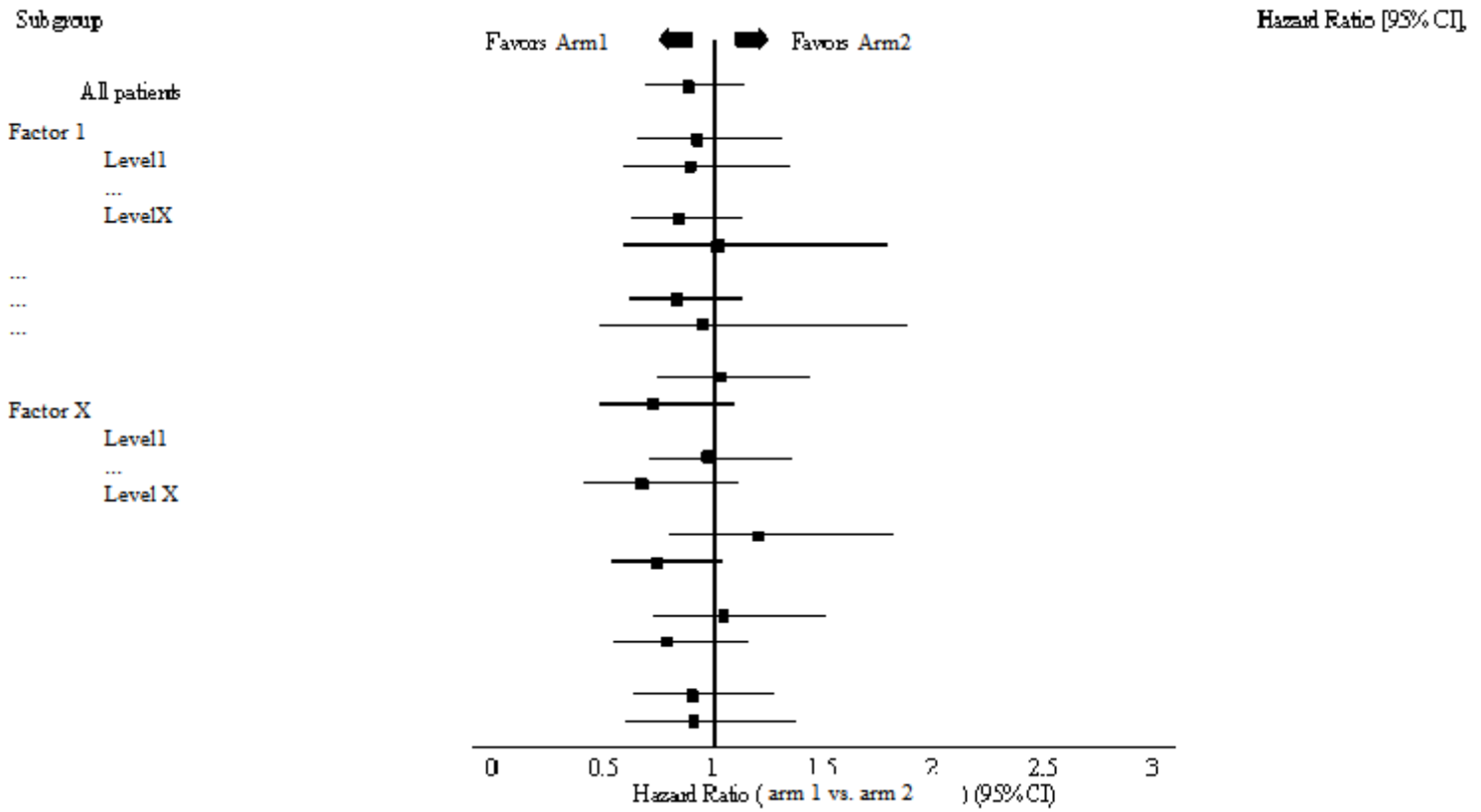
[a] Wald Chi-Square Test
[b] Hazard of arm 1 (relative to arm 2) from Cox Regression including terms for all factors shown.
[c] P-value for interaction with treatment from full model plus the 2-way interaction with just the factor shown (i.e. separate models including only 1 factor crossed with treatment).

Subgroup PFS analysis – FAS population

		Arm 1 (N = xx)	**Arm 2 (N = xx)**
Subgroup			
Variable 1			
Modality 1	n (%)		
	Median[a]		
	95%[b]		
	HR		
	95%		
…			
Modality X	n (%)		
	median[a]		
	95%[b]		
	HR		
	95%		
…			
Variable X			
Modality 1	n (%)		
	median[a]		
	95%[b]		
	HR		
	95%		
…			
Modality X	n (%)		
	median[a]		
	95%[b]		
	HR		
	95%		

[a] *Kaplan-Meier estimates*
[b] *Methodology of Brookmeyer and Crowley*

Forest Plot of Hazard Ratios for Treatment Effect on Radiologic Progression-Free Survival by Selected Subgroups – FAS population



Antitumoral activity - Full Analysis Set (N = xx)
Listing of the tumour response evaluation

Arm	Patient	BOR*	Cycle	OR[#]	last trt intake	with-drawal visit	with-drawal reason	Type ¤	Response lesions	Date	Presence of non-target lesion	Organ site	Method of measure	Sum of diameters (mm)	Relative Change from baseline (%)	Relative Change from nadir (smallest) (%)

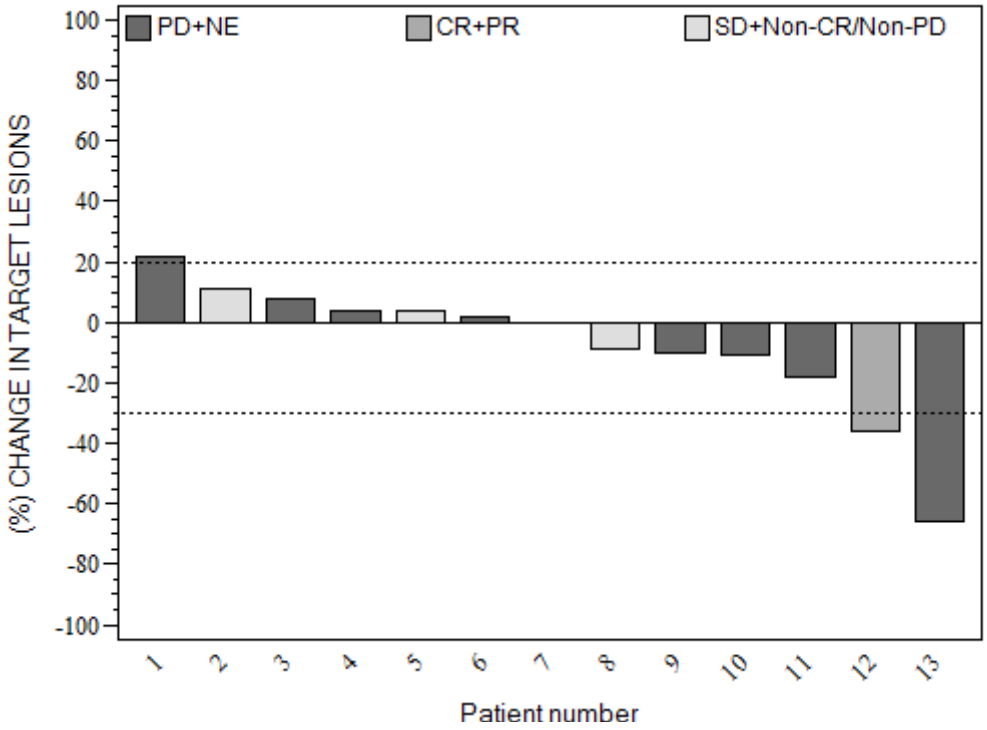
CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, Non CR/Non PD = Non Complete response/ Non progressive disease and NE = non-evaluable
Best Overall Response - Only during the treatment period
[#]Overall Response
¤ Type: T = Target lesion, NT = Non target lesion, NL = New lesion

Antitumoral activity - Full Analysis Set (N = xx)
Listing of the best relative change of the sum of the lesions diameters from baseline

Arm	Patient	Histological type	Diagnosis LLT label	Primary tumor	Lymph nodes	Metastases	BOR*	Best relative change from baseline (%)	At least one new lesion under treatment

** Best Overall Response - Only during the treatment period*
This listing will be sorted by the best relative change value

Antitumoral activity - Full Analysis Set (N = xx)
Bar chart of the best relative change of the sum of the lesions diameters from baseline (%) during the treatment period



3. BIOMARKERS ANALYSIS

3.1. Protein-expression by IHC

In case of several subcellular staining locations for one parameter, analyses will be performed separately for each location.

