SANOFI

STATISTICAL ANALYSIS PLAN (FINAL AMENDED #3)
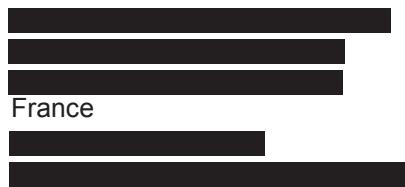
AFLIB_C_06097 A Multicenter, Single arm, Open Label Clinical Trial to Evaluate the Safety and Health-Related Quality of Life of Aflibercept in Patients with Metastatic Colorectal Cancer (mCRC) Previously Treated with an Oxaliplatin-Containing Regimen

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

5-FU	5-Fluorouracil
AE	Adverse Event
ALT (SGPT)	Alanine Aminotransferase (or Serum Glutamate-Pyruvate Transferase)
AST (SGOT)	Aspartate Aminotransferase (or Serum Glutamate-Oxaloacetate Transferase)
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CI	Confidence Interval
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
ECOG	Eastern Cooperative Oncology Group
FUP	Follow-up
FOLFIRI	Irinotecan/bolus-infusion-5-Fluorouracil/Leucovorin
HBP	High Blood Pressure
HLGT	High-level group term
HLT	High-level term
HRQL	Health-Related Quality of Life
HUS	Hemolytic Uremic Syndrome
INR	International Normalized Ratio
IMP	Investigational Medicinal Product
IV	Intravenous
LDH	Lactate Dehydrogenase
LLT	Lower-level term
LV	Leucovorin
mCRC	Metastatic Colorectal Cancer
MedDRA	Medical Dictionary for Regulatory Activities
MID	Minimal Important Difference
NCI	National Cancer Institute
PS	Performance Status
PT	Preferred term

QoL	Quality of Life
RPLS	Reversible posterior leukoencephalopathy syndrome
SOC	System organ class
SAP	Statistical Analyses Plan
SD	Standard Deviation
TMA	Thrombotic micro-angiopathy
ULN	Upper Limit of Normal
UPCR	Urinary Protein-Creatinine Ratio
WHO-DD	World Health Organization-Drug Dictionary
WBC	White Blood Cell

1   OVERVIEW AND INVESTIGATIONAL PLAN

This statistical analysis plan (SAP) provides a comprehensive and detailed description of strategy and statistical technique to be used to realize the analysis of data for aflibercept (AVE0005) study protocols AFLIB_C_06097 (ASQoP) and AFLIB_L_06266 (AFEQT).

1.1   STUDY DESIGN AND RANDOMIZATION

The study **AFLIB_C_06097** is a prospective, phase IIIb/IV, international, multicenter, single arm and open-label study to evaluate the safety and Health-Related Quality of life of aflibercept in patients with metastatic colorectal cancer (mCRC) previously treated with an oxaliplatin-containing regimen.

It is planned to include a total of about 900 patients, from around 150 investigational sites, over about 20 months of accrual.

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These two studies has the same design (patients, visit schedules and treatment) , the same way of collecting data (eCRF) and the same statistical analyses.

1.2   OBJECTIVES

1.2.1   Primary objectives

The objective of study **AFLIB_C_06097** is to document the aflibercept overall safety in the mCRC patients (similar to the ones evaluated in the VELOUR phase III trial) while providing the patients and investigators with access to aflibercept, prior to its marketing authorisation and/or commercial availability.

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1.2.2 Secondary objectives

To document the Health-Related Quality of Life (HRQL) of aflibercept in the same patient population.

1.3 DETERMINATION OF SAMPLE SIZE

No formal sample size calculation has been done. The Safety analyses of this study will be descriptive in nature, and the table below provides the precision (95% CI) associated to a variety of AE event rates for a targeted sample size of 900 [AFLIB_C_06097] /▬▬▬▬▬▬▬▬▬▬] patients:

Overall sample size	p=10%	p=20%	p=30%	p=40%	p=50%
900	[8.0%; 12.0%]	[17.4%; 22.6%]	[27.0%; 33.0%]	[36.8%; 43.2%]	[46.7%; 53.3%]
▬	▬	▬	▬	▬	▬

1.4 STUDY PLAN

The study **AFLIB_C_06097** is started in the second quarter of 2012 in Europe and in the United States, simultaneously or sequentially in the other involved countries.

In each country (except UK and Germany) patient recruitment will end when aflibercept (ZALTRAP) becomes commercially available (i.e. accessible to the patient as per each country regulation). In the UK, study accrual will be terminated when the anticipated number of patients has been achieved across all study sites. In Germany, the recruitment will stop at the end of global study in others countries.

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Patients will be considered screened upon signing the Informed Consent Form (ICF). Baseline period will correspond to the timeframe between the signature of ICF and the first study treatment administration (either Aflibercept or FOLFIRI). The treatment period will consist of 2-week treatment cycles, and will start at first product infusion.

Each patient will be treated until disease progression, unacceptable toxicity, death, Investigator's decision or patient's refusal for further treatment (whichever comes first). The patients will be followed-up during treatment and for at least 30 days after last study treatment administration (either aflibercept or FOLFIRI) administration (for safety assessment). Beyond this date all ongoing SAEs (regardless of relationship with study treatment) as well as ongoing related AEs and new SAEs, that are considered to be related to study treatment, will have to be collected and

followed till resolution/stabilization (stabilization being defined as an event ongoing without any change for at least 3 months).

Health related quality of life evaluation will be performed using the following questionnaires
- o EORTC QLQ-C30 (version 3);
- o EORTC QLQ CR29 (disease specific supplement to QLQ-C30) - optional;
- o EQ-5D^{TM}

Baseline assessment should be obtained from all patients. All the questionnaires will be administered within 3 days prior to the first treatment administration, but in any case before the patient is given the first dose. While on treatment assessments should occur before the treatment administration at the beginning of every odd cycle starting from cycle 3 (day 1 of cycle 3, 5, etc) and at the end of treatment visit. Data will be collected in a patient booklet separated from the e-CRF

Laboratory data (hematology, biochemistry, urinalysis) and vital signs will be collected at baseline and at each cycle.

For more information, see study flowchart of the Protocols.

A summary is presented here below.

Evaluation	Baseline		Treatment		Post-treatment FUP
			Every cycle	End of Treatment (EOT) (30 days after last aflibercept treatment)	
Informed consent	X				
Inclusion/exclusion criteria	X				
Demography	X	I			
Prior Medical/Surgical History & Cancer History, Prior Medication History	X	N C L U S I O N			
Clinical examination	X		X	X	
Hematology (a)	X		X		
Biochemistry (b)	X		X		
Urinalysis (c)	X		X		
Concomitant medication (d)			X	X	
Aflibercept + FOLFIRI (e)			Every 2 weeks (within 3 days from inclusion)		
AE / SAE (f)	X		X	X	X
Health-Related Quality of Life (g) EORTC- QLQ C30/ QLQ-CR29*/ EQ-5D^{TM}	X		X (every odd cycle starting from C3)	X	

1.5   MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL

Changes between the statistical section of the protocol and the present SAP are listed below.

Table 1 – Changes in the statistical section of the protocol

SAP version number	Date approved	Rationale	Description of statistical changes
1	26-Sep-2012	Clarification	Health related quality of life analysis will be performed in the patients, **who have signed the informed consent form and** who completed the questionnaires at baseline and at least one assessment post baseline and have received at least part of one dose of study treatment.
		Upgrade of version	NCI CT version 4.0 to 4.03
2	11-Dec-2012	Definition of the safety population in the context of interim analyses	See section 1.6.1, modification 1
		Definition of the emergence period in the context of interim analyses	See section 1.6.1, modification 1
3		Clarification of variables for extent study treatment exposure	See Section 1.6.2,
		Clarification of the QoL population	See Section 1.6.2
		Clarification of classification according to prior anticancer therapies received	
		Handling of relapse date and adverse event end dates incomplete	
		Files used to build tables concerning AE grouping	
		Clarification on laboratory analysis	
		G-CSF presentation	
		Adverse events clarifications	
		Updates on appendices F and G	
		Reasons of permanent and premature discontinuation	

1.6 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN

1.6.1 Modifications to version 1 made in version 2

1. Given the short time between the cutoff date and the planned date of database lock, the data cleaning process will be only possible for data collected before the cutoff date. Thus, Adverse Events will be analyzed only in cycles that are completed before cutoff date (completed means that administration of next cycle or end of study visit or death, occurred before or at time of cutoff date). In this purpose, the definition of safety population and the emergence period for AE will be modified in the context of interim analyses (sections 3.1 and 3.2):

- for interim analyses, safety population will be defined as the patients who have signed the informed consent form, who received at least part of one dose of study treatment (either aflibercept or FOLFIRI), and who completed cycle 1.

- for patients still on treatment, emergence period for the AE is defined as the period from the first study treatment intake to the end of last cycle completed before the cutoff date

2. Local needs for interim results will occur at very different periods and the frequency of interim analyses initially planned will not cover those needs in term of timing. Moreover, the first interim analysis will concern less patients than expected, and complementary results will be needed later. Finally, it is possible that new countries participate to the study, which will lead to postpone the end of study. Consequently, additional interim analyses will occur during the course of the study. The section 3 of the SAP will be introduced by the following sentence:

- Two interim analyses are planned so far during the course of the study, in order to obtain preliminary results on baseline characteristics, HRQL and safety data. However, depending on regulatory requests in participating countries, additional interim analyses are likely to be planned. Future changes in the calendar of interim analyses will be stated in further amendments of the SAP, if any.

3. For interim analyses, the tables of exposure section are planned to be analyzed on the subpopulation of patients who discontinued the treatment before cutoff date. Only 5 patients discontinued the treatment before 5 November 2012 (i.e. cut-off date for the first IA). Consequently, it has been decided not to produce those tables for this analysis. Consequently, in section 3.1, the following tables have been removed from the list of planned tables: 15.1.4-1, 15.1.4-2, 15.1.4-3, 15.1.4-4 and 15.1.4-5. However, exposure tables are still planned for interim analysis #2.

4. A new table specific for interim analyses has been added (15.1.1-3b), to assess the number of patients (ongoing at time of IAs cut-off) who completed cycle 1, cycle 2… and thereafter. This table will be provided for the safety population. The purpose of this table is to give a picture of patient's disposal at cutoff date, since table 15.1.4-1 is provided only for the subpopulation patients who discontinued the treatment.

5. This version of SAP also includes five additional minor changes:

- In the summary of prior chemotherapy (section 2.1.1), the maintenance therapies based on bevacizumab only have been added.

- In the summary of deaths (section 2.4.5.2), the analysis of all deaths and all fatal AEs will be performed on all included patients. Safety population remains the population of analysis for summary tables of treatment emergent fatal AEs.

- For interim analyses (section 3.1 and 3.2), the table 15.5.2 – 4 that summarizes the visual scale of EQ-5D questionnaire, has been added.

- In section 2.5.4, the handling of unscheduled visits during the same cycle is described more precisely.

- In the Appendix I, the initial formula for fatigue score was incorrect. The right formula is FA $Score = \{(RS - 1) / 3\}\cdot$.

1.6.2 Modifications to version 2 made in final amended version 3

1. Clarifications have been added for derivations of variables used for extent of study treatment exposure.

2. For the second analysis interim the part of the definition of Health related quality of life EQ-5D, EORTC-C30 and EORTC –CR29 analysis population '..who completed the questionnaire at baseline' has been considered as to have an evaluable baseline assessment, independently of the answer reported to the question 'Was the questionnaire completed?' in the module QoL Questionnaires of the eCRF. To have an evaluable assessment means:

    - To have a evaluable single index utility score for health related quality of life EQ-5D:

    - To have at least one evaluable score for any of the scales (Global health status, functional scales or symptom scales/items) for EORTC-C30 .

