Name of Sponsor/Company: *GEMCAD*	***Individual Study Table Referring to Part of the Dossier*** ***Volume:*** ***Page:***	***(For National Authority Use Only)***
Name of Finished Product: *mFOLFOX6 with or without aflibercept*		
Name of Active Ingredient: *mFOLFOX6 with or without aflibercept*		

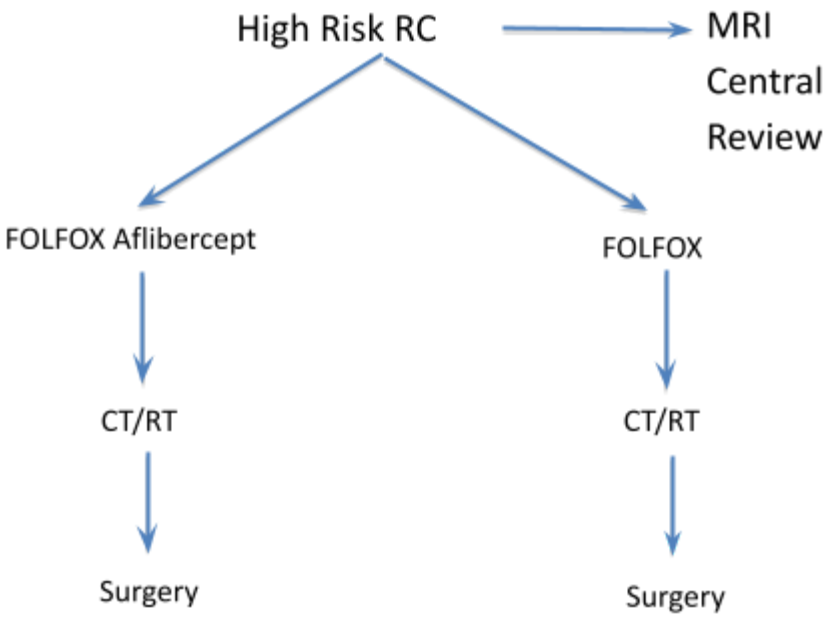
Title of Study:	Induction treatment with FOLFOX, with or without Aflibercept, followed by chemo-radiotherapy in locally advanced high-risk rectum adenocarcinoma. An open, phase II randomized trial (The RIA study)
Investigators:	**Sites and Principal Investigators** 01- IVO - Dr. Carlos Fernández-Martos 02- H. Arnau de Vilanova Lleida - Dra. Antonieta Salud Salvia 03- C. Sanit. Parc Tauli - Dr. Carles Pericay Pijaume 04- H. del Mar - Dra. Clara Montagut 05- H. Clinic i Prov Barcelona - Dr. Joan Maurel Santasusana 06- H. Miguel Servet - Dr. Vicente Alonso Orduña 08- H. de Navarra - Dra. Ruth Vera García 09- H. Gral. U. Elche - Dr. Javier Gallego Plazas 10- H. La Paz - Dra. Núria Rodríguez Salas 11- H. Sta. Creu i Sant Pau - Dra. Marta Martín-Richard 12- C.I.O. Clara Campal - Dr. Antonio Cubillo 13- H. Gral. Alicante - Dr. Bertomeu Massuti 14- H. de Granollers - Dr. Miguel Nogué 15- H. Sant Joan Despí-Moisés Broggi - Dr. Ferrán Losa 16- H. Vall d'Hebrón - Dr. Jaume Capdevila 17- H. Prov. Castellón - Dra. Isabel Busquier Hernández 18- H. Althaia Manresa - Dra. Elena Cillán 20- H. GTiP - Dra. Laura Layos Romero 21- H. Univ. 12 de Octubre - Dra. Rocío García Carbonero 22- H. Univ. Marqués Valdecilla - Dr. Carlos López López
Study centre(s):	**Sites and Principal Investigators** 01- IVO - Dr. Carlos Fernández-Martos 02- H. Arnau de Vilanova Lleida - Dra. Antonieta Salud Salvia 03- C. Sanit. Parc Tauli - Dr. Carles Pericay Pijaume 04- H. del Mar - Dra. Clara Montagut 05- H. Clinic i Prov Barcelona - Dr. Joan Maurel Santasusana 06- H. Miguel Servet - Dr. Vicente Alonso Orduña 08- H. de Navarra - Dra. Ruth Vera García 09- H. Gral. U. Elche - Dr. Javier Gallego Plazas 10- H. La Paz - Dra. Núria Rodríguez Salas 11- H. Sta. Creu i Sant Pau - Dra. Marta Martín-Richard 12- C.I.O. Clara Campal - Dr. Antonio Cubillo 13- H. Gral. Alicante - Dr. Bertomeu Massuti 14- H. de Granollers - Dr. Miguel Nogué