For the following tables and graphs:
- <Analysed> Set (TUMFAS)
- *Parameter* : "name of biomarker" in "subcellular staining location"
- *Group :*Arm1/Arm2
- *Measurement:* H-score/Occupancy

Protein expression by IHC - <Analysed> Set (N = xx)
Measurement **– Description by class – Value at baseline**

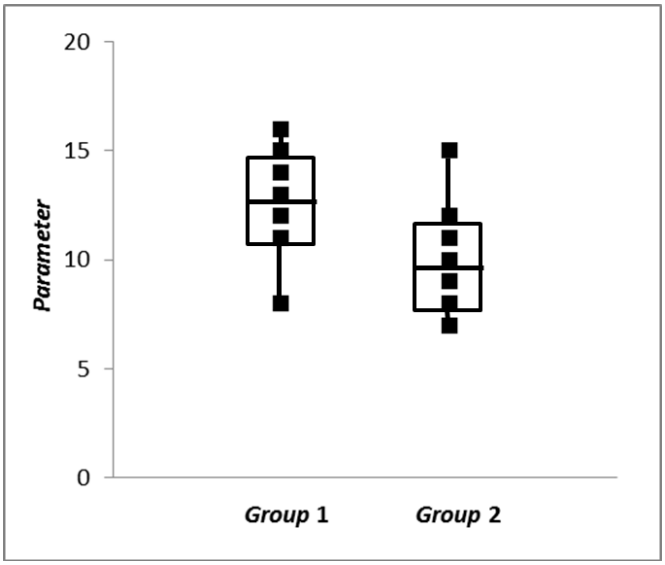
			Arm 1 (N = xx)	Arm 2 (N = xx)
Parameter 1		Nobs		
	>0	n (%)		
	=0	n (%)		
Parameter x		Nobs		
	>0	n (%)		
	=0	n (%)		

Following table and graphic will be provided if, for a given marker, at least 3 patients present an H-score/Occupancy greater than 0.

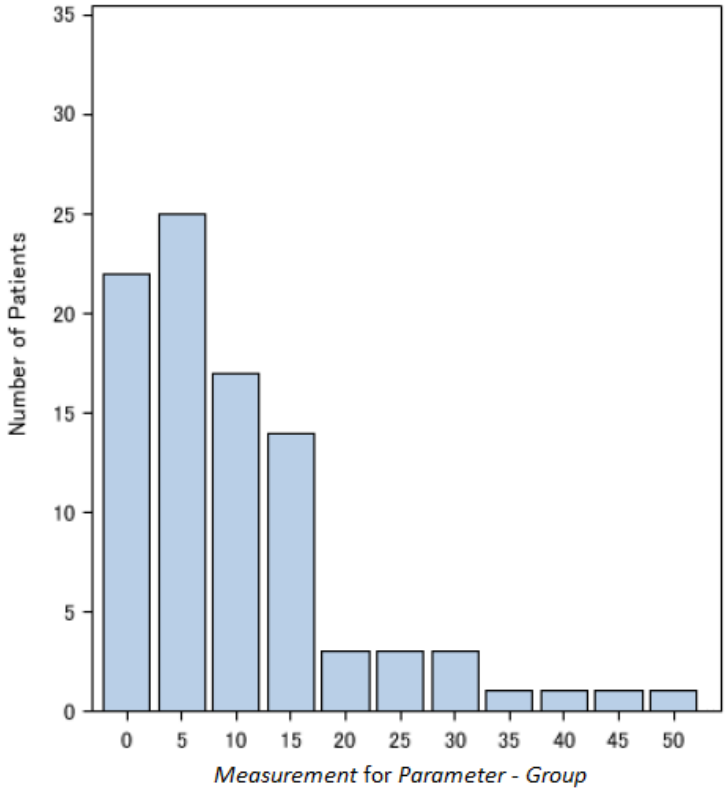
Protein expression by IHC - <Analysed> Set (N = xx)
Measurement **– Description – Value at baseline**

		Arm 1 (N = xx)	Arm 2 (N = xx)
Parameter 1	n		
	Mean ± SD		
	Median		
	Q1 ; Q3		
	Min ; Max		
Parameter x	n		
	Mean ± SD		
	Median		
	Q1 ; Q3		
	Min ; Max		

Protein expression by IHC - <Analysed> Set (N = xx)
Measurement **for *parameter* – Boxplot – Value at baseline**



Protein expression by IHC - <Analysed> Set (N = xx)
Measurement **for** *parameter – Group* **Patients – Histogram – Value at baseline**



3.2. Protein-expression by IHC according to response

In case of several subcellular staining locations for one parameter, analyses will be performed separately for each location.

3.2.1. Protein-expression by IHC according to DCR/ORR

For the following tables and graphs:

- <Analysed> Set (TUMFAS, TUMTR)
- (*) : defined by DCR / defined by ORR
- *Parameter* : "name of biomarker" in "subcellular staining location"
- *Class: bmk+/bmk-*
- *Measurement: H-score/Occupancy*
- *Cutoff:* Cutoff considered as eligible, *i.e.* if there are at least 5 patients in the bmk+ group as well as 5 patients in the bmk- group

Following table and graph will be provided for each cutoff point considered as eligible, *i.e.* if there are at least 5 patients in the bmk+ group as well as 5 patients in the bmk- group.

Analysis of IHC - <Analysed> Set (N = xx)
Parameter **– Patients groups based on** *Measurement* **– Comparison between treatment groups according to response (*)**

				Arm 1 (N = xx)	Arm2 (N = xx)
		Descriptive statistics			
Cutoff 1	*bmk+*				
		Response (*)	Nobs		
		Responder	n (%)		
		Non responder	n (%)		
Cutoff 1	*bmk-*				
		Response (*)	Nobs		
		Responder	n (%)		
		Non responder	n (%)		
Cutoff x	*bmk+*				
		Response (*)	Nobs		
		Responder	n (%)		
		Non responder	n (%)		
Cutoff x	*bmk-*				
		Response (*)	Nobs		
		Responder	n (%)		
		Non responder	n (%)		
Statistical analysis					
Response rate (*)					
Cutoff 1	*bmk+*				
			n (%)		
			95% CI (1)		
			p-value(2)		
Cutoff 1	*bmk-*				
			n (%)		
			95% CI (1)		

(1): 95%CI of the estimate using Clopper-Pearson method
(2): Fisher's exact test p-value

Analysis of IHC - <Analysed> Set (N = xx)
Parameter **– Patients groups based on** *Measurement* **– Comparison between treatment groups according to response (*) (Cont'd)**

		p-value(2)		
Cutoff x	*bmk+*			
		n (%)		
		95% CI (1)		
		p-value(2)		
Cutoff x	*bmk-*			
		n (%)		
		95% CI (1)		
		p-value(2)		

(1): 95%CI of the estimate using Clopper-Pearson method
(2): Fisher's exact test p-value

3.2.2. Protein-expression by IHC according to PFS

3.2.2.1. Protein-expression by IHC according to PFS – study of all eligible cutoffs

For the following tables and graphs:

- <Analysed> Set (TUMFAS)
- *Parameter:* "name of biomarker"
- *Measurement: H-score/Occupancy*
- *Class: bmk+/bmk-*
- *Cutoff:* Cutoff considered as eligible, *i.e.* if there are at least 10 patients in the bmk+ group as well as 10 patients in the bmk- group

Following table and graph will be provided for each cutoff point considered as eligible, *i.e.* if there are at least 10 patients in the bmk+ group as well as 10 patients in the bmk-group, in each arm.

Analysis of IHC - Antitumoral activity - <Analysed> Set (N = xx)
Product-limit of Kaplan-Meier estimates for < Parameter> based on *Measurement*

		Class 1 (N = xx)		Class 2 (N = xx)	
		Arm 1 (N = xx)	Arm 2 (N = xx)	Arm 1 (N = xx)	Arm 2 (N = xx)
Cutoff 1					
Number of censors	Nobs				
Lost to follow-up without new treatment nor PD	n (%)				
Start of new anti-cancer therapy	n (%)				
Alive without new treatment nor PD	n (%)				
Number of events	Nobs				
Progression Disease (PD)	n (%)				
Death	n (%)				
Median (months)					
95% confidence interval[a]					
80% confidence interval[a]					
Min ; Max					
Cutoff x					
Number of censors	Nobs				
Lost to follow-up without new treatment nor PD	n (%)				
Start of new anti-cancer therapy	n (%)				
Alive without new treatment nor PD	n (%)				
Number of events	Nobs				
Progression Disease (PD)	n (%)				
Death	n (%)				
Median (months)					
95% confidence interval[a]					
80% confidence interval[a]					
Min ; Max					

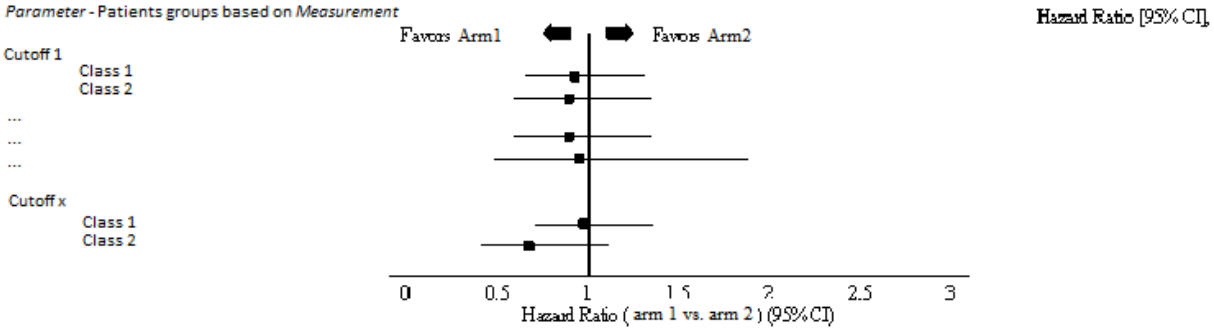
[a] Methodology of Brookmeyer and Crowley

Analysis of IHC - Antitumoral activity - <Analysed> Set (N = xx)
Hazard ratio estimate for < Parameter> - Patients groups based on *Measurement*

		Class 1 (N = xx)		Class 2 (N = xx)	
		Arm 1 (N = xx)	Arm 2 (N = xx)	Arm 1 (N = xx)	Arm 2 (N = xx)
Cutoff 1					
	Hazard ratio* (relative to Arm 2)				
	95% confidence interval				
	80% confidence interval				
	P-value (LOG-RANK)				
Cutoff x					
	Hazard ratio* (relative to Arm 2)				
	95% confidence interval				
	80% confidence interval				
	P-value (LOG-RANK)				