    - To have at least one evaluable score for any of the scales (Functional scales or symptom scales/items) for EORTC-CR29

    The corresponding clarifications have been added to section 2.3.3 HRQL Population.

3. For the second analysis interim in case of having two questionnaires for the same visit, the analysis procedure has been the following:

    - If baseline and cycle 1 questionnaires, the closest to the first administration study drug has been analyzed.

    - For the other cycles, the closest before or the day 1 of cycle has been analyzed.

    - From now on and for future analysis, the following time windows will be used for the QoL analysis (section 2.5.3): only the questionnaires filled in:

- ▪ - "from 21 days before cycle 1 to the day of cycle 1" for the baseline assessment will be kept.

- ▪ -"from 7 days before the cycle to the day of the cycle" for the cycles 3, 5, 7 … assessments will be kept.

- ▪ "for EOT within [15,45] days of last administration

- ▪ if several QoL done for the same patient in a given time window, then the closest to cycle 1 for baseline, and the closest to the cycle for cycles 3, 5, 7 … will be kept

4. Table 15.1.2 -5 (Prior anticancer therapies): The cases:' First Line followed by Not Applicable in the intent field' will be identified and sent to Sanofi in order to be classified in the proper group.".

5. Table 15.1.2 -5 (Prior anticancer therapies): For the second IA, Relapse dates incomplete have been imputed to 15 when the day is missing and to 01JUL when day and month missing since a list of these cases was sent to Sanofi and no doubts regarding the timeframe between end of prior regimen and relapse. However for each interim and final analysis a list will be sent to Sanofi for its approval. See section 2.5

6. For the second interim analysis tables 15.3.1 -20. 15.3.1 -21, 15.3.1 -22 and 15.3.1 -23 concerning AE group terms, have been programmed using the following documents provided by Sanofi:

   - list_for_grouping_Meddra_v151_ASQOP.xls : it gives the list of PT to be used for all AE grouping (except 'Diarrhea' and 'Stomatitis and ulcerations'), column (with Yes) to have the list of PTs to be used.

   - Stomatis_ulceration.xls: it gives the list of PT to be used for AE group 'Stomatitis and ulceration'.

   - These documents will be updated at each upgrade of the MedDRA dictionary

7. To extend the adverse events to the cycles, for incomplete AE end date, the last day of the month will be imputed, as it is the worst case. See section 2.5

8. For demographic characteristics, height (cm) and body surface area (m²), have been added to table 15.1.2- 1a and 15.1.2- 1b. See section 2.1.1 Demographic characteristics.

9. Section 2.1.1 Medical or surgical history, the information will be summarized to system organ class and high level term instead of system organ class and preferred term as indicated the previous version.

10. Section 2.1.1 Prior anticancer therapies, the information 'Bevacizumab among patients with biologic agent' has been added to tables 15.1.2 -5a and 15.1.2 -5b for each intentional group (neoadjuvant/adjuvant, advance only and neoadjuvant/adjuvant +advanced).

11. The laboratory parameters classification has been updated. See section 2.1.4.3

12. Important deviations on inclusion/exclusion criteria have been updated. See section 2.3.2.1

13. G-CSF presentation has been updated. See section 2.4.2 Prior or concomitant medications (other than anticancer therapies) and table 15.1.3 -5 for more details.

14. Analysis of adverse events: the following classifications have been added to section of 'Overview of treatment-emergent adverse events, summarizing number (%) of patients with any' and 'grouping by primary SOC and PT, by worst NCI grade:'

   - Treatment-emergent adverse possibly related

   - Treatment-emergent adverse event leading to permanent treatment discontinuation

   - Treatment-emergent adverse event leading to premature treatment discontinuation (either early discontinuation of FOLFIRI (last component of FOLFIRI) with aflibercept continued, or early discontinuation of aflibercept /with FOLFIRI continued)

   See section 2.4.5.1 for more details.

15. For each of grouping adverse events the summary of : Among patients with any of the above grouped term events, the number of patients with a first occurrence during treatment will be summarized with the cycle of first occurrence, worst grade, cycle of occurrence of the worst grade and action taken regarding the study treatment, has been added to this new version. See section 2.4.5.1 for more details

16. The summary statistics (including number, mean, median, standard deviation, minimum and maximum) of laboratory parameters (and changes from baseline) per visit or study assessment has been deleted for this version..

17. Appendix F and G have been updated, see corresponding section.

18. Reason of premature discontinuation (for aflibercept and FOLFIRI separately) will be also described. See section 2.2 Disposition of patients.

19. EQ-5D questionnaires:

   EQ-5D questionnaires will be also described using a frequency table for each of the 5 dimensions. Shift tables between baseline and other cycles will be provided overall for each of the 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). Change from Baseline in the EQ-5D scores to each of the cycle will also be summarised by overall and each of the 5 dimensions. See section 2.4.7.

- Value for *Stable disease on treatment* will be computed using treatment period assessments starting from baseline instead of cycle 3. See section 2.4.7.
- The 95%CI will be also added for all 'mean' of the tables on QoL 15.5.2- 2 and 15.5.2-4

20. EORTC QLQ-C30 questionnaires:

- The percentage of patients with 'Symptom evolution from baseline' in term of deterioration, (i.e. for GHS and functioning scale a change from baseline equal or smaller than minus 10 and for symptoms scales a change from baseline equal or greater than 10) for each assessment will be also presented by subgroups and overall.
- The 95%CI will be also added for all 'mean' of the tables on QoL 15.5.3- 2, 15.5.3-3 and 15.5.3 -4

21. EORTC QLQ-CR29 questionnaires:

- The percentage of patients with 'Symptom evolution from baseline' in term of deterioration, (i.e. for GHS and functioning scale a change from baseline equal or smaller than minus 10 and for symptoms scales a change from baseline equal or greater than 10) for each assessment will be also presented by subgroups and overall.
- The 95%CI will be also added for all 'mean' of the tables on QoL 15.5.4- 2 and 15.5.4-3

22. Section 3.3 Third Interim Analysis has been added for this version

23. Section 2.1.1 For the fourth Interim Analysis on Prior anticancer therapy, 'With Bevacizumab (Y/N)' will be present for the group neoadjuvant/adjuvant +advanced , when given as advanced.

24. Deaths presentations have been modified . For more details see section 2.4.5.2

25. Section 4.4 Fourth Interim Analysis has been added for this version

26. Parodontopathy has been added to the AE grouping, after the fourth interim analysis, for more details see section 2.4.5.1

27. Summary of reason for permanent treatment discontinuation will also be described. See Section 2.2

28. Any grade 3-4 related TEAE and any Serious related TEAE have been added to Overview of adverse events.

1.6.3 Modifications to version 3 made in final amended version 4

This version of SAP is only applicable for the AFLIB_C_06097 program.

In order to satisfy local and global needs for interim results, an additional interim analysis was planned in Q3 2016. The section 3 of the SAP will be introduced by the following sentence:

The amended #2 SAP takes into account the two first additional interim analyses, and this current amended #3 SAP takes into account this last additional interim analyses.

And the section 3.5 of the SAP will be introduced by the following sentence:

A fifth interim analysis was performed during the second quarter 2016. This interim analysis was concerned patients in AFLIB_C_06097 program only.
The statistical report contained the same tables as the ones planned for the fourth interim analysis.

2   STATISTICAL AND ANALYTICAL PROCEDURES

2.1   ANALYSIS ENDPOINTS

2.1.1 Demographic and baseline characteristics

The baseline is defined as the last value or measurement taken before the first dose of treatment.

All baseline safety parameters (apart from those listed below) are presented along with the on-treatment summary statistics in the safety section (2.4.5).

Demographic characteristics

Demographic variables are:

- gender (Male, Female),

- race (White, Black or African american, Asian, other),

- age in years (quantitative and qualitative variable : <65, [65 - 75[and ≥75 years),

- weight (kg.),

- height (cm.),

- body surface area (m²), computed as $0.007184 \times weight\ (kg)^{0.425} \times height\ (cm)^{0.725}$ (variation of DuBois and DuBois formula).

Medical or surgical history

Medical (or surgical) history including detailed cardiovascular risk factors and prior vascular events if any (see Appendix C for further detail).

This information will be coded using the version of Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at Sanofi at the time of database lock, and the information will be summarized according to system organ class and high level term.

Disease characteristics at baseline

Specific disease history includes primary tumor location (colon, recto sigmoid, rectum and other) histology type (adenocarcinoma and other), metastases site at study entry (liver, lung, distant lymph nodes, ovaries, peritoneum, bone and other), number of metastases sites (qualitative variable : 1, >1), time from initial histological diagnosis to date of inclusion (in months) and ECOG performance status (0-1).

Prior anticancer therapies

Anticancer therapies include chemotherapy, surgery and radiotherapy:

- Prior anticancer therapies (excluding surgeries and radiotherapy)

  o Intent (neoadjuvant/adjuvant, advanced only, neoadjuvant/Adjuvant + advanced)

  o For patient entering directly from neoadjuvant/adjuvant anti-cancer therapy :
    – Relapse more than six months after completion of adjuvant chemotherapy (Y/N)
    – Oxaliplatin(Y/N),
    – Oxaliplatin-based chemotherapy (oxaliplatin only, oxaliplatin + fluoropyrimidine, oxaliplatin + fluoropyrimidine + biologic agent),
    – Bevacizumab (Y/N).
    – Bevacizumab among patients with biologic agent

  o For patient with advanced chemotherapy only :
    – Oxaliplatin (Y/N),
    – Oxaliplatin-based chemotherapy (oxaliplatin only, oxaliplatin + fluoropyrimidine, oxaliplatin + fluoropyrimidine + biologic agent),
    – Bevacizumab (Y/N),
      o Maintenance therapy with bevacizumab only (Y/N).
    – Bevacizumab among patients with biologic agent

  o For patient with neoadjuvant/adjuvant followed by advanced chemotherapy:
    – Relapse less than six months after completion of adjuvant chemotherapy (Y/N),
    – Oxaliplatin(Y/N) in neoadjuvant/adjuvant chemotherapy.
    – Oxaliplatin(Y/N) in advanced chemotherapy.
    – Oxaliplatin-based chemotherapy (oxaliplatin only, oxaliplatin + fluoropyrimidine, oxaliplatin + fluoropyrimidine + biologic agent) in advanced chemotherapy.
    – Bevacizumab (Y/N) in advanced chemotherapy
    – Bevacizumab (Y/N)
      o Maintenance therapy with bevacizumab only (Y/N).
    – Bevacizumab among patients with biologic agent

  o Cumulative duration of oxaliplatin-based regimens (months), time from end of last advanced chemotherapy to inclusion (months), time from end of neoadjuvant/adjuvant treatment to inclusion (months)

  o Reason for discontinuation of prior advanced chemotherapy

- Time from the end of prior adjuvant therapy to inclusion (months) (only for patients included directly after adjuvant)

- Reason for discontinuation of prior adjuvant therapy (only for patients included directly after adjuvant)

- Prior surgery for colorectal cancer (Y/N) and type of surgery (colon primary tumor resection, rectum primary tumor resection, metastasis resection, palliative surgery) & time from last primary tumor or metastasis resection to inclusion (months)

- Prior anti-cancer radiation therapy (Y/N), site (bone, colon, rectum, liver, pelvis and other) and intent (curative and palliative), time from last radiation therapy to inclusion (months)

Vital signs

- Systolic blood pressure (mmHg),
- Diastolic blood pressure (mmHg),

Any technical details related to computation, dates, and handling of missing dates are described in Section 2.5.

2.1.2 Prior or concomitant medications (other than anticancer therapies)

All medications taken within 1 week before the first infusion of the study treatment and until the end of the study are to be reported in the case report form pages.

All medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) version currently in effect at Sanofi at the time of database lock and the information will be summarized by therapeutic class and anatomic class.

- Prior medications are those the patient used prior (within 1 week before the first infusion of the study treatment) to the first dose of study treatment. Prior medications can be discontinued before first administration or can be ongoing during treatment phase.