	15- H. Sant Joan Despí-Moisés Broggi - Dr. Ferrán Losa 16- H. Vall d'Hebrón - Dr. Jaume Capdevila 17- H. Prov. Castellón - Dra. Isabel Busquier Hernández 18- H. Althaia Manresa - Dra. Elena Cillán 20- H. GTiP - Dra. Laura Layos Romero 21- H. Univ. 12 de Octubre - Dra. Rocío García Carbonero 22- H. Univ. Marqués Valdecilla - Dr. Carlos López López	
Publication (reference):	***Interim analysis:*** Journal of Clinical Oncology 36, no. 15_suppl (May 20, 2018) 3518-3518. ***Final results:*** JAMA Oncol . 2019 Aug 29;5(11):1566-1573.	
Studied period (years):	5 years	***Phase of development:*** *Therapeutic exploratory II*
Date of first enrolment:	27.JAN.2015	
Date of last completed:	04.SEP.2019	
Objectives:	**Primary objective:** ● To evaluate the efficacy of induction therapy with mFOLFOX6 +/-aflibercept followed by CT/RT in terms of pathologic complete response (pCR). **Secondary objectives:** ● To evaluate pathological parameters of efficacy: R0 resection, tumor regression grade (TRG), and positive or negative circumferential radial margin (CRM) rate. ● To evaluate the relationship between MRI changes and pathological tumor response. i.e. mrTRG. ● To further characterize the safety and tolerability of mFOLFOX6 +/- aflibercept followed by chemoradiation. ● To determine the rate of 30-day surgical complications. ● To evaluate the 3-year local recurrence and disease free survival (DFS). ● To determine the levels of tumor biomarkers expression at baseline and correlate them with response to treatment with mFOLFOX6 + aflibercept.	
Methodology:	This was an open-label, randomized, multicenter, prospective phase II study to evaluate the efficacy of aflibercept as part of an induction therapy strategy for locally advanced rectal carcinoma in a high-risk population (>35% systemic failure at 5 years) selected by MRI. 20 centers participated in the study. The study population consisted of adult patients with locally advanced high-risk rectal	

cancer (histological type: adenocarcinoma of the rectum), considered by the surgeon as feasible to perform a curative resection.

Once the subjects fulfilled the eligibility criteria (MRI-defined high-risk RC), and had signed the informed consent, a central review was requested to confirm clinical stage, and then the patients were randomized to receive treatment.

All patients enrolled in the study had to receive one cycle of study medication every 14 days, for 6 cycles. After the last cycle, patients received standard chemo-radiotherapy (CT/RT) (capecitabine 825 mg/m^2 twice daily combined with a total of 50.4 Gy in 28 days) followed by surgery, provided they had not progressed.



Patients with PD during the treatment phase were withdrawn from the study and received their treatment according to the investigator's judgement.

If a patient withdrew consent and refused to receive more treatment, the patient had to be followed up for DFS. If a patient withdrew consent and refused to continue in the study, the follow-up evaluations had to be discontinued.

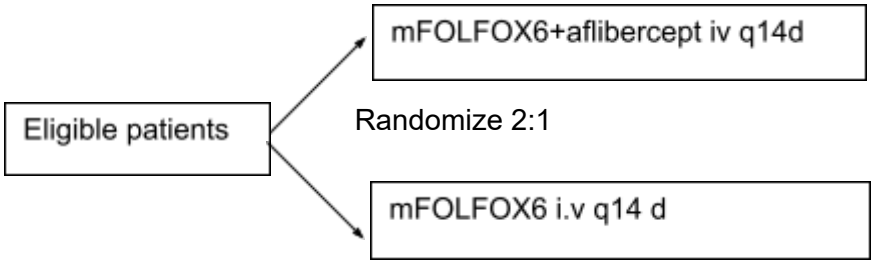
Table 1. STUDY TIMELINES:

Study times	**Time**
Screening (MRI central review)	4 weeks
Study therapy (mFOLFOX +/- aflibercept)	12 weeks
CT-RT	5 weeks
Second MRI (according to investigator´s judgement)	4 weeks +/-5 days after CT-RT
Surgery	6 +/-2 weeks
End of Treatment	4-6 weeks
Follow-up	Up to three years

Randomization

Once it was confirmed that the subjects fulfilled the eligibility criteria and had signed the informed consent, they were randomized 2:1 to receive treatment with or without aflibercept according to the study schema depicted in

Figure 2. Treatment assignment schema



Random assignment of treatment was stratified by EMVI+/EMVI- T3 versus T4 stage, and by study site.

Randomization (2:1) was centralized and done by Pivotal, the selected Contract Research Organization (CRO). The list of randomization codes was generated centrally by the CRO and the treatments were assigned centrally according to the list of randomization codes. The data control centre communicated to the investigator by fax or email the randomization number and treatment group to which each patient had been assigned.

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Name of Active Ingredient: *mFOLFOX6 with or without aflibercept*		

Number of patients	
• **Planned:**	180 (120 patients for mFolfox6 + Aflibercept group and 60 for mFolfox6).
• **Analysed:**	180 (115 patients for mFolfox6 + Aflibercept group and 65 for mFolfox6).
Diagnosis:	*High risk locally advanced rectal carcinoma*
Main criteria for inclusion:	Only patients who fulfilled all the criteria listed below were enrolled in the study. Patients with: 1. Signed and dated informed consent, and willing and able to comply with protocol requirement; 2. Male or female subjects with rectal cancer ≥ 18 and < 75 years of age; 3. High-risk rectal cancer defined by MRI as that with inferior border of the tumor distal to the peritoneal reflection or ≤ 12 cm from the anal margin and considered by the surgeon as feasible to perform a curative resection (including pelvic exenteration as curative resection) Presence of at least 1 of the following high-resolution, thin-slice MRI (3mm): **Middle Third Tumors** -mrT3 Extramural vascular invasion (EMVI) positive Extramural extensión > 5 mms into perirectal fat Mesorectal fascia (MRF) threatened or involved* -mrT4***

