



Clinical trial results:

Induction FOLFOX with or without Aflibercept followed by chemoradiation in High Risk Locally Advanced Rectal Cancer. Phase II randomized, multicenter, open label trial

Summary

EudraCT number	2014-002063-14
Trial protocol	ES
Global end of trial date	04 February 2020

Results information

Result version number	v1 (current)
This version publication date	26 March 2021
First version publication date	26 March 2021
Summary attachment (see zip file)	RIA ICH3 Synopsis (RIA CLINICAL STUDY REPORT EUDRACT.pdf)

Trial information

Trial identification

Sponsor protocol code	GEMCAD-1402
-----------------------	-------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02340949
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Grupo Español Multidisciplinar en Cáncer Digestivo (GEMCAD)
Sponsor organisation address	Pau Alsina, 64-68.Esc.B, entlo. 5ª, Barcelona, Spain,
Public contact	Federico Nepote, MFAR Clinical Research, investigacion@mfar.net
Scientific contact	Federico Nepote, MFAR Clinical Research, investigacion@mfar.net

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	31 January 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 July 2019
Global end of trial reached?	Yes
Global end of trial date	04 February 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of induction therapy with mFOLFOX6 +/- aflibercept followed by CT/RT in terms of pathological Complete Responses (pCR)

Protection of trial subjects:

The protocol, through the schedule of visits and procedures, establishes measures to ensure the minimal risk to patients enrolled in the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 October 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 180
Worldwide total number of subjects	180
EEA total number of subjects	180

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	180
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Locally advanced high-risk rectum adenocarcinoma patients were recruited in 22 centers in Spain

Pre-assignment

Screening details:

Random assignment of treatment will be stratified by T3 versus T4 stage for all patients. Patients will be allocated in a 2:1 ratio to the experimental or active comparator arms respectively.

Period 1

Period 1 title	Baseline and Randomization
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	mFOLFOX6 + Aflibercept

Arm description:

- mFOLFOX-6 scheme: 5-Fluoruracil [5-FU], oxaliplatin and leucovorin will be administered intravenously once every 14 days according to mFOLFOX-6 scheme:

Day 1: Oxaliplatin 85 mg/m² IV infusion in 250-500 mL and leucovorin 200 mg/m² IV, both over two hours, followed by 5-FU 400 mg/m² IV bolus and a 46 h infusion of 5-FU 2400 mg/m².

- Aflibercept, will be administered intravenously (I.V.) at doses of 4 mg/Kg on Day 1 every 14 days. Aflibercept will be supplied to sites by the study Sponsor as 4 ml vials at a concentration of 25 mg/ml. Treatment will continue until six cycles are administered unless unacceptable toxicity or progression occurs.

Aflibercept: Administered I.V. at doses of 4 mg/Kg on Day 1 every 14 days. It will be supplied to sites by Sponsor as 4 ml vials at a concentration of 25 mg/ml

5-Fluoruracil: Once every 14 days. Day 1: 400 mg/m² I.V. bolus and a 46 h infusion of 5-FU 2400 mg/m²

Oxaliplatin: Once every 14 days. Day 1: 85 mg/m² I.V. infusión in 250-500 mL, ove

Arm type	Experimental
Investigational medicinal product name	Aflibercept
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Aflibercept, will be administered intravenously (I.V.) at doses of 4 mg/Kg on Day 1 every 14 days.

Investigational medicinal product name	FOLFOX6 regimen
Investigational medicinal product code	
Other name	5-Fluoruracil [5-FU], oxaliplatin and leucovorin
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

5-Fluoruracil [5-FU], oxaliplatin and leucovorin will be administered intravenously once every 14 days according to mFOLFOX-6 scheme:

Day 1: Oxaliplatin 85 mg/m² IV infusion in 250-500 mL and leucovorin 200 mg/m² IV, both over two hours, followed by 5-FU 400 mg/m² IV bolus and a 46 h infusion of 5-FU 2400 mg/m².

Arm title	mFOLFOX6
------------------	----------

Arm description:

- mFOLFOX-6 scheme: 5-Fluoruracil [5-FU], oxaliplatin and leucovorin will be administered intravenously once every 14 days according to mFOLFOX-6 scheme:

Day 1: Oxaliplatin 85 mg/m² IV infusion in 250-500 mL and leucovorin 200 mg/m² IV, both over two hours, followed by 5-FU 400 mg/m² IV bolus and a 46 h infusion of 5-FU 2400 mg/m².