- Concomitant medications are any treatments received by the patient concomitantly to any study treatment (either aflibercept or FOLFIRI), from the first dose of study treatment to 30 days after the last dose of study treatment. Concomitant medications do not include medications started during the post-treatment period (as defined in the observation period in Section 2.1.4).

- Post-treatment medications are those the patient took in the period starting 31 days after the last study treatment dose (either aflibercept or FOLFIRI).

A given medication can be classified as a prior medication and/or a concomitant medication and/or a post-treatment medication. Any technical details related to computation, dates, imputation for missing dates are described in Section 2.5.

2.1.3 Efficacy endpoints

Not applicable.

2.1.3.1 Primary efficacy endpoint(s)

Not applicable.

2.1.3.2 Secondary efficacy endpoint(s)

Not applicable.

2.1.4 Safety endpoints

The safety analysis will be based on the reported adverse events and other safety information, such as clinical laboratory data, vital signs and ECOG performance status.

Observation period

The observation period will be divided into 3 periods:
- The pre-treatment period is defined as the time from the informed consent date up to the time of the first dose of study treatment (aflibercept or FOLFIRI, whichever is first).
- The on-treatment period is defined as the time from first dose of study treatment (aflibercept or FOLFIRI, whichever is first) up to 30 days after the last dose of study treatment (aflibercept or FOLFIRI, whichever is last).
- The post-treatment period is defined as the period of time starting 31 day after the dose of study treatment (aflibercept or FOLFIRI, whichever is last) up to end of post-treatment follow-up period (see below).

2.1.4.1 Adverse events variables

Adverse events are collected from the time patient gives the informed consent up to 30 days after the last dose of study treatment. After the 30 day FUP period all ongoing SAEs (regardless of relationship with study treatment) as well as ongoing related AEs and new related SAEs will have to be collected and followed till resolution/stabilization (stabilization being defined as an event ongoing without any change for at least 3 months). Adverse events are defined as any newly occurring sign or symptom as well as any pre-existing sign or symptom that worsens in severity.

Adverse event observation period:

- Pre-treatment AEs defined as any adverse event starting (i.e. newly occurring) or worsening in severity (if pre-existing) from the signed informed consent date up to first administration of the study treatment (either aflibercept or FOLFIRI)
- Treatment-emergent AEs (TEAEs): defined as adverse events starting or worsening in severity (if pre-existing) during the on-treatment period defined above.

- Post-treatment AEs are adverse events starting or worsening in severity (if pre-existing) during the post-treatment period

All adverse events will be coded to a lower-level term (LLT), preferred term (PT), high-level term (HLT), high-level group term (HLGT), and associated primary system organ class (SOC) using the version of Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at Sanofi at the time of database lock.

2.1.4.2 Deaths

The deaths observation period are per the observation periods defined above.

- Death on-study: deaths occurring during the on-study observation period

- Death on-treatment: deaths occurring during the treatment-emergent adverse event period or if assessed as related to study treatment any time thereafter.

2.1.4.3 Laboratory safety variables

Clinical laboratory data consists of blood analysis, including hematology, clinical chemistry, and urinalysis. Clinical laboratory values after conversion will be analyzed into standard international units and international units will be used in all listings and tables.

Blood samples for clinical laboratories and urine samples will be taken before each study treatment dosing unless otherwise specified. In case of several labs assessments in the same cycle, the worst result will be chosen. The laboratory parameters will be classified as follows.

- Hematology
  - Hemoglobin
  - platelet count
  - WBC
  - Neutrophils
- INR (only for patients under VKA therapy)
- Electrolytes
  - sodium,
  - Corrected calcium (mg/dL) will be computed as: measured total calcium (mg/dL)-[0.8*serum albumin(g/dL)-4.0]
  - potassium
- Renal and liver function parameters:
  - Creatinine
  - calculated creatinine clearance (3060 mL/mn, ≥30mL/mn and <60mL/mn ≥60mL/mn and <80mL/mn, ≥80mL/mn), as reported by the investigator, calculated either by Cockroft-Gault, or MDRD

- AST,

- ALT,

- Alkaline phosphatase,

- total bilirubin,

- Other biochemistry parameters :

  - glucose,

  - albumin

- Non gradable parameters:

  - LDH,

  - total proteins,

  - BUN

  - urea

  - total protein

- Urine samples will be collected as follows.

  - Dipstick urinalysis - white blood cells, red blood cells , protein

  - Morning spot urinalysis - protein, creatinine, UPCR [if proteinuria is ≥2 on dipstick then UPCR should be performed]

  - 24-hour urinalysis - urinary volume, protein (urine), creatinine (urine), hemoglobin, red blood cells [if UPCR >1, then 24-hour urinalysis should be performed]

The NCI grades for each lab variable will be derived according to NCI-CTCAE 4.03, whenever applicable. For non-gradable parameters, laboratory values "out of normal ranges" will be summarized. For ALT, AST, Alkaline phosphatase, total bilirubin and creatininemia, missing local normal ranges will be replaced by generic normal ranges

Laboratory "out of normal ranges" abnormalities will be derived using laboratory normal ranges.

The formulas used for converting laboratory parameters in standard international units will be provided in the conversion factor panel (*FACTOR_20101119.xls* file).

2.1.4.4   Vital signs variables

Systolic and diastolic blood pressure, weight and ECOG performance status as measured on Day 1 of each cycle.

2.1.4.5   Electrocardiogram variables

Not applicable.

2.1.5 Pharmacokinetic variables

Not applicable.

2.1.6 Pharmacodynamic/genomics endpoints

Not applicable.

2.1.7 Quality-of-life endpoints

Health Related Quality of Life:

- EQ-5D^{TM}: observed values and changes from baseline health-related QoL visual scale and utility score.

- EORTC QLQ-C30 questionnaire: observed values and changes from baseline for the Global health status (scoring of items 29 & 30), the five functional scales (Physical, Role, Emotional, Cognitive and Social), the three symptom scales (Fatigue, Nausea/vomiting and Pain) and the other single items

Exploratory endpoint:

- EORTC QLQ-CR29 questionnaire (specific colorectal module - optional): observed values and changes from baseline for the four scales (body image, anxiety, weight, sexual interest) and the other single items.

EORTC QLQ-CR29 questionnaire is optional in the countries where it is available : Brazil, Canada, Denmark, Germany, Italy, Netherlands, Norway, Spain, Sweden, UK, USA.

2.1.8 Health economic endpoints

Not applicable.

2.1.9 Further therapy after discontinuation of study treatment administration during the study

Further therapies after discontinuation of study treatment (aflibercept and FOLFIRI) include radiation and anti-cancer therapies:

- Further anticancer therapies (excluding surgeries and radiotherapy)

    o Chemotherapies (fluoropyrimidine, irinotecan, oxaliplatin, folonic acid / leuvocorin, other)

    o Biologic agents (bevacizumab, cetuximab, panitumumab, regorafenib, other)

- o Time from last study treatment administration to the start of the new anticancer therapies (months)

- ▪ Anti-cancer radiation therapy (Y/N), site (bone, colon, rectum, liver, pelvis and other), intent (curative and palliative) and time from last study treatment administration to radiation (months).

2.2 DISPOSITION OF PATIENTS

The number and percentage of patients screened, included and treated will be presented by country and overall. Study completion status (for aflibercept and FOLFIRI separately) and reasons for withdrawals will be described as per EOT eCRF forms , using frequency tables. Reasons of permanent and premature discontinuation (for aflibercept and FOLFIRI separately) will be also described.

- ▪ Screened patients: all patients with signed ICF and at least part of baseline assessment performed

- ▪ Included patients: all patients with signed ICF and answer to "will the patient continue into the study" is Yes

- ▪ Screen failure patients: all screened patients who do not continue after the baseline visit

- ▪ Treated patients: all patients who took at least one dose of study treatment.

Additionally, the analysis populations will be summarized in a table by number (%) of patients
- Safety population
- Health related quality of life population(s)

Percentages will be calculated using the number of included patients as the denominator. The disposition of patients will be also presented overall and by country.

2.2.1 Randomization and drug dispensing irregularities

Not applicable.

2.3 ANALYSIS POPULATIONS

2.3.1 Efficacy populations

Not applicable.

2.3.2 Safety population

The safety population will consist of the patients who have signed the informed consent form and who have received at least part of one dose of study treatment (either aflibercept or FOLFIRI).

2.3.2.1 Important protocol deviations

The summary of important protocol deviations will be based on the safety population. Other deviations will not be summarized in the Clinical Study Report.

Important protocol deviations are defined as follows:

- Important deviations on inclusion/exclusion criteria
  - No histologically or cytologically proven adenocarcinoma of the colon or rectum
  - Non-metastatic disease
  - More than one prior chemotherapeutic regimen for advanced disease
  - No prior oxaliplatin containing regimen for advanced disease
  - Relapse more than 6 months ($\geq$ 7 months) after completion of adjuvant oxaliplatin-based chemotherapy, for patients entered in the trial directly after adjuvant chemotherapy.
  - Absence of signed and dated informed consent prior to enrollment in the study
  - Prior therapy with IRINOTECAN
  - No relapse after the 1st line of Oxaliplatin or adjuvant oxaliplatin-based chemotherapy for patients entered in the trial directly after adjuvant chemotherapy
- Other important deviations
  - Other anticancer therapies than Aflibercept and Folfiri during the treatment

2.3.3 HRQL analysis populations

Those populations are subsets of the safety population.

Health related quality of life EQ-5D analysis will be performed in the patients who have signed the informed consent form, who have an evaluable EQ-5D questionnaire at baseline and at least one evaluable assessment post baseline and have received at least part of one dose of study treatment. (either aflibercept or FOLFIRI).

Health related quality of life EORTC-C30 analysis will be performed in the patients who have signed the informed consent form, who have an evaluable EORTC QLQ C30 questionnaire at baseline and at least one evaluable assessment post baseline and have received at least part of one dose of study treatment. (either aflibercept or FOLFIRI).

Health related quality of life EORTC-CR29 analysis will be performed in the patients who have signed the informed consent form, who have an evaluable the EORTC QLQ CR29 questionnaire at baseline and at least one evaluable assessment post baseline and have received at least part of one dose of study treatment. (either aflibercept or FOLFIRI).

To have an evaluable assessment means:

- To have a single index utility score for health related quality of life EQ-5D

- To have at least one score for any of the scales (Global health status, functional scales or symptom scales/items) for EORTC-C30.

- To have at least one score for any of the scales (Functional scales or symptom scales/items) for EORTC-CR29

2.4   STATISTICAL METHODS

All statistical analyses will be descriptive in nature and no formal statistical test will be performed. Analysis of baseline characteristics and safety analyses of safety will be performed on the Safety population.

In general, the descriptive summary for continuous data will include the number of non-missing observations (n), mean, standard deviation, median, 25%-percentile and 75%-percentile, minimum and maximum. The number of patients with missing data will be displayed when relevant.

In general, categorical data will be summarized for each treatment group using counts (n) and percentages (%). The number of patients with missing data will be displayed when relevant, but it will not be included in the denominator for the calculation of percentages unless otherwise specified.

2.4.1   Demographics and baseline characteristics

All Patients will be described at baseline (characteristics of patients, medical history, cancer history - all parameters from section 2.1.1) using descriptive statistics presented at previous section. As part of Quality of Life analysis, the following tables will also be presented for the HQRL analysis population: 15.1.2 – 1, 15.1.2 – 2 and 15.1.2 – 5.

2.4.2   Prior or concomitant medications (other than anticancer therapies)

The prior and concomitant medications will be presented for the safety population.

Medications will be summarized according to the WHO-DD dictionary, considering the first digit of the anatomic category (ATC) class (anatomic category) and the first 3 digits of the ATC class (therapeutic category). All ATC codes corresponding to a medication will be summarized, and patients will be counted once in each ATC category (anatomic or therapeutic) linked to the medication. Therefore patients may be counted several times for the same medication.