Distal Third Tumors (≤ 5 cm from anal verge)
-mrT3 tumor at below levators
-T4 as above

N2**
*tumor or lymph node < 1mm from the mesorectal fascia.
**≥ 4 lymph nodes in the mesorectum showing morphological signs on MRI indicating metastatic disease. ≥ 4 nodes, whether enlarged or not, with a rounded, homogeneous appearance is thus not sufficient.
***T4a: tumor infiltrates peritoneal reflection. T4b: tumor infiltrates adjacent organs.

4. Histological or cytological documentation of adenocarcinoma of the rectum. All other histological types were excluded;
5. ECOG Performance Status of ≤ 1;
6. Hematological status: neutrophils (ANC) ≥ 1.5 x 10^9/L; platelets ≥ 100 x 10^9/L; hemoglobin ≥ 9 g/dL;
7. Adequate renal function: serum creatinine level < 1.5 x ULN;
8. Adequate liver function: serum bilirubin ≤ 1.5 x ULN, alkaline phosphatase < 5 x ULN, AST/ALT < 3 x ULN;
9. Proteinuria < 2+ (dipstick urinalysis) or ≤ 1 g/hour;
10. Regular follow-up feasible;
11. For female patients of childbearing potential, negative serum pregnancy test within 1-week (7 days) prior of starting study treatment;
12. Female patients must commit to using reliable and appropriate methods of contraception until at least three months after the end of study treatment (when applicable). Male patients with a partner of childbearing potential must agree to use contraception in addition to having their partner use another contraceptive method during the trial.

Patients were excluded from the study if they present any of the criteria listed below**:**

1. Prior treatment with aflibercept;

	2. History or evidence upon physical examination of metastasis; 3. Uncontrolled hypercalcemia; 4. Pre-existing permanent neuropathy (NCI grade ≥ 2); 5. Uncontrolled hypertension (defined as systolic blood pressure > 150 mmHg and/or diastolic blood pressure > 100 mmHg), or history of hypertensive crisis, or hypertensive encephalopathy; 6. Concomitant protocol unplanned antitumor therapy (e.g. chemotherapy, molecular targeted therapy, immunotherapy); 7. Treatment with any other investigational medicinal product within 28 days prior to study entry; 8. Other concomitant or previous malignancy, except: i/ adequately treated in-situ carcinoma of the uterine cervix, ii/ basal or squamous cell carcinoma of the skin, iii/ cancer in complete remission for > 5 years; 9. Any other serious and uncontrolled non-malignant disease, major surgery or traumatic injury within the last 28 days; 10. Pregnant or breastfeeding women; 11. Patients with known allergy to any excipient to study drugs; 12. Previous history of stable angina, uncontrolled arrhythmia, and acute coronary syndrome even if controlled with medication or with myocardial infarction or cerebrovascular accident within the last 12 months. 13. Bowel obstruction: Patients with intestinal occlusion, candidates to participate in the trial, may be included in the study after performing a derivative stoma; 14. Appearance of de novo deep vein thrombosis in the 4 weeks prior to randomization.
Test product	
● **Dose:**	**Aflibercept,** was administered intravenously (I.V.) at doses of 4 mg/Kg on Day 1 every 14 days. Aflibercept was supplied to sites by the study Sponsor as 4 ml vials at a concentration of 25 mg/ml.
● **Mode of administration:**	**Aflibercept,** was administered intravenously (I.V.) at doses of 4 mg/Kg on Day 1 every 14 days. Aflibercept was supplied to sites by the study Sponsor as 4 ml vials at a concentration of 25 mg/ml.
● **Batch number:**	Not applicable

● **Duration of treatment**	Treatment continued until six cycles were administered unless unacceptable toxicity or progression occurred
Reference therapy	**<u>mFOLFOX-6 scheme</u>**
● Dose:	**<u>mFOLFOX-6 scheme</u>:** 5-Fluorouracil [5-FU], oxaliplatin and leucovorin were administered intravenously once every 14 days according to mFOLFOX-6 scheme: **Day 1:** Oxaliplatin 85 mg/m^2 IV infusion in 250-500 mL and leucovorin 400 mg/m^2 IV bolus and a 46h infusion of 5-FU 2400 mg/m^2. **<u>Chemo-radiotherapy (CT/RT)</u>** Standard CT/RT consisted of capecitabine 825mg/m^2 twice a day combined with a total dose of 50-4 Gy in 28 days, as neoadjuvant standard therapy. **Surgery** Surgery took place 6 +/- 2 weeks after the last CT/RT induction therapy dose.
● Mode of administration:	**<u>mFOLFOX-6 scheme</u>:** 5-Fluoruracil [5-FU], oxaliplatin and leucoverin were administered intravenously once every 14 days according to mFOLFOX-6 scheme: **Day 1:** Oxaliplatin 85 mg/m^2 IV infusion in 250-500 mL and leucovorin 400 mg/m^2 IV bolus and a 46h infusion of 5-FU 2400 mg/m^2. **<u>Chemo-radiotherapy (CT/RT)</u>** Standard CT/RT consisted of capecitabine 825mg/m^2 twice a day combined with a total dose of 50-4 Gy in 28 days, as neoadjuvant standard therapy. **Surgery** Surgery took place 6 +/- 2 weeks after the last CT/RT induction therapy dose.
● Batch number:	Not applicable
Criteria for evaluation	
● Efficacy	**<u>Efficacy variables:</u>**