** Cox proportional hazard model without adjusting for the stratification factors*

Analysis of IHC - <Analysed> Set (N = xx)
Forest Plot of Hazard Ratios for Treatment Effect on PFS according to *Parameter* **– Patients groups based on** *Measurement*



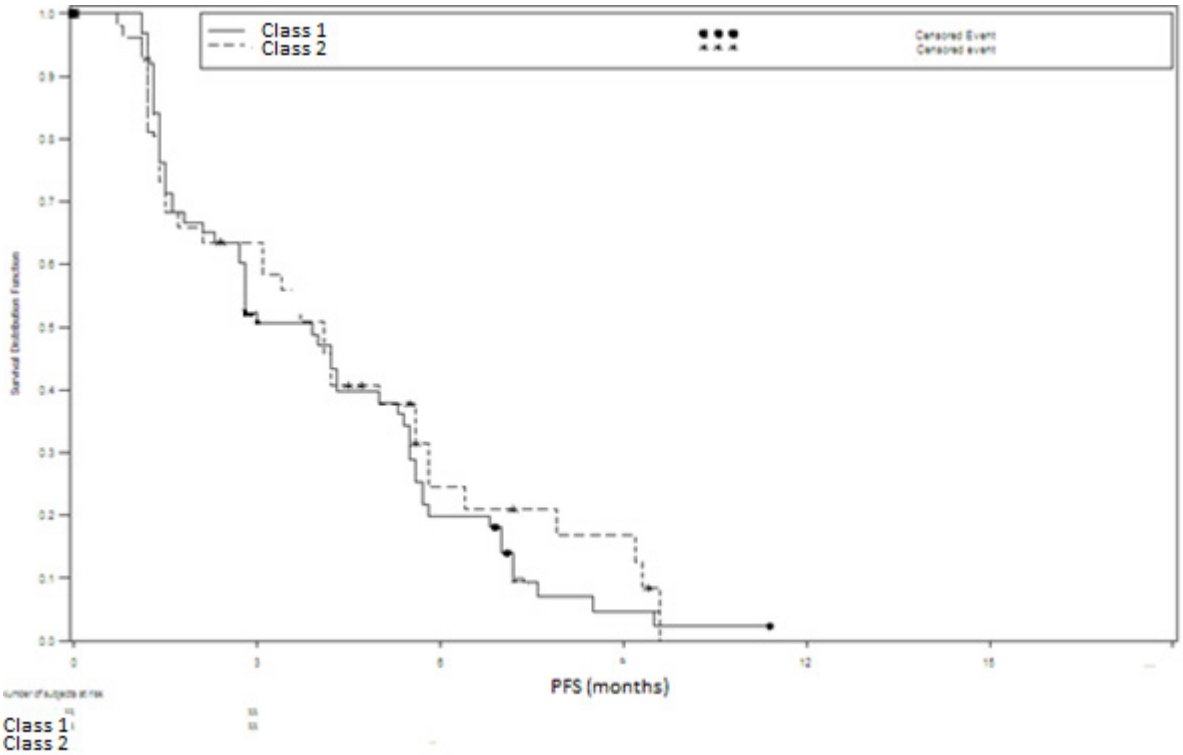
3.2.2.2. Protein-expression by IHC according to PFS – study of best cutoff point

For the following tables and graphs:

- <Analysed> Set (TUMFAS)
- *Parameter* : "name of biomarker"
- *Arm: arm1/arm2*
- *Class: bmk+/bmk-*
- *Cutoff:* best cutoff/median cutoff

Following table and graph will be provided only for best cutoff point, for each parameter.

Analysis of IHC – Antitumoral activity - <Analysed> Set (N = xx)
Kaplan-Meier curves of < Parameter> (*cutoff*) - *Arm*



Analysis of IHC - Antitumoral activity - <Analysed> Set (N = xx)
Hazard ratio estimate for < Parameter> (*cutoff*) – Patients groups based on *Measurement*

	Arm 1 (N = xx)		Arm 2 (N= xx)	
	Class 1 (N = xx)	Class 2 (N = xx)	Class 1 (N = xx)	Class 2 (N = xx)
Hazard ratio* (relative to bmk-)				
95% confidence interval				
80% confidence interval				
P-value (LOG-RANK)				

** Cox proportional hazard model without adjusting for the stratification factors*

Analysis of IHC - PFS - <Analysed> Set (N = xx)
Evaluation of BMK effect and BMK*treatment interaction for < Parameter> (*cutoff*) – Patients groups based on *Measurement*

Factor	Levels	P-Value[a]	Hazard Ratio[b]	95% CI[b] [Low, High]	Interaction P-Value[c]
Treatment	Arm 1, Arm 2				n/a
BMK	bmk+,bmk-				

[a] Wald Chi-Square Test
[b] Hazard of arm 1 (relative to arm 2) from Cox Regression including terms for all factors shown.
[c] P-value for interaction with treatment.

3.3. Microsatellites

For the following tables and graphs:

- <Analysed> Set (TUMFAS, TUMTR)
- (*): defined by DCR / defined by ORR
- (**): MSS/MSI-L patients / MSI-H patients
- Group: Arm1/Arm2
- Class: Response level

Analysis of microsatellites - <Analysed> Set (N = xx)
MSI status – Description by class– Value at baseline

		Arm 1 (N = xx)	Arm 2 (N = xx)
MSI status group	Nobs		
MSS/MSI-L	n (%)		
MSI-H	n (%)		

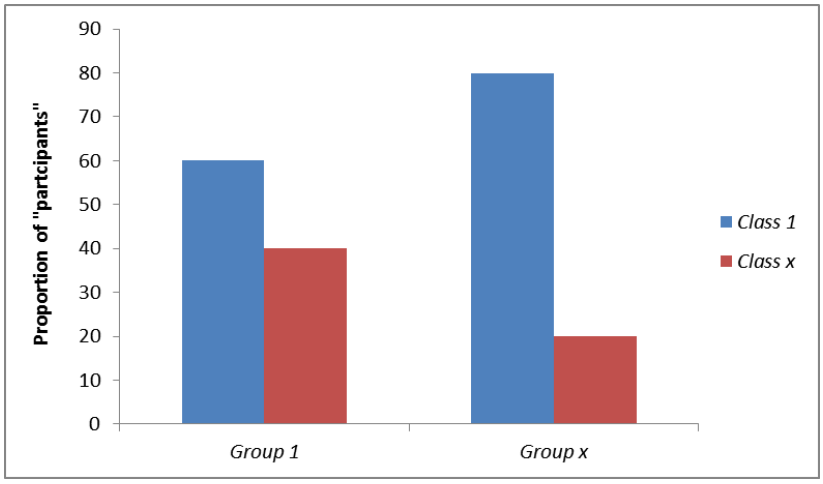
Analysis of microsatellites - <Analysed> Set (N = xx)
For (**) – Comparison between treatment groups according to response (*)

		Arm1 (N = xx)	Arm2 (N = xx)
Descriptive statistics			
Response (*)	Nobs		
Responder	n (%)		
Non responder	n (%)		
Statistical analysis (***)			
Response rate (*)			
	n (%)		
	95% CI (1)		
	p-value (2)		

(1): 95%CI of the estimate using Clopper-Pearson method
(2): Fisher's exact test p-value

***: CI and p-value will be provided only if there are at least 10 MSI-H patients and 5 responding patients in the experimental arm.

Analysis of microsatellites - <Analysed> Set (N = xx)
For (**) – Barplot of response (*)



3.4. Protein-expression by ELISA

For the following tables and graphs:

- *Parameter* : "name of biomarker" "unit"
- *Group* : Arm1/Arm2

Protein expression by ELISA – Serum Full Analysis Set (N = xx)
Description by class – Value at baseline

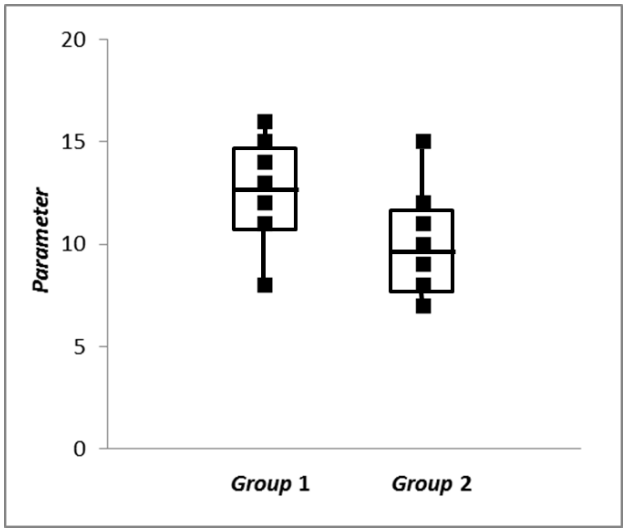
			Arm 1 (N = xx)	Arm 2 (N = xx)
Parameter 1		Nobs		
	Below <lower limit>	n (%)		
	In range	n (%)		
	Above <Upper limit>	n (%)		
Parameter x		Nobs		
	Below <lower limit>	n (%)		
	In range	n (%)		
	Above <Upper limit>	n (%)		

Following table and graphic will be provided if proportion of values In range is >30%.