The table for prior medications will be sorted by decreasing frequency of ATC followed by all other therapeutic classes based on the overall incidence. In case of equal frequency regarding ATCs (anatomic or therapeutic categories), alphabetical order will be used.

Prior anti-hypertensive therapy will be presented by therapeutic class (calcium channel blocker, beta blocker, ACE inhibitor, diuretic, etc) with a distinction between patients having prior hypertension at baseline (information obtained from Medical History form and based on group term), and those who have not.

Prior anti-coagulant therapy will be presented by therapeutic class (vitamin K antagonist, heparins, …) with a distinction between patients having prior thrombovascular event at baseline (based on grouped term), and those without prior thrombovascular event at study entry.

The tables for concomitant medications will be sorted by decreasing frequency of ATC followed by all other therapeutic classes. In case of equal frequency regarding ATCs (anatomic or therapeutic categories), alphabetical order will be used.

G-CSF will be summarized in number (%) at cycle 1 and at any cycle (except cycle 1) and by intent.

G-CSF at cycle 1 will be identified by: start date of G-CSF between two days before first administration (day 1 cycle 1) and the day before day 1 cycle 2.

G-CSF at any cycle (except cycle 1) will be identified by: start date of G-CSF between day 1 cycle 2 and 30 last days after end of treatment.

A listing of post-treatment medications will be provided for the safety population.

2.4.3 Extent of study treatment exposure and compliance

The extent of study treatment exposure will be summarized by actual treatment within the safety population (Section 2.3.2).

2.4.3.1 Extent of study treatment exposure

Extent of exposure will be assessed as follows:

Number of patients treated, number of cycles administered, duration of dosing (weeks) will be summarized for Aflibercept/FOLFIRI together, and for each drug separately. Total actual dose or Cumulative actual dose (mg/kg for aflibercept and mg/m² for FOLFIRI regimen compounds) and dose intensity (mg/kg/week for aflibercept and mg/m²/week for FOLFIRI regimen compounds) and relative dose intensity (%) will be summarized for each drug separately. Dose delays, omissions and dose reductions will also be analyzed.

The overall extent of exposure will be assessed for each patient as:

- Actual number of weeks on treatment is defined as:

  Duration of dosing (weeks) = (date of last cycle day 1 – date of first cycle day 1 + 14)/7.

  regardless of unplanned intermittent discontinuations (see Section 2.5.2 for calculation in case of missing or incomplete data).

- First treatment administration: if aflibercept and FOLFIRI are taken on different dates, the first of both dates will be used.

- Last treatment administration: if aflibercept and FOLFIRI are discontinued on different dates, the last of both dates will be used.

- Total number of cycles (k), determined by the longest duration of each individual drug

In this section, the "dose" refers to a measurement with the unit of mg/kg for aflibercept and mg/m^2 for irinotecan and 5-FU. The exposure will be assessed for the safety population based on following measurements for each patient. The following calculations will be performed for <u>each drug</u> separately (aflibercept, irinotecan and 5FU (bolus+infusion)).

- Total number of cycles of study therapy (K) for <u>each drug and overall</u> (i.e. number of cycles with at least one dose intake of aflibercept and/or FOLFIRI).

The total actual dose by drug (or cumulative dose by drug, mg/kg or mg/m^2) will be calculated for each drug as the sum of the actual doses (in mg/kg or mg/m^2) at each cycle:

$$\text{Total Actual Dose} = \sum_{k=1}^{K} \text{Actual Dose in Cycle}[k]$$

where K = total number of treatment cycles received by the patient.

- The actual dose intensity (mg/m^2/week or mg/kg/week) is defined as the cumulative dose divided by the actual number of weeks on treatment:

$$\text{Actual Dose Intensity} = \frac{\text{Total Actual Dose Received}}{\text{Actual no. of weeks on treatment}}$$

For each drug, the « actual dose intensity" will be calculated based on the overall actual number of weeks on treatment (or duration of dosing, in weeks, as defined above). <u>Example</u>: for a patient who received 12 cycles of aflibercept within 24 weeks, and 10 cycles of FOLFIRI, the actual dose intensity for 5-FU is calculated as: total dose of 5-FU received over 10 cycles, divided by 24 (actual number of weeks on treatment).

- Planned dose intensity (mg/m^2/week or mg/kg/week):

$$\text{Planned Dose Intensity} = \frac{\text{Total Planned Dose}}{\text{Planned \# of weeks on treatment}}$$

The total planned dose will be calculated by the sum of the planned dose at each cycle:

$$\text{Total Planned Dose} = \sum_{k=1}^{K} \text{Planned Dose in Cycle}[k]$$

where K = total number of treatment cycles received by the patient.

The number of weeks on study treatment can be defined as:

$$\text{Planned \# of weeks on treatment} = K*2$$

- The relative dose intensity (in %) is defined as the ratio of the actual dose intensity to the planned dose intensity:

$$\text{Relative Dose Intensity} = \frac{\text{Actual Dose Intensity}}{\text{Planned Dose Intensity}} \times 100.$$

2.4.3.2 Study treatment dosing modifications

Summary statistics will be provided for dose reduction, cycle delay and dose omission as defined below. A dose modification is defined as a dose reduction and/or a dose delay and/or a dose omission. For the first cycle, dose (at Day 1) different from the protocol dose will be considered as dose modified.

- Dose reduction: dose reduction will be derived using the definition provided in Table 2 to Table 4 compared to the previous dose. For the second and subsequent cycles, a dose is deemed to have been reduced if the dose level a patient receives differs from the previous actual dose level The first cycle will not be counted for a reduction

- Dose delays: a cycle is deemed to have been delayed if start date of the current cycle (day 1 cycle n) – start date of previous cycle (day 1 cycle n-1) >16 days (i.e. > 2 days compared to the theoretical length of a cycle)

- Dose omission: for each drug at a given cycle, if the drug is missing but the other drug(s) in the combination is/are not missing, then the missing drug is considered "omitted" for that cycle. After a dose omission, the treatment can re-start at a lower dose level than prior to dose omission. In this case, dose reduction will also be considered at the time the treatment restarts. If treatment is not restarted, it will be considered as premature treatment discontinuation, not dose omission.

Dose information variables will be summarized descriptively (number, mean, SD, median, Q1:Q3, minimum, and maximum).

The following summaries will be provided:
- For each study drug (aflibercept, irinotecan and 5-FU), number of patients with at least one dose modification (dose reduction only, dose omission only, dose reduction followed by dose omission, dose omission followed by dose reduction, dose not given as per protocol at cycle 1 [only for aflibercept] and lower dose at cycle 1 [for irinotecan and 5-FU])
- number of patients with at least one cycle delayed (with delay classification in days: between 3 and 7 days, more than 7 days)
- number of cycles of aflibercept and number of cycles of chemotherapy omitted
- number of cycles of aflibercept and number of cycles of chemotherapy given at a reduced dose, by dose level, excluding dose omission

Table 2 – Aflibercept actual dose level definition

Actual dose level (mg/kg)	Actual dose administered (mg/kg)
Upper dose	$5 \leq$ Dose
4	$3 \leq$ Dose < 5
2	$1 \leq$ Dose < 3
Under dose	$0 <$ Dose < 1
No dose administered	0

Table 3 – Irinotecan actual dose level definition

Actual dose level (mg/m²)	Actual dose administered (mg/m²)
Upper dose	$195 \leq$ Dose
180	$165 \leq$ Dose < 195
150	$135 \leq$ Dose < 165
120	$105 \leq$ Dose < 135
Under dose	$0 <$ Dose < 105
No dose administered	0

Table 4 – 5-FU actual dose level definition (bolus + infusional)

Actual dose level (mg/m²)	Actual dose administered (mg/m²)
Upper dose	$3080 \leq$ Dose
2800	$2520 \leq$ Dose < 3080
2240	$1960 \leq$ Dose < 2520
1680	$1400 \leq$ Dose < 1960
Under dose	$0 <$ Dose < 1400
No dose administered	0

Cases of overdoses:

An overdose of study treatment is defined as:

- FOLFIRI: dosing of 30% above the intended/planned dose of either irinotecan or 5-FU should be considered as an overdosage.

- Aflibercept: an aflibercept overdose is defined as 30% above the intended/planned dose.

The circumstances (i.e., accidental or intentional) should be clearly specified in the verbatim and symptoms, if any, entered on separate AE forms. Based on investigator's best clinical judgment, patients experiencing overdose should be monitored for the onset of known anti-VEGF toxicities (e.g. hypertension, proteinuria, etc.).

A listing summarizing overdoses will be provided.

2.4.3.3 Compliance

Not applicable.

2.4.4 Analyses of efficacy endpoints

Not applicable.

2.4.5 Analyses of safety data

The summary of safety results will be presented overall. Summary of safety data will also be performed by cycle (where applicable)

All safety analyses will be performed on the safety population as defined in Section 2.3.2, unless otherwise specified, using the following common rules:

- Safety data in patients who do not belong to the safety population will be listed separately
- The baseline value is defined as the last available value before the first dose of treatment
- Some summary tables of adverse events will be summarized overall but also by age, and prior bevacizumab status (yes or no). If not specified, the summary will be provided overall only.

2.4.5.1 Analyses of adverse events

The primary focus of adverse event reporting will be on treatment-emergent adverse events (TEAE). Pretreatment and posttreatment adverse events will be described separately.

TEAEs will be summarized with respect to frequency, incidence, intensity/severity (as graded by the NCI CTCAE, version 4.03), relationship, and when appropriate, chronicity and cumulative nature. The following grades are defined: 1, 2, 3 and 4.

Summaries will be provided for all grades combined, for grades (3, 4) combined and for grades (3, 4) separately, unless otherwise specified. The summary tables will provide the number (%) of patients with at least one adverse event. When specified, the number (%) of cycles will be also provided.

Laboratory results are reported as adverse events only if leading to permanent study treatment, discontinuation, to study treatment dose modification (cycle delay or dose reduction), and/or fulfill a seriousness criterion.

If an adverse event date/time of onset (occurrence, worsening, or becoming serious) is incomplete, the adverse event will be considered, according a conservative principle, as treatment emergent unless there is definitive information to determine it is pretreatment or posttreatment. Details on classification of adverse events with missing or partial onset dates are provided in Section 2.5.2.

The following treatment-emergent adverse event summaries will be generated for the safety population.

- Overview of treatment-emergent adverse events, summarizing number (%) of patients with any
  - Treatment-emergent adverse event
  - Treatment-emergent adverse possibly related
  - Grade 3-4 treatment-emergent adverse event (combined)
  - Grade 3-4 related treatment-emergent adverse event
  - Serious treatment-emergent adverse event
  - Serious related treatment-emergent adverse event
  - Treatment-emergent adverse event leading to death
  - Treatment-emergent adverse event leading to permanent treatment discontinuation
  - Treatment-emergent adverse event leading to premature treatment discontinuation (either early discontinuation of FOLFIRI (last component of FOLFIRI) with aflibercept continued, or early discontinuation of aflibercept/with FOLFIRI continued)

The same overview will be provided by patient/cycle (except fatal outcome and permanent and premature discontinuation).

The following frequency distributions of adverse events (incidence tables) will be provided for the safety population and all grades, grades 3-4, grade 3 and grade 4.

- All treatment-emergent adverse event by primary SOC, HLGT, HLT, PT and worst NCI grade, showing number (%) of patients with at least 1 treatment-emergent adverse event sorted by the SOC internationally agreed order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order. This sorting order will be applied to all other similar tables, unless otherwise specified.

- All treatment-emergent adverse events by primary SOC and PT and worst NCI grade, showing the number (%) of patients with at least 1 treatment-emergent adverse event, sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC. This sorting order will be applied to all other similar tables, unless otherwise specified.