	● **Pathological Complete response (pCR):** pCR was defined as the percentage of patients with no tumor viable cells in the surgical sample after induction therapy. ● **Disease-Free Survival**: time from randomization to the appearance of any signs or symptoms of cancer relapse. Patients who withdrew from the study before reaching relapse and without completing the withdrawal consent had to be followed up to determine their status whenever possible. ● **"Vascular Normalization Index Biomarker":** correlation between permeability parameters (BF, BV and k-trans) and MVD and IFP were assessed, as well as the correlation between VEGFR, ANG/ANG2, and IL-2 with response to treatment.
● Safety	The safety profile was determined from the AEs reported by the subjects during the clinical study. Each patient was monitored regularly to detect possible AEs before beginning each cycle. The number and percentage of AEs observed, and their intensity were reported. The intensity of the AEs was classified according to the NCI-CTCAE v4.0. The period of notification of AEs began when the informed consent was signed. Serious and non-serious AEs related to the study treatment that appeared up to 30 days after administration of the last dose had to be recorded. Any AE or laboratory anomaly that was serious and occurred during the development of the study, independently of the treatment received by the patient, had to be reported immediately by the investigator (within 24 hours of first being aware of the case). A follow-up had to be made of the AEs, especially those whose relationship with the medication in investigation could not be classified as "non related", until the baseline situation had been restored or the AE was stabilized. If a clear explanation was established, it was recorded in the eCRF. Treatment-Emergent Adverse Events (TEAEs) were defined as AEs that had occurred or worsened in severity and/or frequency after initiation of therapy. Any event with an onset on the day of the first dose of Trial Drug on which the time of onset was missing was assumed to be a TEAE. For the statistical tables, adverse events

	have been coded according to the Medical Dictionary of Regulatory Activities (MedDRA 20.1) system. Their intensity has been coded by (NCI-CTCAE) v4.0 toxicity criteria. All adverse events included in this report were TEAEs, thus they were named irrespectively as AEs or TEAEs.
Statistical methods:	The primary objective of this study was to evaluate the efficacy of induction therapy with mFolfox6 +/- aflibercept followed by CT/RT in terms of pathologic complete response (pCR). The primary endpoint was to analyze the number of patients achieving pCR after induction therapy with mFolfox6 +/- aflibercept followed by CT/RT. One hundred and sixty-two evaluable patients had to be recruited: 108 patients for mFolfox6 + Aflibercept group and 54 patients for mFolfox6. Assuming 10% of drop-outs a total of 180 patients were recruited (120 patients for mFolfox6 + Aflibercept group and 60 patients for mFolfox6). The assumptions were: ● 2 treatment arms with unequal 2:1 group allocation ● 0.20, two-sided, type-I error ● mFolfox6 efficacy: 15% pCR rate ● Aflibercept + mFolfox6 efficacy: 30% pCR rate ● 80% power to detect a 15% treatment difference ● 2 interim analyses: ○ At 33% of the sample size for safety, futility/efficacy ○ At 66% of the sample size for safety, futility/efficacy ● One final analysis ● Stopping rules: ○ Efficacy: Lan de Mets Alpha spending function (O'Brien-Fleming) ○ Futility: Lan de Mets Alpha spending function (O'Brien-Fleming), non-blinding Study was a two-arm parallel randomized clinical trial with allocation ratio 2:1 (mFolfox6 + Aflibercept: mFolfox6). *<u>Study populations</u>:*

	The primary efficacy analysis was based on the Intent to treat (ITT) Population, although a secondary analysis was also performed based upon the Per Protocol (PP) Population to assess the sensitivity of the analysis to the choice of analysis population. All safety analyses were based upon the Safety Population. ● **Intent to treat population (ITT):** formed by all randomized patients who received at least one dose of Trial Drug. ● **Per protocol population (PP)**: the PP Population included ITT patients who met both of the following criteria: o Received at least 80% of their intended Trial Drug. o Did not have any major protocol violations. The PP Population could be used in efficacy analyses as a sensitivity analysis. ● **Safety population (SAF)**: all the subjects were evaluable for toxicity as long as they had received at least a first administration of the study drugs. All primary analyses of the safety data were conducted using the safety population. The ITT Population was used for all efficacy analyses. The rate of pCR was analyzed as a binary parameter. A z test was used for the differences between percentages (or Fisher's exact test if the assumptions were not met). A 90% confidence interval of the between-group difference was added. Continuous demographic parameters, such as age at the time of enrollment, were summarized for the ITT Population using descriptive statistics (N, mean, median, SD, minimum, and maximum value). Categorical demographic parameters, such as gender, were summarized as a frequency and proportion of the ITT Population. R0 resection, TRG, and CRM rate were analyzed as binary parameters, like the main endpoint: A z test was used for the differences between percentages (or Fisher's exact test if the assumptions were not met). The Kaplan-Meier plots were presented for the Time-to-Event. Log-rank test was applied to the groups' comparison. Hazard ratio through Cox model was calculated (if the assumptions were met). Quantitative parameters, was analyzed through ANCOVA model, including basal value as covariate.