Treatment will continue until six cycles are administered unless unacceptable toxicity or progression occurs.

5-Fluoruracil: Once every 14 days. Day 1: 400 mg/m² I.V. bolus and a 46 h infusion of 5-FU 2400 mg/m²

Oxaliplatin: Once every 14 days. Day 1: 85 mg/m² I.V. infusión in 250-500 mL, over two hours, followed by 5-FU

Leucovorin: Once every 14 days. Day 1: 200 mg/m² I.V., over two hours, followed by 5-FU

Arm type	Active comparator
Investigational medicinal product name	FOLFOX6 regimen
Investigational medicinal product code	
Other name	5-Fluoruracil [5-FU], oxaliplatin and leucovorin
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

5-Fluoruracil [5-FU], oxaliplatin and leucovorin will be administered intravenously once every 14 days according to mFOLFOX-6 scheme:

Day 1: Oxaliplatin 85 mg/m² IV infusion in 250-500 mL and leucovorin 200 mg/m² IV, both over two hours, followed by 5-FU 400 mg/m² IV bolus and a 46 h infusion of 5-FU 2400 mg/m².

Number of subjects in period 1	mFOLFOX6 + Aflibercept	mFOLFOX6
Started	115	65
Completed	115	65

Period 2

Period 2 title	Study treatment period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

No blinding

Arms

Are arms mutually exclusive?	Yes
Arm title	mFOLFOX6 + Aflibercept

Arm description:

- mFOLFOX-6 scheme: 5-Fluoruracil [5-FU], oxaliplatin and leucovorin will be administered intravenously once every 14 days according to mFOLFOX-6 scheme:

Day 1: Oxaliplatin 85 mg/m² IV infusion in 250-500 mL and leucovorin 200 mg/m² IV, both over two hours, followed by 5-FU 400 mg/m² IV bolus and a 46 h infusion of 5-FU 2400 mg/m².

- Aflibercept, will be administered intravenously (I.V.) at doses of 4 mg/Kg on Day 1 every 14 days. Aflibercept will be supplied to sites by the study Sponsor as 4 ml vials at a concentration of 25 mg/ml. Treatment will continue until six cycles are administered unless unacceptable toxicity or progression occurs.

Aflibercept: Administered I.V. at doses of 4 mg/Kg on Day 1 every 14 days. It will be supplied to sites by Sponsor as 4 ml vials at a concentration of 25 mg/ml

5-Fluoruracil: Once every 14 days. Day 1: 400 mg/m² I.V. bolus and a 46 h infusion of 5-FU 2400

mg/m²

Oxaliplatin: Once every 14 days. Day 1: 85 mg/m² I.V. infusión in 250-500 mL, ove

Arm type	Experimental
Investigational medicinal product name	Aflibercept
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Aflibercept, will be administered intravenously (I.V.) at doses of 4 mg/Kg on Day 1 every 14 days.

Investigational medicinal product name	FOLFOX6 regimen
Investigational medicinal product code	
Other name	5-Fluoruracil [5-FU], oxaliplatin and leucovorin
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

5-Fluoruracil [5-FU], oxaliplatin and leucovorin will be administered intravenously once every 14 days according to mFOLFOX-6 scheme:

Day 1: Oxaliplatin 85 mg/m² IV infusion in 250-500 mL and leucovorin 200 mg/m² IV, both over two hours, followed by 5-FU 400 mg/m² IV bolus and a 46 h infusion of 5-FU 2400 mg/m².

Arm title	mFOLFOX6
------------------	----------

Arm description:

- mFOLFOX-6 scheme: 5-Fluoruracil [5-FU], oxaliplatin and leucovorin will be administered intravenously once every 14 days according to mFOLFOX-6 scheme:

Day 1: Oxaliplatin 85 mg/m² IV infusion in 250-500 mL and leucovorin 200 mg/m² IV, both over two hours, followed by 5-FU 400 mg/m² IV bolus and a 46 h infusion of 5-FU 2400 mg/m².

Treatment will continue until six cycles are administered unless unacceptable toxicity or progression occurs.