- All treatment-emergent adverse events by primary SOC and PT and worst NCI grade, showing the number (%) of patient-cycles with at least 1 treatment-emergent adverse event.

- All treatment-emergent adverse events by primary SOC and PT, worst NCI grade and age, showing the number (%) of patients with at least 1 treatment-emergent adverse event.

- All treatment-emergent adverse events by primary SOC and PT, worst NCI grade and prior bevacizumab, showing the number (%) of patients with at least 1 treatment-emergent adverse event.

- All treatment-emergent adverse events possibly related to study treatment by primary SOC and PT and worst NCI grade, showing the number (%) of patients with at least 1 treatment-emergent adverse event.

Analysis of all treatment emergent serious adverse event(s)

- All treatment-emergent serious adverse events by primary SOC, HLGT, HLT, and PT and worst NCI grade, showing the number (%) of patients with at least 1 serious treatment-emergent adverse event.

- All treatment-emergent serious adverse events by primary SOC and PT and worst NCI grade, showing the number (%) of patients with at least 1 treatment-emergent adverse event.

- All treatment-emergent serious adverse events possibly related to study treatment, by primary SOC and PT and worst NCI grade, showing the number (%) of patients with at least 1 treatment-emergent serious adverse event.

Analysis of all treatment emergent non serious adverse event(s)

- All treatment-emergent non serious adverse events by primary SOC and PT and worst NCI grade, showing the number (%) of patients with at least 1 treatment-emergent adverse event with a % > 5 %

Analysis of all treatment-emergent adverse event(s) leading to treatment discontinuation

- All treatment-emergent adverse events leading to permanent treatment discontinuation, by primary SOC, HLGT, HLT, and PT and worst NCI grade, showing the number (%) of patients.

- All treatment-emergent adverse events leading to permanent treatment discontinuation, by primary SOC and PT, by worst NCI grade

- All treatment-emergent adverse events leading to premature treatment discontinuation, by primary SOC and PT, by worst NCI grade

- All treatment-emergent adverse events leading to Aflibercept discontinuation (premature or permanent), by primary SOC and PT, by worst NCI grade

- All treatment-emergent adverse events leading to premature discontinuation of Aflibercept , by primary SOC and PT, by worst NCI grade

- All treatment-emergent adverse events leading to FOLFIRI discontinuation (premature or permanent), by primary SOC and PT, by worst NCI grade.

- All treatment-emergent adverse events leading to premature discontinuation of FOLFIRI , by primary SOC and PT, by worst NCI grade

Analysis of all treatment-emergent adverse event(s) leading to dose modification

- All treatment-emergent adverse events leading to dose modification (reduction and/or interruption and/or delay), by primary SOC and PT and worst NCI grade, showing the number (%) of patients, sorted by the sorting order defined above.

- All treatment-emergent adverse events leading to dose reduction by primary SOC and PT and worst NCI grade, showing the number (%) of patients, sorted by the sorting order defined above.

- All treatment-emergent adverse events leading to dose interruption by primary SOC and PT and worst NCI grade, showing the number (%) of patients, sorted by the sorting order defined above.

- All treatment-emergent adverse events leading to dose delay by primary SOC and PT and worst NCI grade, showing the number (%) of patients, sorted by the sorting order defined above.

Grouping of adverse events and/or laboratory abnormalities

Grouping of adverse events and/or laboratory abnormalities based on MedDRA preferred terms and/or laboratory tests will be performed as clinically relevant. The grouping of adverse events terms will be done for at least the following items (all categories except renal events and proteinuria are fully defined from selected AE preferred terms):

- *Proteinuri*a (derived from AE form when PT is *proteinuria* or *nephrotic syndrome* and from selected preferred term, see 0, or derived from laboratory data, see section 2.4.5.3)

- *Renal failure events* (based on the terms defined below):

  - Calculated creatinine clearance < 30 mL/mn (from laboratory data) , as reported by the investigator (in case of creatinine >ULN), calculated either by Cockroft –Gault, or MDRD

  - Grade 3 or 4 serum creatinine increase (from laboratory data)

  - Grade 3 or 4 renal failures adverse events (reported in the AE page, defined from selected preferred term, see 0).

The following categories will be defined from the CRF AE page, and selected preferred terms (see 0 for further information):

- *Cardiac dysfunction*

- *Neutropenic complications*

- *Arterial thromboembolic event*

- *Venous thromboembolic event*

- *All thrombovascular events, i.e. arterial or venous thromboembolic events*

- *Haemorrhage*

- *Hypertension*

- *Gastrointestinal perforation*

- *Fistula from gastrointestinal origin*

- *Fistula from other origin*

- *Osteonecrosis*

- *Compromised wound healing*

- *Drug reaction* among which *Acute drug reaction* will be identified

- *RPLS*

- *Proteinuria*

- *Renal events* including *Thrombotic microangiopathy (TMA), and Hemolytic and uremic syndrome (HUS))*

- *Diarrhea*

- *Stomatitis and ulcerations*

- *Parodontopathy*

The following summary tables will be provided for those pre-specified grouped term adverse events:

- Treatment-emergent adverse events by grouped term, SOC and PT, and worst NCI grade, showing the number (%) of patients with at least 1 pre-specified adverse event, sorted by alphabetical order of grouped terms and by decreasing incidence of PTs within each grouped term. This sorting order will be applied to all other similar tables, unless otherwise specified.

- Treatment-emergent adverse events by grouped term, SOC and PT, and worst NCI grade, showing the number (%) of patients/cycles with at least 1 adverse event.

- Treatment-emergent adverse events by grouped term, SOC and PT, worst NCI grade, and class of age (<65, ≥65 years), showing the number (%) of patients with at least 1 adverse event.

- Treatment-emergent adverse events by grouped term SOC and PT, worst NCI grade, and prior bevacizumab (Y/N), showing the number (%) of patients with at least 1 adverse event.

For each of these grouped terms AEs, the following summaries will be provided:

- Among patients with any of the above grouped term events, the number of patients with a first occurrence during treatment will be summarized with the cycle of first occurrence, the worst grade, cycle of occurrence of the worst grade and action taken regarding the study treatment.

Hypertension will be described overall and by subgroup: patients with HBP at baseline and patients without HBP at baseline.

- For patients with prior HBP (i.e. registered in Medical History and based on grouped term), anti-hypertensive therapy will be presented as described in section 2.4.2 (see also Appendix G). During the treatment, number of patients with no change in blood pressure control or with a worsening HBP will be summarized, using the cycle of worsening, the worst grade and the cycle of the worst grade. Action taken regarding study treatment will also be summarized and corrective treatment associated will be described.
- Among patients without prior HBP, the number of patients with a first occurrence during treatment will be summarized with the cycle of first occurrence, the worst grade, and cycle of occurrence of the worst grade. The action taken regarding study treatment will also be summarized and the corrective treatment associated will be described

Arterial events will be described overall by age (≥65 vs <65), by prior arterial event at baseline (yes vs no) and by prior bevacizumab (yes vs no);

Incidence of *haemorrhage* may be displayed among patients with thrombocytopenia (any grades)

Thrombovascular events will be described overall and by subgroup:
patients with thrombovascular event at baseline,
patients without thrombovascular events at baseline and without anti-coagulant therapy as prophylaxis and patients without thrombovascular event at baseline but receiving anti-coagulant therapy as prophylaxis.

- For patients with new thrombovascular event and with thrombovascular event at baseline (i.e. registered in Medical History and based on grouped terms), concomitant anti-coagulant therapy will be presented by therapeutic class (vitamin K antagonist, heparins, …). Number of anti-coagulant treatments by patient will also be summarized. List of corresponding ATC codes is provided in Appendix F.
- For patients with new thrombovascular event and without thrombovascular event at baseline), concomitant anti-coagulant therapy will be presented by therapeutic class (vitamin K antagonist, heparins, …). Number of anti-coagulant treatments by patient will also be summarized. List of corresponding ATC codes is provided in Appendix F.

A listing of all adverse events from this list will be provided in Appendix of the CSR with verbatim, preferred term, start date, duration (in days), grade, cycle at onset, corrective therapy, relation with study treatment, action taken with study treatment, seriousness criteria and outcome.

Analysis of pretreatment and post-treatment adverse events

- Listing of all pretreatment adverse events
- Listing of all pretreatment adverse events leading to study discontinuation
- Listing of all post-treatment new related to treatment serious adverse events

Sorting within tables ensures the same presentation for the set of all adverse events within the observation period (pretreatment, treatment-emergent, and posttreatment). For that purpose, the table of all treatment-emergent adverse events presented by SOC and PT sorted by the internationally agreed SOC order and decreasing frequency of PTs within SOCs will define the presentation order for all other tables unless otherwise specified.

Pre and post-treatment AEs will be summarized in separate tables. Among patients with post-treatment AEs, number of patients who received further anti-cancer therapy will be displayed (if started within the on-treatment period).

An overview of pretreatment and/or post-treatment adverse events will be presented as a listing if only a few.

2.4.5.2 Deaths

The following summaries of deaths will be generated for the safety population:

- Number (%) of patients who died during the on-treatment and post-treatment phase death and main cause for death (AE, disease progression, other reasons)

- All TEAEs leading to death by primary SOC , HLGT, HLT, and PT showing number (%) of patients sorted by internationally agreed SOC order, with HLGT, HLT, and PT presented in alphabetical order within each SOC and in order of worst NCI grade

- All TEAEs leading to death, by primary SOC and PT showing number (%) of patients sorted by internationally agreed SOC order, with PT presented in alphabetical order within each SOC and in order of worst NCI grade

- Fatal AEs in the context of disease progression (deaths within 30 days with cause of death equal to disease progression) by primary SOC and PT, and by worst NCI grade, showing number (%) of patients sorted by internationally agreed SOC order, and with PT presented in alphabetical order within each SOC.

- Fatal AEs in other context than disease progression (deaths within 30 days with cause of death different from disease progression, or death more than 30 days with cause of death equal to AE) by primary SOC and PT, and by worst NCI grade, showing number (%) of patients sorted by internationally agreed SOC order, and with PT presented in alphabetical order within each SOC.

- Related AEs leading to death in other context than disease progression (deaths within 30 days with cause of death different from disease progression, or death more than 30 days with cause of death equal to AE) by primary SOC and PT, and by worst NCI grade, showing number (%) of patients sorted by internationally agreed SOC order, and with PT presented in alphabetical order within each SOC.

A summary of deaths for included but not treated patients will be also provided

A listing of all deaths will be provided

2.4.5.3 Analyses of laboratory variables

Hematological and clinical biochemistry toxicities will be assessed from laboratory test parameters. Each test result will be graded by NCI common terminology criteria (version 4.03).

For haematology and biochemistry, each assessment performed from the 2nd day of cycle N to the 1st day of cycle N+1 will be assigned to cycle N. The 1st day of any cycle will be the date of the 1st treatment infusion (aflibercept, irinotecan or 5FU) for this cycle, whichever is first.

Parameters measured on the day of the first infusion (cycle 1, day 1) will be considered as baseline measurements. On-treatment period will start at first infusion + 1 day for all laboratory parameters.

For the last cycle, any assessment performed from the 2nd day of the cycle and within 30 days from the last infusion of the cycle, whichever the last, will be assigned to this last cycle.

For a given parameter, a patient (respectively, a cycle) will be considered as evaluable if at least one measure of this parameter is available on-treatment.

The frequency tables of each laboratory parameter by worst NCI grade during the treatment period based on the number of patients will be provided. The summary tables will present the frequency of patients with any grade (All grades) of abnormal laboratory tests and with Grade 3 and grade 4 pooled and separately abnormal laboratory tests.

For the non-NCI gradable parameter (chloride, urea, total protein, BUN. LDH), frequency of patients outside normal ranges during the treatment period will be provided.