	Any other continuous parameters: ANCOVA model on the changes from baseline with treatment, baseline value and any stratification factors as fixed effects. A 95% confidence interval of the between-group difference was added.
SUMMARY CONCLUSIONS	
Efficacy Outcomes	One hundred and eighty patients were recruited: 115 patients in Aflibercept + mFOLFOX-6 arm and 65 patients in mFOLFOX-6. Twenty patients didn't complete the treatment, 16 in Aflibercept + mFOLFOX-6 arm and 4 in mFOLFOX-6 arm. Disease progression was the primary cause for withdrawal from the study treatment for 8 subjects (40%) with 6 subjects (75%) belonging to the aflibercept+mFOLFOX-6 arm and 2 subjects (25%) mFOLFOX-6 arm. Adverse events were the reason for withdrawal from the study treatment for 6 patients (4 subjects in aflibercept+mFOLFOX-6 arm and 2 in mFOLFOX-6 arm). Two subjects withdrew consent (both in Aflibercept + mFOLFOX-6 arm that was 1.74% and none from the mFOLFOX-6 arm). Death was the reason for premature study termination in 3 cases (1.67%), all of them in Aflibercept + mFOLFOX-6 arm. One patient was withdrawn from the study at the discretion of the Investigator or Sponsor. A detail of patient allocation and study treatment compliance is shown in Table 2. Table 2. Patients that did not complete the study treatment (Neoadjuvant CT or Neoadjuvant CT/RT) and end of treatment reasons

End of treatment				
		AFLIBERCEPT + mFOLFOX-6 (N=115)	**mFOLFOX-6 (N=65)**	**Total (N=180)**
Treatment withdrawal?				
Yes	n (%)	16 (13.91)	4 (6.15)	20 (11.11)
No	n (%)	99 (86.09)	61 (93.85)	160 (88.89)
Reasons of withdrawal				
Toxicity, AE	n (%)	4 (3.48)	2 (3.08)	6 (3.33)
Withdrawal of informed consent and/or rejection of the treatment and/or uncooperativeness	n (%)	2 (1.74)	0 (0.00)	2 (1.11)
Progression disease	n (%)	6 (5.22)	2 (3.08)	8 (4.44)

Death	n (%)	3 (2.61)	0 (0.00)	3 (1.67)
NA	n (%)	99 (86.09)	61 (93.85)	160 (88.89)
At the discretion of the Investigator or Sponsor	n (%)	1 (0.87)	0 (0.00)	1 (0.56)

The distribution of the 180 patients for the populations considering the treatment group are described in table 3.

Table 3. Analysis populations

Populations in the study				
		AFLIBERCEPT + mFOLFOX-6 (N=115)	**mFOLFOX-6 (N=65)**	**Total (N=180)**
ITT population				
Yes	n (%)	115 (100.00)	65 (100.00)	180 (100.00)
ITT population with curative surgery				
Yes	n (%)	103 (89.57)	62 (95.38)	165 (91.67)
No	n (%)	12 (10.43)	3 (4.62)	15 (8.33)
PP population				
Yes	n (%)	103 (89.57)	62 (95.38)	165 (91.67)
No	n (%)	12 (10.43)	3 (4.62)	15 (8.33)
PP population with curative surgery				
Yes	n (%)	96 (83.48)	60 (92.31)	156 (86.67)
No	n (%)	19 (16.52)	5 (7.69)	24 (13.33)
SAF population				
Yes	n (%)	115 (100.00)	65 (100.00)	180 (100.00)

ITT population (ITT). It included all randomized patients who received at least one dose of Trial experimental treatment.

ITT population with curative surgery included all ITT patients that received curative surgery.

PP population (PP) included ITT patients who met both of the following criteria:

- Received at least 80% of their intended Trial experimental treatment
- Did not have any major protocol violations

PP population with curative surgery included all PP patients that received a curative surgery.

Safety Population (SAF): It consists of all patients who received at least a first administration of Trial experimental treatment.

All primary analyses of the efficacy data were conducted using the ITT population and safety analyses were performed for the SAF population. The PP population was used for efficacy analyses as a sensitivity analysis.

Demographics by treatment arm in ITT population are shown at Table 4.

One hundred eighty patients were included in total, among them 116 males (64.44%) and 64 females (35,55%). Mean age was 58.40 years for aflibercept + mFOLFOX-6 arm and 62.22 years for mFOLFOX-6 arm.