Protein expression by ELISA – Serum Full Analysis Set (N = xx)
Description – Value at baseline

		Arm 1 (N = xx)	Arm 2 (N = xx)
Parameter 1	n		
	Mean ± SD		
	Median		
	Q1 ; Q3		
	Min ; Max		
Parameter x	n		
	Mean ± SD		
	Median		
	Q1 ; Q3		
	Min ; Max		

Protein expression by ELISA – Serum Full Analysis Set (N = xx)
Parameter **- Boxplot – Value at baseline**



3.5. Consistency of mutation results

For the following tables and graphs:

- *Parameter*: "name of gene" at exon level
- *Mutation*: "name of mutation"
- *Group*: Arm1 / Arm2

Mutation results – Serum Full Analysis Set (N = xx)
Parameter **- In** *group* **(N = xx) - Restricted to patient having local and central values available - Comparison between local and central results**

	Local result				All
	Exon 1	Exon x	Exon Not available	No mutation	
	n (%)	n (%)	n (%)	n (%)	n (%)
Central result					
Exon 1					
Exon x					
Exon Not available					
No mutation					
All					

- *Parameter* : "name of gene" at gene level

Mutation results – Serum Full Analysis Set (N = xx)
Parameter **- Restricted to patient having local and central values available - Comparison between local and central results**

		Arm 1 (n = xx)			Arm 2 (n = xx)			All
		Mutation	Mutation not available	No mutation	Mutation	Mutation not available	No mutation	
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
	Central result							
Arm 1 (n = xx)	Mutation							
	Mutation not available							
	No mutation							
Arm 2 (n = xx)	Mutation							
	No mutation							
	Mutation not available							
	All							

4. SAFETY ANALYSIS

4.1. DLTs

Not applicable.

4.2. Adverse events

- (*) EAE / Serious EAE (with sponsor upgrade)

(*) – Safety Set (N = xx) – Crude incidence by PT
On treatment

PT	Arm 1 (N = xx)			Arm 2 (N = xx)			ALL (N = xx)		
	NEAE	n	%	NEAE	n	%	NEAE	n	%
ALL									
PT - aaaa									
PT – bbab									
PT - abaa									
…									

STD table created using macro %_AE_TAB1

N: Number of patients by arm
NEAE: Number of (*)
*n: Number of patients with at least one (*) / %: (n/N)*100*

EAE – Safety Set (N=xx) – Crude incidence by SOC
On treatment

Primary SOC	Arm 1 (N = xx)			Arm 2 (N = xx)			ALL (N = xx)		
	NEAE	n	%	NEAE	n	%	NEAE	n	%
ALL									
SOC – a									
SOC – b									
SOC – c									
…									

STD table created using macro % AE TAB2

N: Number of patients by arm
NEAE: Number of EAE
*n: Number of patients with at least one EAE / %: (n/N)*100*

For the following table:

- (*) Serious AE (with sponsor upgrade)
  (**) During the study
- (*) EAE / EAE leading to IMP withdrawal / EAE related to IMP or associated agent (with sponsor upgrade) / Serious EAE (with sponsor upgrade) / Severe EAE / *EAE* of interest (hematological toxicities) / Non Serious EAE
  (**) On treatment

(*)- Safety Set (N = xx) - Crude incidence by SOC and PT
(**)

	Arm 1 (N=xx)			**Arm 2 (N=xx)**			**ALL (N=xx)**		
PRIMARY SOC / PT	**(#)**	**n**	**%**	**(#)**	**n**	**%**	**(#)**	**%**	**(#)**
ALL									
SOC - a									
PT – aaaa									
PT – aaab									
…									
SOC - b									
PT – baaa									
PT – baab									
…									

N: Number of patients by arm
(#) Number of (*)
*n: Number of patients with at least one (*) / %: (n/N)*100*

EAE - Safety Set (N = xx) – Distribution by outcome and SOC and PT
On treatment
ALL or Arm 1 or Arm 2 (N = xx)

			RECOVERED/RESOLVED				RECOVERED/RESOLVED WITH SEQUELAE													
	ALL		ALL		RECOVERED/ RESOLVED		RECOVERED/ RESOLVED WITH SEQUELAE		RECOVERING/ RESOLVING		NOT RECOVERED/ NOT RESOLVED		FATAL		UNKNOWN		MISSING	
PRIMARY SOC / PT	**NEAE**	**%**	**NEAE**	**%**	**NEAE**	**%**	**NEAE**	**%**	**NEAE**	**%**	**NEAE**	**%**	**NEAE**	**%**	**NEAE**	**%**	**NEAE**	**%**
ALL		**100.0**																
SOC - a																		
PT – aaaa																		
PT – aaab																		
…																		
SOC - b																		
PT – baaa																		
PT – baab																		
…																		

Latest outcome is considered
N: Number of patients by arm
*NEAE: Number of EAE / %: (NEAE by outcome / Total NEAE)*100*

EAE requiring additional therapy– Safety Set (N = xx) – Crude incidence
On treatment

REQUIRED ADDITIONAL THERAPY	All (N = xx)		
	NEAE	n	%
ALL			
New treatment or increase of on-going trt			
Surgical/medical procedure			

STD table created using macro %_AE_TAB9

A patient can report more than one EAE and can be counted in several class levels
N: Number of patients by arm
NEAE: Number of EAE
*n: Number of patients with at least one EAE / %: (n/N)*100*

EAE by action taken – Safety Set (N = xx) – Crude incidence
On treatment

ACTION TAKEN	All (N = xx)	
	NEAE	%
ALL		100.00
DRUG WITHDRAWN		
DOSE REDUCED		
DOSE NOT CHANGED		
UNKNOWN		
NOT APPLICABLE		
TEMPORARILY INTERRUPTED		
TREATMENT DELAYED		
TREATMENT DELAYED AND REDUCED		
MISSING		

A patient can report more than one EAE and can be counted in several class levels
N: Number of patients by arm
NEAE: Number of EAE
*n: Number of patients with at least one EAE / %: (n/N)*100*
Missing: Action taken is considered as missing if for an EAE, action taken is missing for all episodes

For the following table:

- (*) Summary table of EAE (with sponsor upgrade)

(*) – Safety Set (N = xx) – Crude incidence by SOC and PT
On treatment

ALL or Arm 1 or Arm 2 (N = xx)

	EAE			Severe EAE			Serious EAE			EAE leading to *IMP* withdrawal			EAE related to *IMP*			EAE leading to *IMP* withdrawal and related to study drug			EAE related to bevacizumab		
PRIMARY SOC/PT	**NEAE**	**n**	**%**	**NEAE**	**n**	**%**	**NEAE**	**n**	**%**	**NEAE**	**n**	**%**	**NEAE**	**n**	**%**	**NEAE**	**n**	**%**	**NEAE**	**n**	**%**
ALL																					
SOC - a																					
PT - aaaa																					
PT - aaab																					
…																					
SOC - b																					
PT - baaa																					
PT - baab																					
…																					

STD table created using macro %_AE_TAB10A

N: Number of patients by arm
NEAE: Number of EAE
*n: Number of patients with at least one EAE / %: (n/N)*100*

For the following table:

- (*) Serious EAE (with sponsor upgrade) / Severe EAE (with sponsor upgrade)

Summary table of (*) – Safety Set (N = xx) - Crude incidence by SOC and PT
On treatment

ALL or Arm 1 or Arm 2 (N = xx)

	(*)			(*) leading to IMP withdrawal			(*) related to IMP			(*) leading to IMP withdrawal and related to IMP			(*) related to bevacizumab		
PRIMARY SOC/PT	**NEAE**	**n**	**%**	**NEAE**	**n**	**%**	**NEAE**	**n**	**%**	**NEAE**	**n**	**%**	**NEAE**	**n**	**%**
ALL															
SOC - a															
PT – aaaa															
PT - aaab															
…															
SOC - b															
PT – baaa															
PT – baab															
…															

STD table created using macro %_AE_TAB11A

N: Number of patients by arml
NEAE: Number of EAE
*n: Number of patients with at least one EAE / %: (n/N)*100*

For the following table:

- (*) EAE / EAE leading to IMP withdrawal / EAE related to IMP or associated agent (with sponsor upgrade) / Serious EAE (with sponsor upgrade) / Serious EAE related to IMP or associated agent / *EAE of interest* (hematological toxicities) on treatment

(*) - Safety Set (N=xx) - Distribution of the number of (**) by worst grade
Descriptive statistics by primary system organ class and preferred term on treatment
ALL or Arm 1 or Arm 2 (N = xx)

PRIMARY SOC/PT	WORST GRADE													
	Not graded or missing		Grade 1		Grade 2		Grade 3		Grade 4		Grade 5		Any grade	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
ALL														
SOC - a														
PT – aaaa														
PT - aaab														
…														
SOC - b														
PT – baaa														
PT – baab														

STD table created using macro %_AE_TAB3A/B/C

(**) event/patient
If (**) = patient
N: Number of patients by arm
*n: Number of patients with at least one (*) by worst grade / %: (n/N)*100*
If (**) = event
N: Number of (*) by arm
*n Number of (*) by worst grade / %: (n/N)*100*

Summary table of Serious EAE (EudraCT) – Safety Set (N = xx) - Crude incidence by SOC and PT
On treatment