INR will be summarized by the upper value by patient using frequencies by class: <1.5, $1.5 \leq$ and < 3, $3 \leq$ and < 5, ≥ 5.

Creatinine clearance will be summarized by the lowest value recorded by patient and by patient-cycles, using summary statistics. Frequencies by class ($(\geq 80$ mL/mn, ≥ 60 mL/mn and <80 mL/mn, ≥ 30 mL/mn and < 60 mL/mn, < 30 mL/mn) will also be provided.

For proteinuria, the grade will be derived based on the following table:

Table 5 – Derivation of Proteinuria grade

Grade	Spot urine protein (mg/dL)	24-hour proteinuria (g/24h)	Dipstick result
Grade 1	30-100	<1.0	1+
Grade 2	>100-300	1.0-3.4	2+ 3+
Grade 3	>300	>=3.5	NA
Grade 4		NA as per CTC v 4.0.3	-

A frequency table (n and %) of proteinuria by worst grade, assessed either by spot sample (dipstick/urine protein) or 24h urine collection, during the treatment period based on number of evaluable patients and number of evaluable cycles will be provided. In case both spot urine sample and 24h urine collection are available, only worst grade will be kept, whichever type of measurement

A frequency table of hematuria (positive dipstick for RBC: +; ++ or +++) will be presented.

The time (weeks) to onset of grade ≥2 proteinuria will be calculated as well as the duration of this event from the grade ≥2 occurrence to recovery to a grade <2. In addition, the occurrence of grade ≥2 proteinuria concomitant or not to hematuria (positive dipstick for RBC or reported in AE page) will be summarized.

The urine protein-to-creatinine ratio (UPCR) will be derived based on protein and creatinine values assessed on morning spot urinalysis. UPCR will be described according to the following classes: [0-1],]1-2],]2-3], >3. Time to UPCR>1 and duration of UPCR >1 will be summarized. In addition, the occurrence of UPCR >1 concomitant or not to hematuria (positive dipstick for RBC or reported in AE page) will be summarized.

The occurrence of grade ≥2 proteinuria concomitant or not to hematuria (positive dipstick for RBC or reported in AE page) and concomitant or not to HBP (from AE page, i.e. new hypertension or worsening hypertension, as previously defined in section 2.4.5.1) will be summarized. Concomitance of events will be defined as follows:

- if proteinuria was diagnosed from 24h or spot urine sample or dipstick and hematuria from dipstick, events will be considered as concomitant if diagnosed on the same day ± 3 days.

- if proteinuria was diagnosed from 24h or spot urine sample or dipstick and hematuria was reported in AE page, events will be considered as concomitant if proteinuria was diagnosed in the interval [hematuria start date; hematuria stop date] ± 3 days.

- proteinuria will be considered as concomitant with hypertension if grade≥3 proteinuria was diagnosed (from spot urine sample or from 24h urine sample) at the same cycle as cycle of first occurrence of grade 3 hypertension.

The occurrence of UPCR >1 concomitant or not to hematuria will be summarized. Concomitance will be defined applying the same rule as defined above.

A listing will be provided for all patients with concomitant proteinuria and hematuria, the listing should include thrombotic microangiopathy/HUS if present (at any time).

2.4.5.4 Analyses of vital sign variables

For vital signs, each assessment performed from the 2nd day of cycle N to the 1st day of cycle N+1 will be assigned to cycle N. Parameters measured during baseline visit or on the day of the first infusion (Cycle 1, Day 1) will be considered as baseline measurements. On-treatment period will start at first infusion + 1 day for all parameters.

For the last cycle, any assessment performed from the 2nd day of the cycle and within 30 days from the last infusion of the cycle, whichever the last, will be assigned to this last cycle.

For a given parameter, a patient (respectively a cycle) will be considered as evaluable if at least one measure of this parameter is available on-treatment.

The summary statistics (including number, mean, median, Q1, Q3, standard deviation, minimum and maximum) of all vital signs variables (and changes from baseline) will be calculated for each visit or study assessment (baseline, on-treatment within 30 days of last treatment intake).

- For Blood pressure (SBP, DBP), the summary statistics will be provided for measurements and change-from-baseline at each cycle. The BPs are also summarized based on the number of patients with at least one potentially clinically significant abnormality criteria (PCSA) occurring during the on treatment period according to baseline status. The PCSA criteria are provided in Appendix A.
- For ECOG performance status, a shift table will be provided for the last and worst evaluations respectively relative to baseline.

2.4.5.5 Analyses of electrocardiogram variables

Not applicable.

2.4.5.6 Analyses of other safety endpoints

Not applicable.

2.4.6 Analyses of pharmacokinetic and pharmacodynamic variables

Not applicable.

2.4.7 Analyses of quality of life/health economics variables

The analysis of HRQL will be performed in patients of the HQRL analysis populations. For a given questionnaire, a patient will be considered as evaluable if at least one baseline and one post-baseline assessment of this questionnaire is available. The scoring algorithms of the questionnaires are presented in Appendix H and Appendix I.

The HQRL populations will be divided in subgroups according to the reason of treatment discontinuation (Disease progression vs. Adverse Events or Other). For the interim analyses, a third subgroup will consist of patients still on-treatment. If there are not enough patients (at least 20 per subgroup), patients who discontinued for other reasons than disease progression, will be pooled with on-treatment patients.

The compliance profile over time will be summarized (number and percentage of forms received versus expected, and number and percentage of forms evaluable versus expected).

- EQ-5D^{TM} questionnaire

Single index utility score and VAS will be described at baseline and at cycle 3, cycle 5, cycle 7… and within 30 days of last treatment using descriptive statistics (n, mean, standard deviation, median, minimum and maximum), by subgroup and overall. Changes of health-related quality of life (single index utility score and VAS) from baseline to other cycles will be summarized using standard descriptive statistics. Change from baseline will also be presented by subgroup and overall.

EQ-5D questionnaires will be also described using a frequency table for each of the 5 dimensions. Shift tables between baseline and other cycles will be provided overall for each of the 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). Change from Baseline in the EQ-5D scores to each of the cycle will also be summarised by overall and each of the 5 dimensions.

Mean and SD values of single index utility score will be computed for each of the following status: *Stable disease on treatment*, *Discontinued Stable disease*, *Progressive disease*.

- Value for *Stable disease on treatment* will be computed using treatment-period assessments, starting from baseline to last cycle. Since there are several measures per patient, the mean will be estimated using the mean of patients means.

- Value for *Discontinued Stable disease* will be computed using the QoL within 30 days of last treatment for those patients discontinuing not due to disease progression

- Value for *Progressive disease* will be computed using the QoL within 30 days of last treatment for those patients discontinuing due to disease progression

- EORTC QLQ-C30 questionnaire

A descriptive summary by assessment and change from baseline to each assessment for the Global health status (scoring of items 29 & 30), the five functional scales (Physical, Role, Emotional, Cognitive and Social), the three symptom scales (Fatigue, Nausea/vomiting and Pain) and the other single items will be described, by subgroup and overall.

The percentage of patients with 'Symptom evolution from baseline' in term of deterioration , (i.e. for GHS and functioning scale a change from baseline equal or smaller than minus 10 and for symptoms scales a change from baseline equal or greater than 10) and improvement (i.e. for GHS and functioning scale a change from baseline equal or greater than 10 and for symptoms scales a change from baseline equal or smaller than minus 10) for each assessment will be also presented by subgroups and overall.

- EORTC QLQ-CR29 questionnaire (specific colorectal module - optional)

A descriptive summary by assessment and change from baseline to each assessment for the four scales (body image, anxiety, weight, sexual interest) and the other single items will be described, by subgroup and overall.

The percentage of patients with 'Symptom evolution from baseline' in term of deterioration , (i.e. for functioning scale a change from baseline equal or smaller than

minus 10 and for symptoms scales a change from baseline equal or greater than 10) and improvement (i.e. for functioning scale a change from baseline equal or greater than 10 and for symptoms scales a change from baseline equal or smaller than minus 10) will be also presented by subgroups and overall.

2.4.8 Further therapy after discontinuation of study treatment administration during the study

A summary table will be provided for further anti-cancer therapies and further radiotherapy. The number of patients, the drugs received (chemotherapies and/or biologicals) and the time from last treatment received to first therapy start (in weeks) will be summarized.

2.5   DATA HANDLING CONVENTIONS

Some general rules of data handling conventions are listed below

2.5.1   General conventions

In general, the baseline value of an analysis variable is defined as the last observation before the first dose of the treatment.

2.5.2   Missing data

For categorical variables, patients with missing data are not included in calculations of percentages unless otherwise specified. When relevant, the number of patients with missing data is presented.

In general, no imputation is planned for missing data. The following approaches are default methods for missing data handling. Some exploratory analyses can be planned with different strategies for treating missing outcomes.

Categorical data at baseline will be summarized using counts (n) and percentages (%). The number of patients with missing data may be mentioned, but will not be included in the denominator for the calculation of percentages unless otherwise specified.

Continuous data: The analyses and summaries for variables with continuous scales will be based on observed data only. However, the number of patients with missing observations will be provided.

Handling of missing data for adverse events

AE: missing data will not be imputed. When any information (start date of AE, first study treatment administration date, cycle 1 date) is missing, the TEAE will be determined by the following conservative principle: an AE will be considered a TEAE if it cannot be confirmed that the event is not a TEAE due to missing data.

To extend the adverse events to the cycles, for incomplete AE end date (day missing), the last day of the month will be imputed, as it is the worst case.

Handling of missing assessment of relationship of adverse events to study treatment

If the assessment of the relationship to study treatment is missing, then the relationship to study treatment has to be assumed and the adverse event considered as such in the frequency tables of possibly related adverse events, but no imputation should be done at the data level.

Handling of missing grades of adverse events

If the grade is missing for 1 of the treatment-emergent occurrences of an adverse event, the maximal severity on the remaining occurrences will be considered. If the severity is missing for all the occurrences, a "missing" category will be added in the summary table.

For determination of concomitance of hematuria (reported as AE) with proteinuria or with UPCR, no imputation will be performed in case of incomplete date of AE. Events will be considered concomitant if they occurred in the same cycle.

Handling of partial date of histological diagnosis

Partial date of diagnosis of mCRC will be imputed to calculate the time from initial histological diagnosis till study entry.
- If the month is present the 15 of the month will be used (day is not collected).
- If year is present and month is missing then the 1st July will be used.

No replacement will be done in listings

Handling of medication missing/partial dates

No imputation of medication start/end dates will be performed. If a medication date is missing or partially missing, so it can not be determined whether it was taken prior or concomitantly, it will be considered as a prior **and** concomitant medication.

Incomplete date of first further therapy: if the day of first further therapy date is missing, the date will be imputed to the first day of the month or the day after last study treatment administration, whichever comes last.

Handling of missing data in HQRL questionnaires

EQ-5D

There will be no imputation of missing data. If one of the five answers of the Quality of life questionnaire is missing, the single index score will not be calculated.

EORTC QLQ-C30 and CR29

Missing values for the subscales of the EORTC QLQ-C30 and the QLQ-CR29 will be calculated according to the EORTC Scoring Manual [1, 2]. Scales will utilize all completed items to derive the score of each scale. For a multi-item subscale, if **at least** 50% of the constituent items have been completed, the subscale will be calculated using all the items that have been completed (see example in Appendix I). However, if **less than** 50% of the constituent items have been answered, then the scale score will be considered missing. Using this scoring algorithm, none of the single-item subscales will be computed and hence missing values will remain missing.

In addition to the above, in the event that there are entirely missing assessments (i.e., the measure was not completed at a specific time point), no imputation will occur.

2.5.3 Windows for time points

For summaries on AE and exposure, cycles based on CRF data will be used. Each cycle consists of 14 days (+/- 2 days). Cycle length may be extended if additional time is required for resolution of Aflibercept-related or Folfiri-related toxicities, but up to a maximum of 2 weeks.