Table 4. Demographic Characteristics ITT

Demographic Characteristics ITT				
		AFLIBERCEPT + mFOLFOX-6 (N=115)	**mFOLFOX-6 (N=65)**	**P Value Test**
Age (years)				
	n	115	65	
	Mean (SD)	58.40 (10.37)	62.22 (9.18)	Wilcoxon: 0.0173
	Median [Q1,Q3]	60.00 [51.00, 67.00]	65.00 [56.00, 69.00]	
	Min, Max	32.00, 75.00	39.00, 75.00	
Sex				
Female	n (%)	38 (33.04)	26 (40.00)	Chi-Square: 0.3490
Male	n (%)	77 (66.96)	39 (60.00)	
ECOG performance status				
0	n (%)	78 (67.83)	34 (52.31)	Chi-Square: 0.0391
1	n (%)	37 (32.17)	31 (47.69)	
Clinical T stage (middle and distal)				

Missing	n (%)	1 (0.87)	1 (1.54)	Fisher (MC): 0.9345
mrT2	n (%)	1 (0.87)	0 (0.00)	
mrT3	n (%)	17 (14.78)	12 (18.46)	
mrT3B	n (%)	8 (6.96)	8 (12.31)	
mrT3A	n (%)	1 (0.87)	0 (0.00)	
mrT3C	n (%)	47 (40.87)	22 (33.85)	
mrT3D	n (%)	7 (6.09)	4 (6.15)	
mrT4	n (%)	9 (7.83)	6 (9.23)	
mrT4A	n (%)	16 (13.91)	7 (10.77)	
mrT4B	n (%)	8 (6.96)	5 (7.69)	
Clinical T stage (grouped)				
Missing	n (%)	1 (0.87)	1 (1.54)	Fisher (MC): 1.0000
T2/T3	n (%)	81 (70.43)	46 (70.77)	
T4	n (%)	33 (28.70)	18 (27.69)	
FMR				
FMR + (distance <=1 mm)	n (%)	68 (59.13)	37 (56.92)	Chi-Square: 0.7729
NR	n (%)	47 (40.87)	28 (43.08)	
EMVI				
EMVI - (score 0/1/2)	n (%)	60 (52.17)	34 (52.31)	Chi-Square: 0.9862
EMVI + (score 3/4)	n (%)	55 (47.83)	31 (47.69)	
N2				

N2	n (%)	79 (68.70)	46 (70.77)	Chi-Square: 0.7718
NR	n (%)	36 (31.30)	19 (29.23)	
Location				
Distal	n (%)	30 (26.09)	18 (27.69)	Fisher (MC): 0.9311
Middle	n (%)	84 (73.04)	46 (70.77)	
Missing	n (%)	1 (0.87)	1 (1.54)	
Histology				
Adenocarcinoma	n (%)	115 (100.00)	65 (100.00)	NA

Primary Efficacy Analysis in the ITT Population

The primary objective of this study was to assess the efficacy of induction therapy with mFOLFOX +/- Aflibercept followed by CT/RT in terms of pathologic response (pCR) (Yes/No). pCR was defined as the absence of viable tumor cells in the primary tumor and in the lymph nodes (ypT0N0). The values from ypTNM stage were taken to create pCR categorical variables (Yes/No).

Table 5. pCR Response in the ITT Population

pCR response (ITT)				
		AFLIBERCEPT + mFOLFOX-6 (N=115)	**mFOLFOX-6 (N=65)**	**P Value Test**
pCR (Yes/No)				
Yes	n (%)	25 (21.74)	9 (13.85)	Chi-Square: 0.1938
No	n (%)	90 (78.26)	56 (86.15)	

Thirty-four patients (18.88%) achieved pCR after induction therapy. Twenty-five (21.74%) in aflibercept + mFOLFOX-6 arm and 9 (13.85%) in mFOLFOX-6 arm. The pCR response rate was slightly better in the aflibercept + mFOLFOX-6 arm but it was not statistically significant.

The secondary efficacy objectives were the following:

- To evaluate pathological parameters of efficacy: R0 resection. **Endpoint**: To determine CRM negative (negative vs positive) and R0 resection rates (Yes/No)
- To evaluate the relationship between MRI changes and pathological tumor response. i.e mrTRG. **Endpoint**: TRG; residual tumor after preoperative therapy was evaluated according to the 5-point regression grading scale established by Mandard. Involvement of the histologic CRM was defined as tumor ≤ 2 mm from the resection margin.
- T Downstaging (Yes/No): defined as a lower pathologic T stage compared to pretreatment mrT stage.
- To evaluate the 3 years local recurrence and disease-free survival. **Endpoint**: To determine the rate of local recurrence and disease-free survival (DFS) at 3-years.

Table 6 shows the results related to the first three secondary efficacy variables.

Table 6. Secondary Efficacy Objectives in the ITT Population

Secondary efficacy objectives (ITT)				
		AFLIBERCEPT + mFOLFOX-6 (N=115)	**mFOLFOX-6 (N=65)**	**P Value Test**
Resection type				
NA	n (%)	12 (10.43)	3 (4.62)	Fisher: 0.1260
R0	n (%)	101 (87.83)	60 (92.31)	
R1	n (%)	0 (0.00)	2 (3.08)	
R2	n (%)	1 (0.87)	0 (0.00)	
RX	n (%)	1 (0.87)	0 (0.00)	
Circumferential Resection Margin (CRM)				
<= 1 mm	n (%)	3 (2.61)	3 (4.62)	Fisher: 0.4779
> 1 mm	n (%)	96 (83.48)	56 (86.15)	
NA	n (%)	12 (10.43)	3 (4.62)	
NR	n (%)	4 (3.48)	3 (4.62)	
Tumor Regression Grade (TRG)				
TRG1	n (%)	27 (23.48)	11 (16.92)	Fisher: 0.4759
TRG2	n (%)	32 (27.83)	19 (29.23)	
TRG3	n (%)	28 (24.35)	23 (35.38)	
TRG4	n (%)	13 (11.30)	8 (12.31)	
NR	n (%)	1 (0.87)	1 (1.54)	
NA	n (%)	12 (10.43)	3 (4.62)	
TRG5	n (%)	2 (1.74)	0 (0.00)	
TRG1+TRG2 vs others?				
No	n (%)	56 (48.70)	35 (53.85)	Chi-Square: 0.5068
Yes	n (%)	59 (51.30)	30 (46.15)	