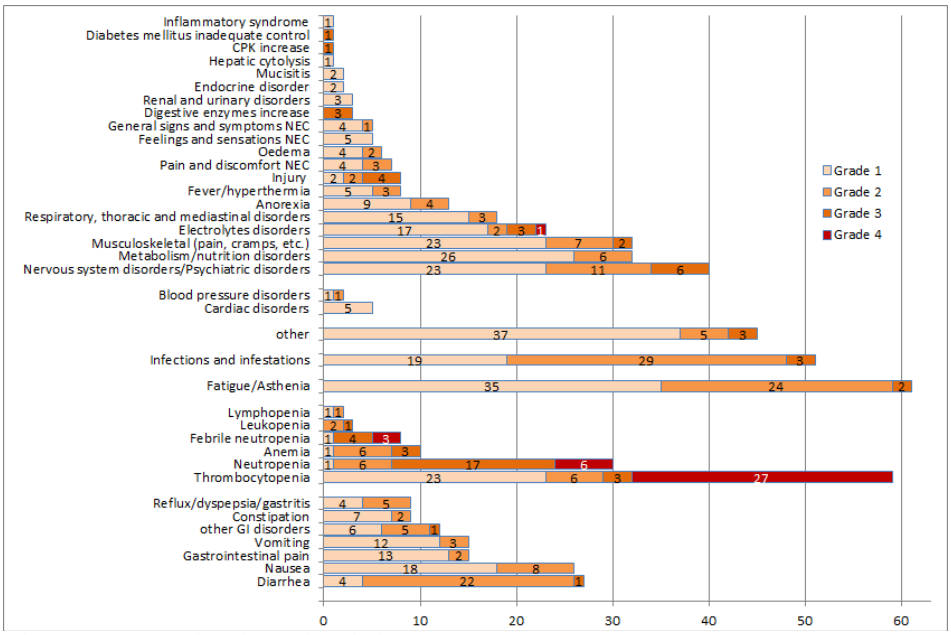
ALL or Arm 1 or Arm 2 (N = xx)

	Serious EAE			Serious EAE related IMP			Serious EAE leading to death			Serious EAE leading to death and related to IMP		
PRIMARY SOC/PT	**NEAE**	**n**	**%**	**NEAE**	**n**	**%**	**NEAE**	**n**	**%**	**NEAE**	**n**	**%**
ALL												
SOC - a												
PT – aaaa												
PT - aaab												
…												
SOC - b												
PT – baaa												
PT – baab												
…												

STD table created using macro %_AE_TAB11A

N: Number of patients by arm
NEAE: Number of EAE
*n: Number of patients with at least one EAE / %: (n/N)*100*
Seriousness according to the investigator or sponsor opinion/ Relation according to investigator opinion

EAE related to (*) - Safety Set (N = xx)
Horizontal bar chart of the ten most frequent events according to the percentage of patients by worst grade and preferred term on treatment
ALL (N = xx)



The x-axis corresponds to the number of adverse events.
For each preferred term grouped by primary system organ class, the number of adverse events by grade will be given.
Preferred terms with at least two events will be defined as the adverse events of interest.

(*)S 95005 or bevacizumab (arm1) / capecitabine or bevacizumab (arm2)

For the following table:

- (*) EAE / Serious EAE (with sponsor upgrade)

(*) – Safety Set (N = xx) – Time to onset by SOC and PT – (°)
On treatment

ALL or Arm1 or Arm 2 (N = xx)

		TIME TO ONSET											
		1st week of cycle 1		*Xth week of cycle 1*		*Cycle 2*		*Cycle 3*		*Cycle 4*		*> Cycle 4*	
PRIMARY SOC/PT	**n**	**nt**	**%**	**nt**	**%**	**nt**	**%**	**nt**	**%**	**nt**	**%**	**nt**	**%**
ALL													
SOC - a													
PT - aaaa													
PT - aaab													
…													
SOC - b													
PT - baaa													
PT - baab													
…													

STD table created using macro %_AE_TAB4

N: number of patients by arm
Time to onset: time between the first study drug intake date and the onset date of the first emergent episode of AE
n: Number of patients with at least one EAE
*nt: Number of patients with their first EAE in the class of time to onset / %: (nt / n)*100*

(°) Arm1/Arm2

4.3. Death

Death - Safety Set (N = xx)
Descriptive statistics during the treatment and follow-up period by treatment arm

		Arm 1 (N = xx)	Arm 2 (N = xx)	ALL (N = xx)
DEATH	Nobs			
YES	n (%) (%)			
NO	n (%)			
DEATH DURING THE TREATMENT PERIOD	Nobs			
YES	n (%) (%)			
NO	n (%)			
DEATH DURING THE FOLLOW-UP PERIOD	Nobs			
YES	n (%)			
NO	n (%)			

Death - Safety Set (N = xx)
Descriptive statistics during the treatment and follow-up period by treatment arm

		Arm 1 (N = xx)	Arm 2 (N = xx)	ALL (N = xx)
CATEGORY OF DEATH	Nobs			
RADIOLOGIC DISEASE PROGRESSION	n (%)			
CLINICAL DISEASE PROGRESSION	n (%)			
TOXICITY	n (%)			
OTHER	n (%)			
NOT COLLECTED	n (%)			

Death - Safety Set (N = xx)
Descriptive statistics by primary system organ class and preferred term during the treatment period

PRIMARY SYSTEM ORGAN CLASS / PREFERRED TERM	Arm 1 (N = xx)		Arm 2 (N = xx)		ALL (N = xx)	
	n	%	n	%	n	%
ALL						
SOC-a						
PT-aaaa						
PT-aaab						
...						
SOC-b						
PT-bbab						
...						

N: Number of patients by arm
*n: Number of patients with at least one fatal AE / %: (n/N)*100*

Death - Safety Set (N = xx)
Listing of patients who died during the treatment period or during the follow-up period

Arm	Patient number	Disoncintuation reason	Reason of death	Period of death	Serious Adverse Event (Preferred Term)	Non-serious Adverse Event with action taken of discontinuation (Preferred Term)

4.4. Clinical laboratory evaluation

For the following table:

- Gradable parameters
  Albumin, Alkaline Phosphatase, Total Bilirubin, Calcium, GGT, Glucose, Potassium, Magnesium, Phosphate, Sodium, AST, ALT, Hemoglobin, WBC, Platelets:
  - Lymphocytes, Neutrophils, Serum creatinine, APTT and INR.
  - - (*) Biochemical parameters / Haematological parameters / Coagulation.
  - - (**) Low Albumin, high Alkaline Phosphatase, high Total Bilirubin, hypercalcemia, hypocalcemia, high GGT, hyperglycemia, hypoglycaemia, hyperkalemia, hypokalemia.
  - hypermagnesemia, hypomagnesemia, hypophosphatemia, hyponatremia, hypernatremia, high AST, high ALT, high haemoglobin, anemia, leucocytosis, low WBC, low platelets, high lymphocyte, low lymphocyte, low Neutrophils, high creatinine, aPTT prolonged/high aPTT and high INR.
  - (***) Change from baseline to the worst value.

(*): (**) - Safety set (N = xx) - Shift table of worst values on treatment according to baseline using grades

ALL or Arm 1 or Arm 2 (N = xx)

		On treatment											
	Arm (N = xx)	**Grade 0 (1)**		**Grade 1 (2)**		**Grade 2 (3)**		**Grade 3 (4)**		**Grade 4 (5)**		**All (6)**	
		n	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Baseline	**Grade 0**												
	Grade 1												
	Grade 2												
	Grade 3												
	Grade 4												
	Any grade												
	Missing												
	All												(100.0)

(1) Nb and % of patients with a worst grade = 0 on treatment
(2) Nb and % of patients with a worst grade = 1 on treatment
(3) Nb and % of patients with a worst grade = 2 on treatment
(1) Nb and % of patients with a worst grade = 3 on treatment
(5) Nb and % of patients with a worst grade = 4 on treatment
(6) Nb and % of patients with at least one value on treatment post-inclusion
*% = n/N*100*

(*): (**) - Safety set (N = xx) – (***) under treatment

		Arm 1 (N = xx)	Arm 2 (N = xx)	All (N = xx)
Overall	Nobs			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			

(*): (**) - Safety set (N = xx) – Descriptive statistics

		Arm 1 (N = xx)	Arm 2 (N = xx)	All (N = xx)
Value at baseline	Nobs			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
Grade 0	n (%)			
Grade 1	n (%)			
Grade 2	n (%)			
Grade 3	n (%)			
Grade 4	n (%)			
Value at planned post-baseline visit 1	Nobs			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
Grade 0	n (%)			
Grade 1	n (%)			
Grade 2	n (%)			
Grade 3	n (%)			
Grade 4	n (%)			
Value at planned post-baseline visit X	Nobs			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
Grade 0	n (%)			
Grade 1	n (%)			
Grade 2	n (%)			
Grade 3	n (%)			
Grade 4	n (%)			

For the following table:

- Non-gradable parameters:
  Chloride, LDH, Total Protein, Basophils, Eosinophils, Hematocrit, Monocytes, RBC, Bicarbonate, BUN and creatinine clearance:
  - - (*) Biochemical parameters / Haematological parameters / Coagulation.
  - - (**) high chloride, low chloride, high LDH, high Proteins, low total proteins, low Basophils, high Eosinophils, low Haematocrit, high Haematocrit, high Monocytes, high RBC, low RBC, low Bicarbonate, high Bicarbonate, high BUN and creatinine clearance.
  - (***) Change from baseline to worst value.