5-Fluoruracil: Once every 14 days. Day 1: 400 mg/m² I.V. bolus and a 46 h infusion of 5-FU 2400 mg/m²

Oxaliplatin: Once every 14 days. Day 1: 85 mg/m² I.V. infusión in 250-500 mL, over two hours, followed by 5-FU

Leucovorin: Once every 14 days. Day 1: 200 mg/m² I.V., over two hours, followed by 5-FU

Arm type	Active comparator
Investigational medicinal product name	FOLFOX6 regimen
Investigational medicinal product code	
Other name	5-Fluoruracil [5-FU], oxaliplatin and leucovorin
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

5-Fluoruracil [5-FU], oxaliplatin and leucovorin will be administered intravenously once every 14 days according to mFOLFOX-6 scheme:

Day 1: Oxaliplatin 85 mg/m² IV infusion in 250-500 mL and leucovorin 200 mg/m² IV, both over two hours, followed by 5-FU 400 mg/m² IV bolus and a 46 h infusion of 5-FU 2400 mg/m².

Number of subjects in period 2	mFOLFOX6 + Aflibercept	mFOLFOX6
Started	115	65
Completed treatment as per protocol	99	61
Completed	99	61
Not completed	16	4
Adverse event, serious fatal	3	-

Consent withdrawn by subject	2	-
Physician decision	1	-
Adverse event, non-fatal	4	2
Lack of efficacy	6	2

Baseline characteristics

Reporting groups

Reporting group title	mFOLFOX6 + Aflibercept
-----------------------	------------------------

Reporting group description:

- mFOLFOX-6 scheme: 5-Fluoruracil [5-FU], oxaliplatin and leucovorin will be administered intravenously once every 14 days according to mFOLFOX-6 scheme:

Day 1: Oxaliplatin 85 mg/m² IV infusion in 250-500 mL and leucovorin 200 mg/m² IV, both over two hours, followed by 5-FU 400 mg/m² IV bolus and a 46 h infusion of 5-FU 2400 mg/m².

- Aflibercept, will be administered intravenously (I.V.) at doses of 4 mg/Kg on Day 1 every 14 days. Aflibercept will be supplied to sites by the study Sponsor as 4 ml vials at a concentration of 25 mg/ml. Treatment will continue until six cycles are administered unless unacceptable toxicity or progression occurs.

Aflibercept: Administered I.V. at doses of 4 mg/Kg on Day 1 every 14 days. It will be supplied to sites by Sponsor as 4 ml vials at a concentration of 25 mg/ml

5-Fluoruracil: Once every 14 days. Day 1: 400 mg/m² I.V. bolus and a 46 h infusion of 5-FU 2400 mg/m²

Oxaliplatin: Once every 14 days. Day 1: 85 mg/m² I.V. infusión in 250-500 mL, ove

Reporting group title	mFOLFOX6
-----------------------	----------

Reporting group description:

- mFOLFOX-6 scheme: 5-Fluoruracil [5-FU], oxaliplatin and leucovorin will be administered intravenously once every 14 days according to mFOLFOX-6 scheme:

Day 1: Oxaliplatin 85 mg/m² IV infusion in 250-500 mL and leucovorin 200 mg/m² IV, both over two hours, followed by 5-FU 400 mg/m² IV bolus and a 46 h infusion of 5-FU 2400 mg/m².

Treatment will continue until six cycles are administered unless unacceptable toxicity or progression occurs.

5-Fluoruracil: Once every 14 days. Day 1: 400 mg/m² I.V. bolus and a 46 h infusion of 5-FU 2400 mg/m²

Oxaliplatin: Once every 14 days. Day 1: 85 mg/m² I.V. infusión in 250-500 mL, over two hours, followed by 5-FU

Leucovorin: Once every 14 days. Day 1: 200 mg/m² I.V., over two hours, followed by 5-FU

Reporting group values	mFOLFOX6 + Aflibercept	mFOLFOX6	Total
Number of subjects	115	65	180
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
arithmetic mean	58.4	62.2	
standard deviation	± 10.4	± 9.2	-
Gender categorical			
Units: Subjects			
Female	38	26	64
Male	77	39	116