Local invasion (ypT)				
NA	n (%)	12 (10.43)	3 (4.62)	Fisher: 0.0804
T0	n (%)	25 (21.74)	9 (13.85)	
T1	n (%)	4 (3.48)	6 (9.23)	
T2	n (%)	24 (20.87)	18 (27.69)	
T3	n (%)	45 (39.13)	24 (36.92)	
T4A	n (%)	0 (0.00)	2 (3.08)	
T4B	n (%)	3 (2.61)	0 (0.00)	
TIS	n (%)	2 (1.74)	3 (4.62)	
T-Downstaging				
Yes	n (%)	68 (59.13)	46 (70.77)	Chi-Square: 0.1196
No	n (%)	47 (40.87)	19 (29.23)	
T-Downstaging (details)				
Yes	n (%)	68 (59.13)	46 (70.77)	Chi-Square: 0.2789
No	n (%)	35 (30.43)	15 (23.08)	
At least one value not recorded in CRF	n (%)	12 (10.43)	4 (6.15)	

Regarding the evaluation of pathological parameters of efficacy, one hundred and one (87.83%) patients in aflibercept + mFOLFOX-6 arm and 60 (92.31%) in mFOLFOX-6 arm had a R0. There was not a statistical difference.
In the same way, three (2.61%) patients in aflibercept + mFOLFOX-6 arm and 3 (4.62%) in mFOLFOX-6 arm presented a CRM $\leq$ 1mm. There was not a statistical difference either.
Regarding the evaluation of the relationship between MRI changes and pathological tumor response, there was not a statistical difference between the two arms.
Likewise, there was not a statistical difference between the two arms regarding T Downstaging.

In Table 7 it is shown the DFS of ITT population.

Table 7. Disease free survival ITT

	AFLIBERCEPT + mFOLFOX-6	**mFOLFOX-6**
Summary of events		
No of patients	115	65
No of patients with event	29 (25.22%)	14 (21.54%)
No of censored patients	86 (74.78%)	51 (78.46%)
Progression free survival ITT		
Median (95% CI)	NA (NA, NA)	NA (NA, NA)
25th-75th percentile	36.84 - NA	41.15 - NA

Percent Survival (%, 95% CI)			
0 Months		100.00 (100.00, 100.00)	100.00 (100.00, 100.00)
12 Months		87.73 (80.17, 92.54)	89.23 (78.73, 94.71)
24 Months		78.95 (70.26, 85.36)	81.54 (69.79, 89.07)
36 Months		75.21 (66.14, 82.18)	81.54 (69.79, 89.07)
48 Months		73.68 (64.21, 81.01)	73.41 (56.74, 84.48)
Kaplan_Meier Model			
P-value (Log-rank)			0.5638
Cox Model		**Hazard ratio (95% CI)**	**Cox Model P-value**
mFOLFOX-6 vs AFLIBERCEPT + mFOLFOX-6		0.8290 (0.4380, 1.5688)	0.5644

There was not a significant statistical difference in terms of Disease-free survival between the 2 arms of treatment in ITT population (p=0.5638).

Likewise, there was not a statistical difference between the two arms in any efficacy endpoint when the PP population was analyzed.

Safety outcomes

All adverse events included in this report were TEAEs, thus they were named irrespectively as AEs or TEAEs. For the statistical tables, adverse events have been coded according to the Medical Dictionary of Regulatory Activities (MedDRA 20.1) system. Their intensity has been coded by (NCI-CTCAE) v4.0 toxicity criteria.

All patients presented at least one adverse event (Table 8).

Table 8. Summary of TEAEs during the Study Period

		AFLIBERCEPT + mFOLFOX-6 (N=115)	mFOLFOX-6 (N=65)	Total (N=180)	P-Value
Summary of adverse events (Study period)					
Patients with at least one adverse event	n (%)	115 (100.00)	65 (100.00)	180 (100.00)	NA
Patients with at least one grade 3/4 adverse event	n (%)	83 (72.17)	31 (47.69)	114 (63.33)	Chi-Square: 0.0011
Patients with at least one adverse event that led to permanently treatment discontinuation	n (%)	20 (17.39)	4 (6.15)	24 (13.33)	Chi-Square: 0.0331
Patients with at least one adverse event that led to death	n (%)	3 (2.61)	0 (0.00)	3 (1.67)	Fisher: 0.5542
Patients with at least one serious adverse event	n (%)	45 (39.13)	16 (24.62)	61 (33.89)	Chi-Square: 0.0481