(*): (**) - Safety set (N = xx) - Shift table of worst values on treatment according to baseline using reference ranges

		On treatment							
	Arm (N=xx)	**< LL (1)**		**[LL-UL] (2)**		**> UL (3)**		**All (4)**	
		n	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Baseline	**< LL**								
	[LL-UL]								
	> UL								
	Missing								
	All								(100.0)

STD table created using macro %_LB_TAB5

(1) Nb and % of patients with a worst value < LL on treatment
(2) Nb and % of patients with a worst value in [LL-UL] on treatment
(3) Nb and % of patients with a worst value > UL on treatment
(4) Nb and % of patients with at least one value on treatment post-inclusion
*% = n/N*100*

Note: For some parameters, one single type of abnormality will be presented depending on the interest (High abnormality or Low abnormality) (ex: AST, ALT, Cholesterol...). When both types of abnormality are of interest, two tables need to be produce, one for each abnormality (e.g. Hypokalemia, Hyperkalemia)

Biochemical parameter: Creatinine clearance - Safety set (N = xx) - Shift table of worst values on treatment according to baseline using reference ranges

		Worst value on treatment									
	ALL (N = xx)	**normal (1)**		**mild (2)**		**moderate (3)**		**severe (4)**		**All (5)**	
		n	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Baseline	**normal**										
	mild										
	moderate										
	severe										
	missing										
	All										(100.0)

STD table created using macro %_LB_TAB5

(1) Nb and % of patients with a worst value normal on treatment
(2) Nb and % of patients with a worst value mild on treatment
(3) Nb and % of patients with a worst value moderate on treatment
(4) Nb and % of patients with a worst value severe on treatment
(5) Nb and % of patients with at least one value on treatment post-baseline
*% = n/Nb of patients with at least one available post-baseline value on treatment*100*

(*): (**) - Safety set (N = xx) – (***) under treatment

		Arm 1 (N = xx)	Arm 2 (N = xx)	All (N = xx)
Overall	Nobs			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			

(*): (**) - Safety set (N = xx) – Descriptive statistics

		Arm 1 (N = xx)	Arm 2 (N = xx)	All (N = xx)
Value at Baseline	Nobs			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
< LL	n (%)			
LL-UL]	n (%)			
> UL	n (%)			

For the following table:

- Urinalysis parameters:
  - (**)Proteinuria, Glucosuria, Urobilinogen, Haematuria, Leucocyturia.
  - (***) Change from baseline to worst value.

Urinalysis: (**) - Safety set (N = xx) - Shift table of worst values on treatment according to baseline using reference ranges

ALL or Arm 1 or Arm 2 (N = xx)

		On treatment							
Arm (N = xx)		**Negative (1)**		**Trace (2)**		**Positive (3)**		**All (4)**	
		n	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Baseline	**Negative**								
	Trace								
	Positive								
	Missing								
	All								(100.0)

STD table created using macro %_LB_TAB5

(1) Nb and % of patients with a worst value negative on treatment
(2) Nb and % of patients with a worst value trace on treatment
(3) Nb and % of patients with a worst value positive on treatment
(4) Nb and % of patients with at least one value on treatment post-inclusion
*% = n/N*100*

Urinalysis - Safety set (N = xx) - Shift table of worst values positive on treatment according to baseline (**)

ALL (N = xx)		Worst value positive on treatment							
		+ (1)		++ (1)		++ (1)		All (2)	
		n	(%)	n	(%)	n	(%)	n	(%)
Baseline	+								
	++								
	+++								
	Missing								
	All								(100.0)

(1) Nb and % of patients with a worst value positive on treatment
(2) Nb and % of patients with at least one value on treatment post-baseline
*% = n/Nb of patients with at least one available post-baseline value on treatment*100*

(*): (**) - Safety set (N = xx) – (***) under treatment

		Arm 1 (N = xx)	Arm 2 (N = xx)	All (N = xx)
Overall	Nobs			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			

Urinalysis: (**) - Safety set (N = xx) – Descriptive statistics

		Arm 1 (N = xx)	Arm 2 (N = xx)	All (N = xx)
Value at Baseline	Nobs			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
Negative	n (%)			
Trace	n (%)			
Positive	n (%)			

- Tumor markers (CEA)
  - (***) Relative change from baseline to worst value

Tumor markers: (CEA) - Safety set (N = xx) - Shift table of worst values on treatment according to baseline

ALL or Arm 1 or Arm 2 (N = xx)

		On treatment					
	Arm (N = xx)	**Normal (1)**		**Abnormal (2)**		**All (3)**	
		n	**(%)**	**n**	**(%)**	**n**	**(%)**
Baseline	**Normal**						
	Abnormal						
	Missing						
	All						

(1) Nb and % of patients with a worst value normal on treatment
(2) Nb and % of patients with a worst value abnormal on treatment
(3) Nb and % of patients with at least one value on treatment post-inclusion
*% = n/N*100*

Tumor markers: (CEA) - Safety set (N = xx) – (***) under treatment

		Arm 1 (N = xx)	**Arm 2 (N = xx)**	**All (N = xx)**
Overall	Nobs			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			

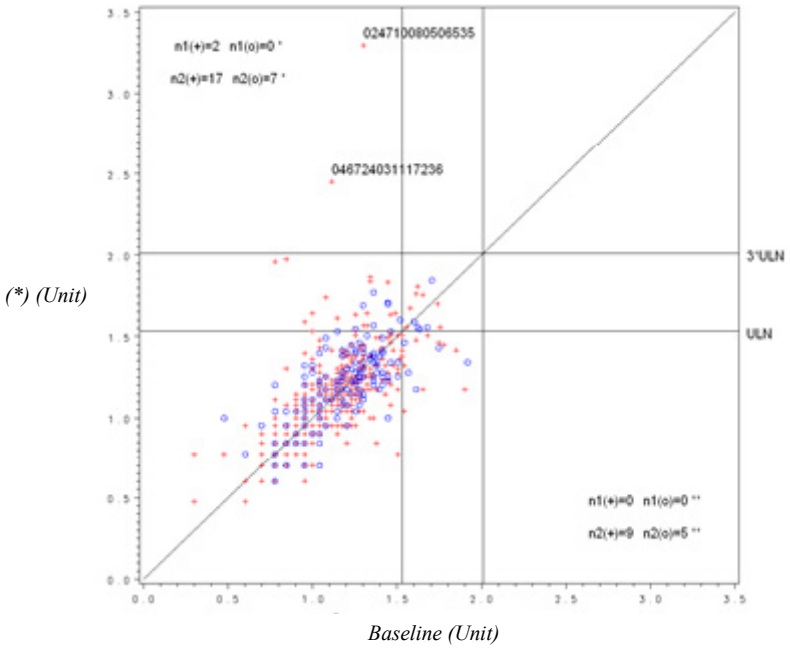
Tumor markers: (CEA) - Safety set (N = xx) – Descriptive statistics

		Arm 1 (N = xx)	**Arm 2 (N = xx)**	**All (N = xx)**
Baseline	Nobs			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
Normal	n (%)			
Abnormal	n (%)			

For the following tables:

- Parameters of special interest:
  - (*) Haemoglobin, neutrophils, platelets, low WBC, bilirubin, ASAT, ALAT, creatinine clearance, serum creatinine and proteinuria.

(*) - Safety set (N = xx) - Scatter plot, value on treatment according to baseline



o Arm 1 (N= XX) o Arm 2 (N = XX)

(**) worst value on treatment

Safety set (N = xx)

Days to Most Extreme Value and Magnitude of Nadir for Laboratory Parameters of Interest With Grade 3 or 4 Abnormalities, or with moderate or severe renal impairment (for creatinine clearance) that Worsened from baseline by at Least One Grade or level of impairment (for creatinine clearance)

Parameter	Cycle	Group	Days to Nadir[a]				Value for Nadir			
			N[b]	Mean (SD)	Median	(Min, Max)	N[b]	Mean (SD)	Median	(Min, Max)
Haemoglobin high (g/L)	1	Arm1								
		Arm2								
	…									
	All	Arm1								
		Arm2								
Haemoglobin low (g/L)	1	Arm1								
		Arm2								
	…									
	All	Arm1								
		Arm2								
Neutrophils (10E9/L)	1	Arm1								
		Arm2								
	…									
	All	Arm1								
		Arm2								

[a] *Days reflect cycle days (from start of cycle indicated) for cycles 1 - 4 and study days (from start of cycle 1) for All cycles.*
[b] *Patients with a Grade 3 or 4 value, or with moderate or several renal impairment (for creatinine clearance), recorded any time after first dose that worsened from baseline by at least one grade, or level of impairment (for creatinine clearance) (or had a missing baseline). In the event a patient had the same nadir at multiple times for a cycle, the first occurrence was selected.*

Safety set (N = xx)

Days to Most Extreme Value and Magnitude of Nadir for Laboratory Parameters of Interest With Grade 3 or 4 Abnormalities, or with moderate or severe renal impairment (for creatinine clearance) that Worsened from baseline by at Least One Grade or level of impairment (for creatinine clearance)

Parameter	Cycle	Group	Days to Nadir[a]				Value for Nadir			
			N[b]	Mean (SD)	Median	(Min, Max)	N[b]	Mean (SD)	Median	(Min, Max)
Platelets (10E9/L)	1	Arm1								
		Arm2								
	…									
	All	Arm1								
		Arm2								
Leukocytis (10E9/L)	1	Arm1								
		Arm2								
	…									
	All	Arm1								
		Arm2								
Bilirubin (µmol/L)	1	Arm1								
		Arm2								
	…									
	All	Arm1								
		Arm2								
ASAT (IU/L)	1	Arm1								
		Arm2								
	…									
	All	Arm1								
		Arm2								
ALAT (IU/L)	1	Arm1								
		Arm2								
	…									
	All	Arm1								
		Arm2								
Creatinine clearance (mL/min)	1	Arm1								
		Arm2								
	…									
	All	Arm1								
		Arm2								
Serum creatinine (mmol/L)	1	Arm1								
		Arm2								
	…									
	All	Arm1								
		Arm2								

[a] Days reflect cycle days (from start of cycle indicated) for cycles 1 - 4 and study days (from start of cycle 1) for All cycles.
[b] Patients with a Grade 3 or 4 value, or with moderate or several renal impairment (for creatinine clearance), recorded any time after first dose that worsened from baseline by at least one grade, or level of impairment (for creatinine clearance) (or had a missing baseline). In the event a patient had the same nadir at multiple times for a cycle, the first occurrence was selected.