For haematology biochemistry and vital signs, each assessment performed from the 2nd day of cycle N to the 1st day of cycle N+1 will be assigned to cycle N. The 1st day of any cycle will be the date of the 1st treatment infusion (aflibercept, irinotecan or 5FU) for this cycle, whichever is first. Parameters measured on the day of the first infusion (cycle 1, day 1) will be considered as baseline measurements. On-treatment period will start at first infusion + 1 day. For the last cycle, any assessment performed from the 2nd day of the cycle and within 30 days from the last infusion of the cycle, whichever the last, will be assigned to this last cycle.

The following time windows will be used for the QoL assessments:

Value	Window
Baseline	from 21 days before cycle 1 to the day of cycle 1
On-treatment values	from 7 days before the cycle to the day of the cycle
End of Treatment	[15,45] days after last administration

In case that several QoL assessments are done for the same patient in a given time window, then it will be kept the closest assessment to the specific cycle and before administration (e.g. cycle 1 for baseline, and the closest to the cycle for cycles 3, 5, 7 …).

2.5.4 Unscheduled visits

Additional visit measurements of laboratory data and vital signs will be used for computation of baseline and worst values and/or grades. If several visits occur during the same cycle, then, for each parameter, only the value corresponding to the worst grade toxicity will be analyzed; if several values correspond to the worst grade, then the one occurring first will be analyzed.

If several visits occur before cycle 1, the baseline parameters will be those measured at the last visit before cycle 1.

2.5.5 Pooling of centers for statistical analyses

No analysis using pooled centers is planned.

2.5.6 Statistical technical issues

Not applicable

3   INTERIM ANALYSES

Two interim analyses during the course of the study were planned in the initial SAP, in order to obtain preliminary results on baseline characteristics, HRQL and safety data. ███████████ ███ The amended #2 SAP takes into account the two first additional interim analyses, and this current amended #3 SAP takes into account this last additional interim analyses.

3.1   FIRST INTERIM ANALYSIS

An interim analysis was performed in January 2013, this interim analysis concerned patients in both programs AFLIB_C_06097 and ████████████.

For interim analyses, safety population was defined as the patients who have signed the informed consent form, who received at least part of one dose of study treatment (either aflibercept or FOLFIRI), and who completed cycle 1. Data analyzed correspond to data obtained at Baseline and on-treatment and all adverse events declared from baseline to 30 days after last cycle. For patients withdrawn, all declared adverse events were taken into account.

For patients still on treatment, emergence period for the AE was defined as the period from the first study treatment intake to the end of last cycle completed before the cutoff date.

Laboratory data were not presented in this interim analysis.

For quality of life, only patient with one baseline and one post baseline assessment were taken into account.

The statistical report contained the following tables:
- Demographic data :15.1.1-1, 15.1.1-2, 15.1.1-3 (subpopulation of patients who ended treatment), 15.1.1-3b, 15.1.2-1 (safety population and HQRL EQ-5D population) , 15.1.2-2 (safety population and HQRL EQ-5D population), 15.1.2-3, 15.1.2-4, 15.1.2-5 (safety population and HQRL EQ-5D population),
- Adverse events and deaths:15.3.1-1, 15.3.1-2, 15.3.1-4, 15.3.1-5, 15.3.1-6, 15.3.1-7, 15.3.1-8, 15.3.1-10, 15.3.1-11, 15.3.1-13 (subpopulation of patients who ended treatment), 15.3.1-16, 15.3.1-20, 15.3.1-21, 15.3.1-22, 15.3.1-23, 15.3.2-1, 15.3.2-3, 15.3.2-4, 15.3.2-5, 15.3.2-6, 15.3.2-7, 15.3.2-8
- QoL data:15.5.1-1, 15.5.2-1, 15.5.2-2, 15.5.2-3, 15.5.2-4, 15.5.3-1, 15.5.3-2, 15.5.3-3, 15.5.3-4, 15.5.4-1, 15.5.4-2, 15.5.4-3.
- Listings 15.3.1-2 and 15.3.2-1 will also be presented.

Subpopulation of patients who ended treatment stands for patients who ended both Aflibercept and FOLFIRI and with last cycle completed; patients still taking one product or patients with last cycle ongoing on cutoff date will not be part of this subgroup. Tables will be adapted to the visits selected for this interim analysis. Separate analyses with local patients only were also performed

with patients from UK.

3.2   SECOND INTERIM ANALYSIS

A second interim analysis was performed during 2nd semester 2013. This interim analysis concerned patients in both programs AFLIB_C_06097 and ▮▮▮▮▮▮▮▮

For interim analyses, safety population wasdefined as the patients who have signed the informed consent form, who received at least part of one dose of study treatment (either aflibercept or FOLFIRI), and who completed cycle 1. Data analyzed wascorresponded to all data obtained from baseline up to the minimum between 30 days after the last cycle before the cutoff date and the day before the subsequent cycle (the number of cycles can vary from one patient to another). For patients still on treatment, emergence period for the AE was defined as the period from the first study treatment intake to the end of last cycle completed before the cutoff date.

Laboratory data was not presented in this interim analysis.

For quality of life, only patient with one baseline and one post baseline assessment was taken into account.

The statistical report contained the following tables:
- Demographic data :15.1.1-1, 15.1.1-2, 15.1.1-3 (subpopulation of patients who ended treatment), 15.1.1-3b, 15.1.2-1 (safety population and HQRL EQ-5D population) , 15.1.2-2 (safety population and HQRL EQ-5D population), 15.1.2-3, 15.1.2-4, 15.1.2-5 (safety population and HQRL EQ-5D population), 15.1.2-6, 15.1.2-7
- Exposure: 15.1.4-1(subpopulation of patients who ended treatment), 15.1.4-2 (subpopulation of patients who ended treatment), 15.1.4-3 (subpopulation of patients who ended treatment), 15.1.4-4 (subpopulation of patients who ended treatment), 15.1.4-5 (subpopulation of patients who ended treatment),
- Adverse events and deaths:15.3.1-1, 15.3.1-2, 15.3.1-4, 15.3.1-5, 15.3.1-6, 15.3.1-7, 15.3.1-8, 15.3.1-10, 15.3.1-11, 15.3.1-13 (subpopulation of patients who ended treatment), 15.3.1-16, 15.3.1-20, 15.3.1-21, 15.3.1-22, 15.3.1-23, 15.3.2-1, 15.3.2-3, 15.3.2-4, 15.3.2-5, 15.3.2-6, 15.3.2-7, 15.3.2-8
- QoL data:15.5.1-1, 15.5.2-1, 15.5.2-2, 15.5.2-3, 15.5.2-4, 15.5.3-1, 15.5.3-2, 15.5.3-3, 15.5.3-4, 15.5.4-1, 15.5.4-2, 15.5.4-3.

- Listings 15.3.1-2 and 15.3.2-1 was also presented.

This analysis was also performed by country (only for a selection of countries).

3.3   THIRD INTERIM ANALYSIS

A third interim analysis was performed during last quarter 2013. This interim analysis was concerned patients in both programs AFLIB_C_06097 and ▮▮▮▮▮▮▮

The statistical report contained the following tables:

15.1 DEMOGRAPHIC DATA
15.1.1 DISPOSITION OF PATIENTS
Table 15.1.1 - 1 Summary of patients included in the study – All patients
Table 15.1.1 - 2 Number of patients by country, site and treatment received – All patients
Table 15.1.1 - 3 End of treatment – Patients who ended treatment [a]
Listing 15.1.1 -3: Listing of patients who ended treatment [a] for 'other reason'
Table 15.1.1 – 3 b Number of treated patients by cycle number – Safety Population (interim analyses only)
Table 15.1.1 - 4 Important protocol deviations – Safety Population

15.1.2 DEMOGRAPHIC, BASELINE DATA AND MEDICATIONS
Table 15.1.2 - 1a Demographic and baseline characteristics– Safety Population
Table 15.1.2 - 1b Demographic and baseline characteristics– QOL EQ-5D Population
Table 15.1.2 - 2a Disease characteristics– Safety Population
Table 15.1.2 - 2b Disease characteristics– QOL EQ-5D Population
Table 15.1.2 - 3 Prior Surgeries – Safety Population
Table 15.1.2 - 4 Prior Radiation – Safety Population
Table 15.1.2 – 5 Prior Anti-Cancer Therapies – Safety Population
Table 15.1.2 - 5b Prior Anti-Cancer Therapies – QOL EQ-5D Population
Table 15.1.2 - 7 Summary of hematological parameters at baseline by NCI grade – Safety Population
Table 15.1.2 - 8 Summary of INR at baseline by ranges – Safety Population
Table 15.1.2 - 9 Summary of electrolytes at baseline by NCI grade – Safety Population
Table 15.1.2 - 10 Summary of renal and liver function parameters at baseline by NCI grade – Safety Population
Table 15.1.2 - 11 Summary of creatinine clearance at baseline – Safety Population
Table 15.1.2 - 12 Summary of other biochemistry parameters at baseline by NCI grade – Safety Population
Table 15.1.2 - 13 Summary of non gradable biochemistry parameters at baseline – Safety Population
Table 15.1.2 - 14 Summary of urinary analyses at baseline –Safety Population

15.1.4 STUDY EXPOSURE
Table 15.1.4 - 1 Number of patients by cycle and Overall treatment exposure – Safety Population Only for Patients who ended treatmet (For Interim Analysis)
Table 15.1.4 -1bNumber of patients by cycle and Overall treatment exposure- Safety Population
Table 15.1.4 - 2 Aflibercept treatment exposure, cumulative dose and dose intensity – Safety Population Only for Patients who ended treatment (For Interim Analysis)
Table 15.1.4 - 3 5-FU treatment exposure, cumulative dose and dose intensity – Safety Population Only for Patients who ended treatment (For Interim Analysis)
Table 15.1.4 - 4 Irinotecan treatment exposure, cumulative dose and dose intensity – Safety Population Only for Patients who ended treatment (For Interim Analysis)
Table 15.1.4 - 5 Summary of patients with cycle delay and/or dose modification (by study drug) –

Safety Population Only for Patients who ended treatment (For Interim Analysis)

15.3 SAFETY DATA

15.3.1 DISPLAY OF ADVERSE EVENTS

Table 15.3.1 - 1 Overview of adverse events: Number (%) of patients – Safety Population

Table 15.3.1 - 2 Overview of adverse events: Number (%) of patient-cycles – Safety Population

Table 15.3.1 - 4 Summary of TEAEs by system organ class and preferred term and worst NCI grade – Number (%) of patients – Safety Population

Table 15.3.1 - 5 Summary of TEAEs by system organ class and preferred term and worst NCI grade – Number (%) of patient-cycles – Safety Population

Table 15.3.1 - 6 Summary of TEAEs by primary system organ class and preferred term, worst NCI grade and age – Number (%) of patient – Safety Population

Table 15.3.1 - 7 Summary of TEAEs by primary system organ class and preferred term, worst NCI grade and prior bevacizumab – Number (%) of patient – Safety Population

Table 15.3.1 - 8 All treatment-emergent adverse events possibly related to study treatment by primary SOC and PT and worst NCI grade.-Safety Population

Table 15.3.1 - 10 All treatment-emergent serious adverse events by primary SOC and PT and worst NCI grade.-Safety Population

Table 15.3.1 - 11 All treatment-emergent serious adverse events possibly related to study treatment, by primary SOC and PT and worst NCI grade. –Safety Population

Table 15.3.1 - 14 All treatment-emergent adverse events leading to permanent treatment discontinuation, by primary SOC, PT and worst NCI grade. .- Patients Who Ended Treatment

Table 15.3.1 - 15 All treatment-emergent adverse events leading to premature treatment discontinuation, by primary SOC, PT and worst NCI grade-Safety Population

Table 15.3.1 - 16 All treatment-emergent adverse events leading to Aflibercept discontinuation (premature or permanent), by primary SOC and PT and worst NCI grade.-Safety Population