Patients with at least one adverse event that the investigator considered related with study medication	n (%)	105 (91.30)	59 (90.77)	164 (91.11)	Chi-Square: 0.9036
Patients with at least one grade 3/4 adverse event that the investigator considered related with study medication	n (%)	64 (55.65)	17 (26.15)	81 (45.00)	Chi-Square: 0.0001
Patients with at least one adverse event that the investigator considered related with study medication and lead to death	n (%)	0 (0.00)	0 (0.00)	0 (0.00)	NA
Patients with at least one adverse event that the investigator considered related and led to permanently treatment discontinuation	n (%)	17 (14.78)	3 (4.62)	20 (11.11)	Chi-Square: 0.0371
Patients with at least one serious adverse event	n (%)	25 (21.74)	3 (4.62)	28 (15.56)	Chi-Square: 0.0023

Patients in the arm with Aflibercept presented significantly more grade 3/4 adverse events (72.17%) that patients in the arm without Aflibercept (47.69%) (p=0.0011) (Table 8).

Likewise, patients in the arm with Aflibercept presented more frequently (17.39%) at least one adverse event that led to permanently treatment discontinuation, in comparison with the patients in the arm without Aflibercept (6.15%) (p=0.0331) (Table 8).

Three patients (all of them in the arm with Aflibercept) had at least one adverse event that led to death (Table 8).

There were more patients with at least one serious adverse event in the arm with Aflibercept (39.13%) in comparison with the patients in the arm without Aflibercept (24.62%) (p=0.0481).

In the same way, there were more patients with one grade 3/4 that the investigator considered related with study medication in the arm with Aflibercept (55.65%) in comparison with the patients in the arm without Aflibercept (26.15%) (p=0.0001); but none patient with at least one adverse event that the investigator considered related with study died due to this AE (Table 8).

There were more patients with at least one adverse event that the investigator considered related with study medication and led to permanently treatment discontinuation in arm with Aflibercept (14.78%) than in the arm without Aflibercept (4.62%) (p=0.0371) (Table 8).

	Finally, there were more patients with at least one serious adverse event in arm with Aflibercept (21.74%) than in the arm without Aflibercept (4.62%) (p=0.0023) (Table 8). The most frequent adverse events (30%) were: asthenia (58.33%), neuropathy peripheral (45%), diarrhea (42.22%), mucosal inflammation (36.67%), nausea (33.89%), hypertension (33.89%) and neutropenia (31.67%). The main differential toxic effect was grade 3/4 hypertension during the induction phase. Postoperative morbidity was similar in both arms (8.32% in arm with aflibercept and 6.91% in arm without aflibercept). **Deaths** Nineteen patients (10.65%) died during the study, 12 (10.43%) in aflibercept + mFOLFOX-6 arm and 7 (10.77%) in mFOLFOX-6 arm. In relation to causes of death fourteen patients (7.78%) died due to progression disease, 9 (7.83%) in aflibercept + mFOLFOX-6 arm and 5 (7.69%) in mFOLFOX-6 arm. Three patients (1.67%) died due to intercurrent causes (see narratives of patient 11-002, 16-008 and 21-001) all of them in aflibercept + mFOLFOX-6 arm, and for causes not related to the study treatment. One patient (0.56%), that was in mFOLFOX-6 arm died due to other causes (non-specified). There were not significant differences between number of deaths and causes of death between the two arms.
Conclusion	Despite lack of statistically significant differences between arms, the findings of the study suggest that adding aflibercept to an induction regimen using mFOLFOX6 plays a role in increasing the pCR rate in patients with high-risk rectal adenocarcinoma, without substantially increasing toxicity. This study provides a rationale for phase III trials.
Date of report	31.JAN.2021

Annex I: Distribution of patients by sites

Centres	Investigators	Patients enrolled
01- IVO	Dr. Carlos Fernández-Martos	12
02- H. Arnau de Vilanova Lleida	Dra. Antonieta Salud Salvia	8
03- C. Sanit. Parc Taulí	Dr. Carles Pericay Pijaume	21
04- H. del Mar	Dra. Clara Montagut	4
05- H. Clinic i Prov Barcelona	Dr. Joan Maurel Santasusana	6
06- H. Miguel Servet	Dr. Vicente Alonso Orduña	9
08- H. de Navarra	Dra. Ruth Vera García	9
09- H. Gral. U. Elche	Dr. Javier Gallego Plazas	9
10- H. La Paz	Dra. Núria Rodríguez Salas	14
11- H. Sta. Creu i Sant Pau	Dra. Marta Martín-Richard	12
12- C.I.O. Clara Campal	Dr. Antonio Cubillo	1
13- H. Gral. Alicante	Dr. Bertomeu Massuti	1
14- H. de Granollers	Dr. Miguel Nogué	8
15- H. Sant Joan Despí-Moisés Broggi	Dr. Ferrán Losa	17
16- H. Vall d'Hebrón	Dr. Jaume Capdevila	9
17- H. Prov. Castellón	Dra. Isabel Busquier Hernández	2
18- Althaia Manresa	Dra. Elena Cillán	5
20- H. GTiP	Dra. Laura Layos Romero	14
21- H. Univ. 12 de Octubre	Dra. Rocío García Carbonero	15
22- H. Univ. Marqués Valdecilla	Dr. Carlos López López	4