Safety set (N = xx)

Recovery from the most extreme value for laboratory parameters of interest with grade 3 or 4 abnormalities, or moderate or severalimpairment (for creatinine clearance) that worsened from baseline by at least one grade or level of impairment (for creatinine clearance)

Parameter	Group	Grade 3 or 4 N[a]	Patients with non-censored data n (%)[b]	Days to recovery: Median(min,max)[c]
Haemoglobin high (g/L)	Arm 1			
	Arm 2			
Haemoglobin low (g/L)	Arm 1			
	Arm 2			
Neutrophils (10E9/L)	Arm 1			
	Arm 2			
Platelets (10E9/L)	Arm 1			
	Arm 2			
Low WBC (10E9/L)	Arm 1			
	Arm 2			
Bilirubin (µmol/L)	Arm 1			
	Arm 2			
ASAT (IU/L)	Arm 1			
	Arm 2			
ALAT (IU/L)	Arm 1			
	Arm 2			
Creatinine clearance (mL/min)	Arm 1			
	Arm 2			
Serum creatinine (mmol/L)	Arm 1			
	Arm 2			

[a] Patients with a Grade 3 or 4 value, or with moderate or several renal impairment(for creatinine clearance), recorded any time after first dose that worsened from baseline by at least one grade, or level of impairment(for creatinine clearance) (or had a missing baseline).

[b] Non-censored = patients who recovered (had a least one measurement recorded after the nadir that had grade <2 or <= the baseline grade, or that had mild or normal renal impairment (for creatinine clearance)).

[c] Median days are obtained from Kaplan-Meier estimates that allows for inclusion of patients that did not recover (censored at last subsequent values recorded). Minimum and Maximum values may come from actual observed recovery times or from censoredobservations.

4.5. Vital signs and clinical examination

Vital signs - Safety Set (N = xx)
ECOG - Descriptive statistics at baseline

		Arm 1 (N = xx)	Arm 2 (N = xx)	ALL (N = xx)
BASELINE	Nobs			
0	n (%)			
1	n (%)			
2	n (%)			
3	n (%)			
4	n (%)			

For the following 2 tables:

- (*): SBP (mmHg), DBP (mmHg), Heart rate (bpm) / Weight (kg) / BSA (m²), Temperature (°C), Respiratory rate (breaths/min).

Vital signs - Safety Set (N = xx)
(*) - Descriptive statistics under treatment

		Arm 1 (N = xx)	Arm 2 (N = xx)	ALL (N = xx)
BASELINE	Nobs			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
(*)				
Level 1				
Level 2				
.....				
Level k				
WORST (lowest value)	Nobs			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
(*)				
LEVEL 1	n (%)			
LEVEL 2	n (%)			
.....				
LEVEL K	n (%)			
WORST (highest value)	Nobs			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
(*)				
Level 1	n (%)			
Level 2	n (%)			
.....				
Level k	n (%)			

(**): for SBP, DBP and Heart rate only

Vital signs - Safety Set (N = xx)
(*) - Descriptive statistics on change from baseline to worst value under treatment

		Arm 1 (N = xx)	Arm 2 (N = xx)	ALL (N = xx)
WORST (lowest) - BASELINE	Nobs			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
WORST (highest) - BASELINE	Nobs			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			

For the following table:

- (*): SBP (mmHg) / DBP (mmHg) / Heart rate (bpm) / ECOG

Vital signs - Safety set (N = xx)
(*) - Descriptive statistics on worst value according to baseline by classes
ALL or Arm 1 or Arm 2 (N = xx)

		Worst				
		LEVEL 1	LEVEL 2	....	LEVEL K	All
BASELINE	LEVEL 1	n (%)				
	LEVEL 2					
	...					
	LEVEL K					
	Missing					
	All					Nobs (100%)

Worst: Worst post-baseline value under treatment
Worst lowest and worst highest for SBP, DBP and Heart rate
Nobs = Total number of patients with at least one post-baseline value under treatment

4.6. Electrocardiogram

ECG - Safety Set (N = xx)
Descriptive statistics at withdrawal visit

		Arm 1 (N = xx)	Arm 2 (N = xx)	ALL (N = xx)
PRESENCE OF CLINICALLY SIGNIFICANT ECG ABNORMALITY	n (%)			
RR interval (msec)	Nobs			
≤ 450 ms	n (%)			
]450;480 ms]	n (%)			
]480;500 ms]	n (%)			
> 500 ms	n (%)			
ABSOLUTE PROLONGATION OF UNCORRECTED QT				
≤ 450 ms	n (%)			
]450;480 ms]	n (%)			
]480;500 ms]	n (%)			
> 500 ms	n (%)			
CHANGE OF UNCORRECTED QT				
≤ 30 ms	n (%)			
]30;60] ms	n (%)			
> 60 ms	n (%)			

ECG - Safety Set (N = xx)
List of clinically significant ECG abnormalities at withdrawal visit

Arm	Patient	Cycle	Analysis date	Analysis value	Clinically significant ECG abnormalies?

4.7. LVEF

Not applicable.

5. QOL

Quality of life – Quality of life Set 30 (N = xx) – QLQ-C30
Response time from 1st intake to each timepoint

Timepoint		**Arm 1 (N = xx)**	**Arm 2 (N = xx)**	**All (N = xx)**
Baseline	Nobs			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
12 weeks	Nmissing			
	Nnon evaluable			
	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
24 weeks	Nmissing			
	Nnon evaluable			
	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
…..	Nmissing			
	Nnon evaluable			
	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			

* Analyses are done on evaluable questionnaires (more than 2/3 of the questions answered at the timepoint)

Quality of life – Quality of life Set 29 (N = xx) – QLQ-C29
Response time from 1st intake to each timepoint

Timepoint		**Arm 1 (N=xx)**	**Arm 2 (N=xx)**	**All (N=xx)**
Baseline	Nobs			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
12 weeks	Nmissing			
	Nnon evaluable			
	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
24 weeks	Nmissing			
	Nnon evaluable			
	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
…..	Nmissing			
	Nnon evaluable			
	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			

* Analyses are done on evaluable questionnaires (more than 2/3 of the questions answered at the timepoint)

Quality of life – Quality of life Set 30 (N = xx) – QLQ-C30
Descriptive statistics of the score at baseline

		Arm 1 (N = xx)	**Arm 2 (N = xx)**	**All (N = xx)**
Global health status (QL2)	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
Physical functioning (PF2)	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
Role functioning (RF2)	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
Emotional functioning (EF)	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
Cognitive functioning (CF)	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
Social functioning (SF)	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
Fatigue	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
Nausea and vomiting	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			

*Analyses are done on evaluable questionnaires (more than 2/3 of the questions answered at the timepoint)

Quality of life – Quality of life Set 30 (N = xx) – QLQ-C30
Descriptive statistics of the score at baseline (Cont'd)

		Arm 1 (N = xx)	**Arm 2 (N = xx)**	**All (N = xx)**
Pain	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
Dyspnoea	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
Insomnia	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
Appetite loss	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
Constipation	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
Diarrhoea	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
Financial difficulties	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			

* Analyses are done on evaluable questionnaires (more than 2/3 of the questions answered at the timepoint)

Quality of life – Quality of life Set 29 (N = xx) – QLQ-CR29
Descriptive statistics of the score at baseline

		Arm 1 (N = xx)	**Arm 2 (N = xx)**	**All (N = xx)**
Body image	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
Anxiety	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
Sexual function men	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
Sexual function women	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
Urinary frequency	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
Blood and mucus in stool	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
Stool frequency	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
Urinary incontinence	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			

*Analyses are done on evaluable questionnaires (more than 2/3 of the questions answered at the timepoint)

Quality of life – Quality of life Set 29 (N = xx) – QLQ-CR29
Descriptive statistics of the score at baseline (Cont'd)

		Arm 1 (N = xx)	**Arm 2 (N = xx)**	**All (N = xx)**
Dysuria	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
Abdominal pain	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
Buttock pain	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
Bloated feeling	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
Dry mouth	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
Hair loss	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
Trouble with taste	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
Weight	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			

*Analyses are done on evaluable questionnaires (more than 2/3 of the questions answered at the timepoint)

Quality of life – Quality of life Set 29 (N = xx) – QLQ-CR29
Descriptive statistics of the score at baseline (Cont'd)

		Arm 1 (N = xx)	**Arm 2 (N = xx)**	**All (N = xx)**
Flatulence	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
Faecal incontinence	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
Sore skin	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
Embarrassed by bowel movement	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
Stoma care problems	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
Impotence	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
Dyspareunia	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			

*Analyses are done on evaluable questionnaires (more than 2/3 of the questions answered at the timepoint)

Quality of life – Quality of life Set 30 (N = xx) – QLQ-C30
Change of the score from baseline to (*)

		Arm 1 (N = xx)	**Arm 2 (N = xx)**	**All (N = xx)**
Global health status (QL2)	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
Physical functioning (PF2)	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
Role functioning (RF2	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
Emotional functioning (EF)	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
Cognitive functioning (CF)	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
Social functioning (SF)	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
Fatigue	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
Nausea and vomiting	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			