Table 15.3.1 - 17 All treatment-emergent adverse events leading to premature discontinuation of Aflibercept, by primary SOC and PT and worst NCI grade.-Safety Population

Table 15.3.1 - 18 All treatment-emergent adverse events leading to FOLFIRI discontinuation (premature or permanent), by primary SOC and PT and worst NCI grade.-Safety Population

Table 15.3.1 - 19 All treatment-emergent adverse events leading to premature discontinuation of FOLFIRI, by primary SOC and PT and worst NCI grade.-Safety Population

Table 15.3.1 - 20 All treatment-emergent adverse events leading to dose modification, by primary SOC and PT and worst NCI grade.-Safety Population

Table 15.3.1 - 24 Summary of TEAEs of specific interest by grouped terms, primary system organ class and preferred term, and worst NCI grade – Number (%) of patient – Safety Population

Table 15.3.1 - 25 Summary of TEAEs of specific interest by grouped terms, primary system organ class and preferred term, and worst NCI grade – Number (%) of patient-cycles – Safety Population

Table 15.3.1 - 26 Summary of TEAEs of specific interest by grouped terms, primary system organ class and preferred term, worst NCI grade and age – Number (%) of patient – Safety Population

Table 15.3.1 - 27 Summary of TEAEs of specific interest by grouped terms, primary system organ class and preferred term, worst NCI grade and prior bevacizumab – Number (%) of patient – Safety Population

Table 15.3.1 -56 Summary of Pre-Treatment AEs by System Organ Class and Preferred Term and Worst NCI Grade- Number of patients – Safety Population

15.3.2 ANALYSIS OF DEATHS

Table 15.3.2 - 1 Summary of deaths and cause of deaths – All Included patients

Table 15.3.1- 1a Summary of deaths and cause of deaths – Safety Population

Table 15.3.2 - 3 All fatal adverse events by primary SOC and PT and worst NCI grade– All included patients.

Table 15.3.2 - 4 Treatment emergent adverse events leading to death by primary SOC and PT and worst NCI grade– Safety population.

Table 15.3.2 - 5 Treatment emergent adverse events leading to death during the on treatment period in the context of disease progression by primary SOC and PT and worst NCI grade– Safety population.

Table 15.3.2 - 6 Treatment emergent adverse events leading to death in other context than disease progression by primary SOC and PT and worst NCI grade– Safety population.

Table 15.3.2 - 7 Treatment emergent adverse events possibly related to study treatment leading to death in other context than disease progression by primary SOC and PT and worst NCI grade– Safety population.

15.3.3 ANALYSIS OF LABORATORY VARIABLES

Table 15.3.3 - 1 Summary of abnormal hematological parameters during treatment (worst grade per patient) – Safety Population

Table 15.3.3 - 2 Summary of INR during treatment (worst value per patient) – Safety Population

Table 15.3.3 - 3 Summary of abnormal electrolytes during treatment (worst grade per patient)– Safety Population

Table 15.3.3 - 4 Summary of renal and liver function parameters during treatment (worst grade per patient)– Safety Population

Table 15.3.3 - 5 Summary of creatinine clearance during treatment (worst value per patient) – Safety Population

Table 15.3.3 – 6 Summary of other biochemistry parameters during treatment (worst grade per patient)- Safety Population

Table 15.3.3 - 7 Summary of non gradable biochemistry parameters during treatment (worst value per patient)– Safety Population

Table 15.3.3 - 8 Summary of patients with proteinuria events – Safety Population

Table 15.3.3 - 9 Summary of of proteinuria and UPCR during treatment - Number (%) of patients– Safety Population

Table 15.3.3 - 14 Summary of patients with renal failure events – Safety Population

15.5 QUALITY OF LIFE

15.5.1 ENROLLMENT

Table 15.5.1 - 1 Enrollement summary – All patients

15.5.2 EQ-5D QUESTIONNAIRE

Table 15.5.2 - 1 QOL EQ-5D Completion Rates by Cycle – Safety Population

Table 15.5.2 - 2 Quality of life: Single index utility score – QOL EQ-5D population

Table 15.5.2 - 3 Single index utility score by assessment status - QOL EQ-5D population

Table 15.5.2 - 4 Quality of life: Visual Analogue Scale - QOL EQ-5D population

Table 15.5.2 - 5 Quality of life: Description of the EQ-5D questionnaire - QOL EQ-5D population

Table 15.5.2- 6a Quality of life: Description of the EQ-5D questionnaire- Mobility- Shift table between baseline and each cycle –QOL-EQ-5D population

Table 15.5.2- 6b Quality of life: Description of the EQ-5D questionnaire- Self-care- Shift table

between baseline and each cycle –QOL-EQ-5D population
Table 15.5.2- 6c Quality of life: Description of the EQ-5D questionnaire- Usual activities- Shift table between baseline and each cycle –QOL-EQ-5D population
Table 15.5.2- 6d Quality of life: Description of the EQ-5D questionnaire- Pain/discomfort- Shift table between baseline and each cycle –QOL-EQ-5D population
Table 15.5.2- 6e Quality of life: Description of the EQ-5D questionnaire- Anxiety/Depression- Shift table between baseline and each cycle –QOL-EQ-5D population
Table 15.5.2- 7a Quality of life: Description of the EQ-5D questionnaire- Evolution of Mobility- at each cycle –QOL-EQ-5D population
Table 15.5.2- 7b Quality of life: Description of the EQ-5D questionnaire- Evolution of Self-care- at each cycle –QOL-EQ-5D population
Table 15.5.2- 7c Quality of life: Description of the EQ-5D questionnaire- Evolution of Usual activities- at each cycle –QOL-EQ-5D population
Table 15.5.2- 7d Quality of life: Description of the EQ-5D questionnaire- Evolution of Pain/discomfort- at each cycle –QOL-EQ-5D population
Table 15.5.2- 7e Quality of life: Description of the EQ-5D questionnaire- Evolution of Anxiety/Depression- at each cycle –QOL-EQ-5D population

15.5.3 EORTC-QLQ C30 QUESTIONNAIRE
Table 15.5.3 - 1 EORTC-QLQ C30 Completion Rates by Cycle –Safety Population
Table 15.5.3 - 2 EORTC-QLQ C30 : Global health status - QOL EORTC30 population
Table 15.5.3 - 3 EORTC-QLQ C30 : Functional scales - QOL EORTC30 population
Table 15.5.3 - 4 EORTC-QLQ C30 : Symptoms scales / items - QOL EORTC30 population
15.5.4 EORTC-QLQ CR29 QUESTIONNAIRE
Table 15.5.4 - 1 EORTC-QLQ CR29 Completion Rates by Cycle- Safety Population
Table 15.5.4 - 2 EORTC-QLQ CR29 : Functional scales - QOL EORTC CR29 population
Table 15.5.4 - 3 EORTC-QLQ CR29 : Symptoms scales / items - QOL EORTC30 population
Listing 15.3.2 - 1 All adverse events leading to death.

3.4   FOURTH INTERIM ANALYSIS

A fourth interim analysis was performed during the first quarter 2014. This interim analysis was concerned patients in both programs AFLIB_C_06097 and ▇▇▇▇▇▇▇▇▇.

The statistical report contained the following tables:

15.1 DEMOGRAPHIC DATA
15.1.1 DISPOSITION OF PATIENTS
Table 15.1.1 - 1 Summary of patients included in the study - All patients
Table 15.1.1 - 2 Number of patients by country, site and treatment received - All patients
Table 15.1.1 - 3 Summary of reason for permanent treatment discontinuation - Patients who ended treatment[a]

15.3 SAFETY DATA
15.3.1 DISPLAY OF ADVERSE EVENTS
Table 15.3.1 - 1 Overview of adverse events: Number (%) of patients - Safety population
Table 15.3.1 - 2 Overview of adverse events: Number (%) of patient-cycles - Safety population
Table 15.3.1 - 3 Number of patients with TEAEs by Primary SOC, HLGT, HLT and PT and Worst NCI Grade - Safety Population
Table 15.3.1 - 4 Summary of TEAEs by Primary SOC and PT and Worst NCI Grade - Number of patients - Safety Population
Table 15.3.1 - 5 Summary of TEAEs by Primary SOC and PT and Worst NCI Grade - Number of patients-cycles - Safety Population
Table 15.3.1 - 6 Summary of TEAEs by Primary SOC and PT and Worst NCI Grade and Age - Number of patients - Safety Population
Table 15.3.1 - 7 Summary of TEAEs by Primary SOC and Preferred Term and Worst NCI Grade and Prior Bevacizumab - Number of patients – Safety Population
Table 15.3.1 - 8 All TEAEs Possibly Related to Study Treatment by Primary SOC and PT and Worst NCI grade - Number of patients - Safety Population
Table 15.3.1 - 9 All Serious TEAEs by Primary SOC, HLGT, HLT and PT and Worst NCI Grade - Number of patients- Safety Population
Table 15.3.1 - 10 All Serious TEAEs by Primary SOC and PT and Worst NCI grade - Number of patients - Safety Population
Table 15.3.1 - 11 All Serious TEAEs Possibly Related to Study Treatment by Primary SOC and PT and Worst NCI grade - Number of patients – Safety Population
Table 15.3.1 - 13 All TEAEs leading to permanent discontinuation by Primary SOC, HLGT, HLT and PT and Worst NCI Grade - Number of patients - Patients who ended treatment
Table 15.3.1 - 14 All TEAEs Leading to Permanent Treatment Discontinuation by Primary SOC and PT and Worst NCI grade - Number of patients - Patients Who Ended Treatment
Table 15.3.1 - 15 All TEAEs Leading to Premature Treatment Discontinuation by Primary SOC and PT and Worst NCI grade - Number of patients – Safety Population
Table 15.3.1 - 16 All TEAEs Leading to Aflibercept Discontinuation (premature or permanent) by Primary SOC and PT and Worst NCI grade - Number of patients - Safety Population
Table 15.3.1 - 17 All TEAEs Leading to Premature Discontinuation of Aflibercept by Primary SOC and PT and Worst NCI grade - Number of patients - Safety Population
Table 15.3.1 - 18 All TEAEs Leading to FOLFIRI Discontinuation (premature or permanent) by Primary SOC and PT and Worst NCI grade - Number of patients - Safety Population
Table 15.3.1 - 19 All TEAEs Leading to Premature Discontinuation of FOLFIRI by Primary SOC and PT and Worst NCI grade - Number of patients - Safety Population
Table 15.3.1 - 20 All TEAEs Leading to Dose Modification by Primary SOC and PT and Worst NCI grade - Number of patients - Safety Population
Table 15.3.1 - 21 All TEAEs Leading to Dose Reduction by Primary SOC and PT and Worst NCI grade - Number of patients - Safety Population
Table 15.3.1 - 22 All TEAEs Leading to Dose Interruption by Primary SOC and PT and Worst NCI grade - Number of patients - Safety Population
Table 15.3.1 - 23 All TEAEs Leading to Dose Delay by Primary SOC and PT and Worst NCI grade - Number of patients - Safety Population
Table 15.3.1 - 24 Summary of TEAEs of Specific Interest by Grouped Terms, Primary SOC and

15.3.2 ANALYSIS OF DEATHS

15.3.3 ANALYSIS OF LABORATORY VARIABLES

3.5   FIFTH INTERIM ANALYSIS

A fifth interim analysis was performed during the second quarter 2016. This interim analysis was concerned patients in AFLIB_C_06097 program only.

The statistical report contained the same tables as the ones planned for the fourth interim analysis.

4   DATABASE LOCK

The database is planned to be locked around 8 weeks after last patient last visit. We will have 2 Database lock (1 AFEQT and 1ASQoP) at different time.

5   SOFTWARE DOCUMENTATION

All summaries and statistical analyses will be generated using SAS version 9.2 or higher.

6   REFERENCES

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