Clinical stage Tumor-nodes-metastasis (TNM)			
TNM clinical stage. The T refers to the size and extent of the main tumor. The main tumor is usually called the primary tumor. The higher the number after the T, the larger the tumor or the more it has grown into nearby tissues. The range is from T0 to T4. T's may be further divided to provide more detail, such as T3a and T3b.			
Units: Subjects			
Mising	1	1	2
mrT2	1	0	1
mrT3	17	12	29
mrT3B	8	8	16
mrT3A	1	0	1
mrT3C	47	22	69
mrT3D	7	4	11
mrT4	9	6	15
mrT4A	16	7	23
mrT4B	8	5	13
Clinical Stage TNM Nodes (n2)			
Used to describe regional lymph node involvement of the tumor. Lymph nodes function as biologic filters, as fluid from body tissues are absorbed into lymphatic capillaries and flows to the lymph nodes.[1] N0 indicates no regional nodal spread, while N1-N3 indicates some degree of nodal spread, with a progressively distal spread from N1 to N3.			
Units: Subjects			
N2	115	65	180
Location			
Location of primary tumor in the rectum			
Units: Subjects			
Distal	30	18	48
Middle	84	46	130
Missing	1	1	2
Histology			
Type of tumor cell composition found by histopathology analysis.			
Units: Subjects			
Adenocarcinoma	115	65	180
Other	0	0	0
Mesorectal Fascia (FMR)			
Distance from tumor to mesorectal fascia grouped in two categories depending on the distances: close (distance <=1 mm) or distal (NR).			
Units: Subjects			
FMR + (distance <=1 mm)	68	37	105
NR	47	28	75
EMVI score			
Extramural vascular invasion (EMVI) is the direct invasion of a blood vessel (usually a vein) by a tumor. In rectal cancer, this can occur on a macroscopic level and be detected on staging MRI. It is a significant prognostic factor, being a predictor of haematogenous spread. Score range from 0 to 4. Higher score means higher risk of distant metastasis.			
Units: Subjects			
Score 0/1/2	60	34	94
Score 3/4	55	31	86

End points

End points reporting groups

Reporting group title	mFOLFOX6 + Aflibercept
Reporting group description:	
- mFOLFOX-6 scheme: 5-Fluoruracil [5-FU], oxaliplatin and leucovorin will be administered intravenously once every 14 days according to mFOLFOX-6 scheme: Day 1: Oxaliplatin 85 mg/m² IV infusion in 250-500 mL and leucovorin 200 mg/m² IV, both over two hours, followed by 5-FU 400 mg/m² IV bolus and a 46 h infusion of 5-FU 2400 mg/m². - Aflibercept, will be administered intravenously (I.V.) at doses of 4 mg/Kg on Day 1 every 14 days. Aflibercept will be supplied to sites by the study Sponsor as 4 ml vials at a concentration of 25 mg/ml. Treatment will continue until six cycles are administered unless unacceptable toxicity or progression occurs. Aflibercept: Administered I.V. at doses of 4 mg/Kg on Day 1 every 14 days. It will be supplied to sites by Sponsor as 4 ml vials at a concentration of 25 mg/ml 5-Fluoruracil: Once every 14 days. Day 1: 400 mg/m² I.V. bolus and a 46 h infusion of 5-FU 2400 mg/m² Oxaliplatin: Once every 14 days. Day 1: 85 mg/m² I.V. infusión in 250-500 mL, ove	
Reporting group title	mFOLFOX6
Reporting group description:	
- mFOLFOX-6 scheme: 5-Fluoruracil [5-FU], oxaliplatin and leucovorin will be administered intravenously once every 14 days according to mFOLFOX-6 scheme: Day 1: Oxaliplatin 85 mg/m² IV infusion in 250-500 mL and leucovorin 200 mg/m² IV, both over two hours, followed by 5-FU 400 mg/m² IV bolus and a 46 h infusion of 5-FU 2400 mg/m². Treatment will continue until six cycles are administered unless unacceptable toxicity or progression occurs. 5-Fluoruracil: Once every 14 days. Day 1: 400 mg/m² I.V. bolus and a 46 h infusion of 5-FU 2400 mg/m² Oxaliplatin: Once every 14 days. Day 1: 85 mg/m² I.V. infusión in 250-500 mL, over two hours, followed by 5-FU Leucovorin: Once every 14 days. Day 1: 200 mg/m² I.V., over two hours, followed by 5-FU	
Reporting group title	mFOLFOX6 + Aflibercept
Reporting group description:	
- mFOLFOX-6 scheme: 5-Fluoruracil [5-FU], oxaliplatin and leucovorin will be administered intravenously once every 14 days according to mFOLFOX-6 scheme: Day 1: Oxaliplatin 85 mg/m² IV infusion in 250-500 mL and leucovorin 200 mg/m² IV, both over two hours, followed by 5-FU 400 mg/m² IV bolus and a 46 h infusion of 5-FU 2400 mg/m². - Aflibercept, will be administered intravenously (I.V.) at doses of 4 mg/Kg on Day 1 every 14 days. Aflibercept will be supplied to sites by the study Sponsor as 4 ml vials at a concentration of 25 mg/ml. Treatment will continue until six cycles are administered unless unacceptable toxicity or progression occurs. Aflibercept: Administered I.V. at doses of 4 mg/Kg on Day 1 every 14 days. It will be supplied to sites by Sponsor as 4 ml vials at a concentration of 25 mg/ml 5-Fluoruracil: Once every 14 days. Day 1: 400 mg/m² I.V. bolus and a 46 h infusion of 5-FU 2400 mg/m² Oxaliplatin: Once every 14 days. Day 1: 85 mg/m² I.V. infusión in 250-500 mL, ove	
Reporting group title	mFOLFOX6
Reporting group description:	
- mFOLFOX-6 scheme: 5-Fluoruracil [5-FU], oxaliplatin and leucovorin will be administered intravenously once every 14 days according to mFOLFOX-6 scheme: Day 1: Oxaliplatin 85 mg/m² IV infusion in 250-500 mL and leucovorin 200 mg/m² IV, both over two hours, followed by 5-FU 400 mg/m² IV bolus and a 46 h infusion of 5-FU 2400 mg/m². Treatment will continue until six cycles are administered unless unacceptable toxicity or progression occurs. 5-Fluoruracil: Once every 14 days. Day 1: 400 mg/m² I.V. bolus and a 46 h infusion of 5-FU 2400 mg/m² Oxaliplatin: Once every 14 days. Day 1: 85 mg/m² I.V. infusión in 250-500 mL, over two hours, followed by 5-FU Leucovorin: Once every 14 days. Day 1: 200 mg/m² I.V., over two hours, followed by 5-FU	