Quality of life – Quality of life Set 30 (N = xx) – QLQ-C30
Change of the score from baseline to (*) (Cont'd)

		Arm 1 (N = xx)	**Arm 2 (N = xx)**	**All (N = xx)**
Pain	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
Dyspnoea	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
Insomnia	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
Appetite loss	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
Constipation	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
Diarrhoea	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
Financial difficulties	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			

(*) timepoint = xxxx / yyyy / …
*Analysis are done on evaluable questionnaires (more than 2/3 of the questions answered at the timepoint)

Quality of life – Quality of life Set 29 (N = xx) – QLQ-CR29
Change of the score from baseline to (*)

		Arm 1 (N = xx)	**Arm 2 (N = xx)**	**All (N = xx)**
Body image	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
Anxiety	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
Sexual function men	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
Sexual function women	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
Urinary frequency	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
Blood and mucus in stool	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
Stool frequency	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			

(*) timepoint = / xxxx / yyyy / …
*Analysis are done on evaluable questionnaires (more than 2/3 of the questions answered at the timepoint)

Quality of life – Quality of life Set 29 (N = xx) – QLQ-CR29
Change of the score from baseline to (*) (Cont'd)

		Arm 1 (N = xx)	Arm 2 (N = xx)	All (N = xx)
Urinary incontinence	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
Dysuria	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
Abdominal pain	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
Buttock pain	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
Bloated feeling	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
Dry mouth	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
Hair loss	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			

(*) timepoint = / xxxx / yyyy / …
*Analysis are done on evaluable questionnaires (more than 2/3 of the questions answered at the timepoint)

Quality of life – Quality of life Set 29 (N = xx) – QLQ-CR29
Change of the score from baseline to (*) (Cont'd)

		Arm 1 (N = xx)	**Arm 2 (N = xx)**	**All (N = xx)**
Trouble with taste	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
Weight	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
Flatulence	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
Faecal incontinence	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
Sore skin	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
Embarrassed by bowel movement	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
Stoma care problems	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			

(*) timepoint = / xxxx / yyyy / …
*Analysis are done on evaluable questionnaires (more than 2/3 of the questions answered at the timepoint)

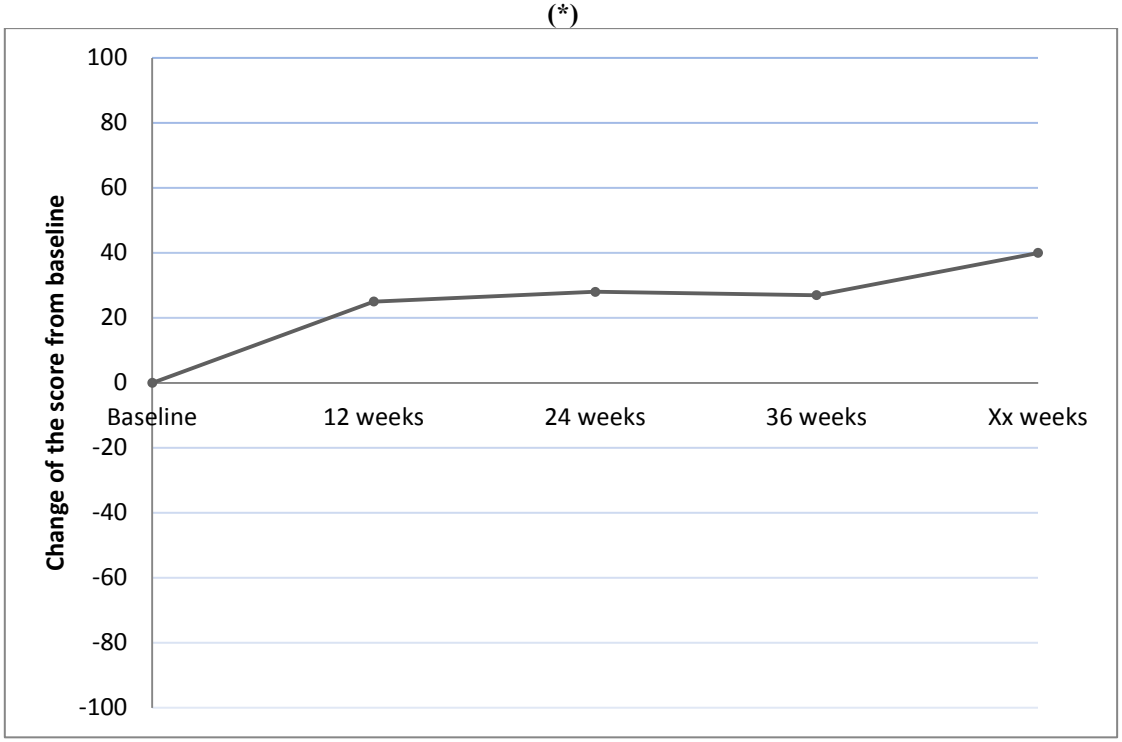
Quality of life – Quality of life Set 29 (N = xx) – QLQ-CR29
Change of the score from baseline to (*) (Cont'd)

		Arm 1 (N = xx)	Arm 2 (N = xx)	All (N = xx)
Impotence	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			
Dyspareunia	Nevaluable*			
	Mean ± SD			
	Median			
	Q1 ; Q3			
	Min ; Max			

(*) timepoint = / xxxx / yyyy / …
*Analysis are done on evaluable questionnaires (more than 2/3 of the questions answered at the timepoint)

- Scales of QLQ-30:
  - (*) Global health status (QL2), Physical functioning (PF2), Role functioning (RF2), Emotional functioning(EF), Cognitive functioning (CF), Social functioning (SF) , Fatigue, Nausea and vomiting, Pain, Dyspnoea, Insomnia, Appetite loss, Constipation, Diarrhoea, Financial difficulties scores.

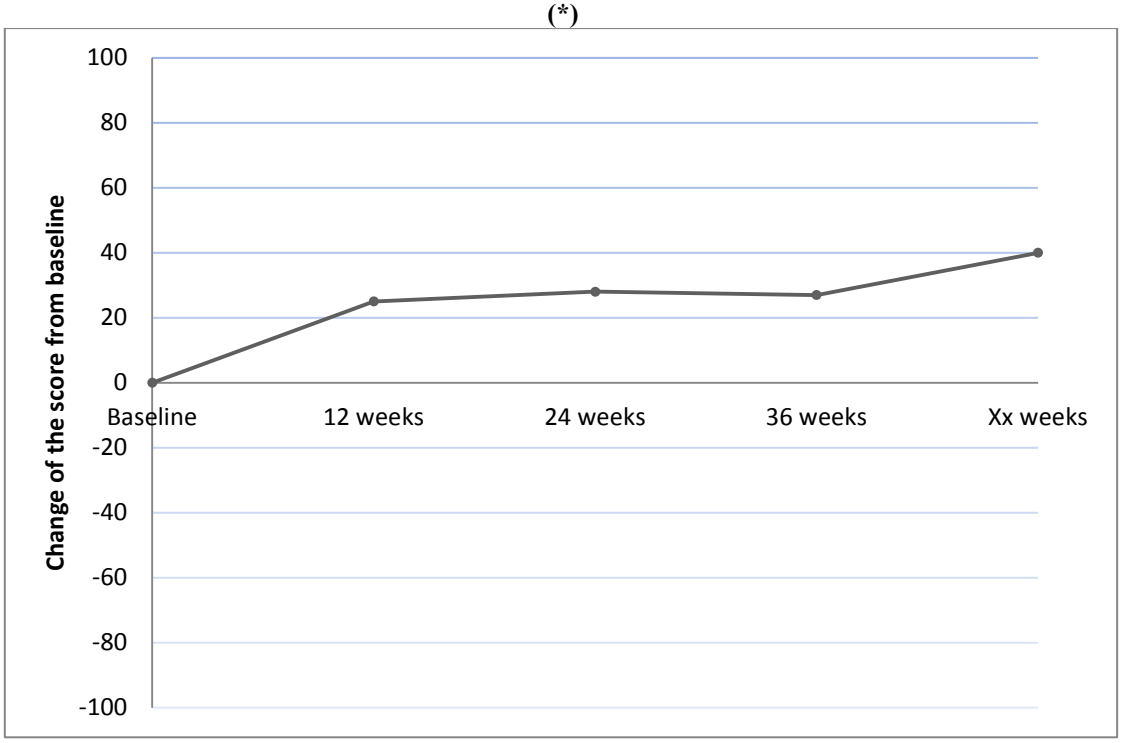
Quality of life – Quality of life Set 30 (N = xx) – QLQ-C30
Mean change of the score from baseline to each timepoint (*)



Analysis are done on evaluable questionnaires (more than 2/3 of the questions answered at the timepoint)

- Scales of QLQ-29
  - (*) Body image, Anxiety, Sexual function men, Sexual function women, Urinary frequency, Blood and mucus in stool, Stool frequency, Urinary incontinence, Dysuria, Abdominal pain, Buttock pain, Bloated feeling, Dry mouth, Hair loss, Trouble with taste, Weight, Flatulence, Faecal incontinence, Sore skin, Embarrassed by bowel movement, Stoma care problems, Impotence, Dyspareunia.

Quality of life – Quality of life Set 29 (N = xx) – QLQ-C29
Mean change of the score from baseline to each timepoint
(*)



Analysis are done on evaluable questionnaires (more than 2/3 of the questions answered at the timepoint)