Primary: Number of Patients Achieving pCR

End point title	Number of Patients Achieving pCR
-----------------	----------------------------------

End point description:

To analyze the number of patients achieving pCR after induction therapy with mFOLFOX6 +/- aflibercept followed by CT/RT. pCR will be defined as the absence of viable tumor cells in the primary tumor and in the lymph nodes (ypT0N0)

End point type	Primary
----------------	---------

End point timeframe:

Until 2 years and 2 months

End point values	mFOLFOX6 + Aflibercept	mFOLFOX6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115	65		
Units: Patients				
Yes	25	9		
No	90	56		

Statistical analyses

Statistical analysis title	Chi square test
Comparison groups	mFOLFOX6 v mFOLFOX6 + Aflibercept
Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.1938
Method	Chi-squared

Secondary: Efficacy: R0 Resection

End point title	Efficacy: R0 Resection
-----------------	------------------------

End point description:

To determine R0 resection rates. Number of patients achieving a R0, optimal surgical outcome.

End point type	Secondary
----------------	-----------

End point timeframe:

Until 2 years and 2 months

End point values	mFOLFOX6 + Aflibercept	mFOLFOX6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115	65		
Units: Patients				
Yes	101	60		
No	2	2		
Not Available	12	3		

Statistical analyses

No statistical analyses for this end point

Secondary: TRG; residual tumor after preoperative therapy

End point title	TRG; residual tumor after preoperative therapy
End point description: TRG; residual tumor after preoperative therapy will be semiquantitatively evaluated according to the 5-point regression grading scale established by Mandard.	
End point type	Secondary
End point timeframe: Until 2 years and 2 months	

End point values	mFOLFOX6 + Aflibercept	mFOLFOX6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115	65		
Units: Patients				
Yes	59	30		
No	56	35		
Not available	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: CRM ≤ 1

End point title	CRM ≤ 1
End point description: CRM will be defined as tumor ≤ 1 mm from the resection margin. Number of patients with CRM ≤ 1	
End point type	Secondary
End point timeframe: Until 2 years and 2 months	

End point values	mFOLFOX6 + Aflibercept	mFOLFOX6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115	65		
Units: Patients				
Yes	3	3		
No	96	56		
Not available	16	6		

Statistical analyses

No statistical analyses for this end point

Secondary: To evaluate the relationship between MRI changes with outcome.

End point title	To evaluate the relationship between MRI changes with outcome.
End point description:	
T Downstaging: defined as a lower pathologic T stage compared to pre-treatment mrT stage.	
End point type	Secondary
End point timeframe:	
Until 2 years and 2 months	

End point values	mFOLFOX6 + Aflibercept	mFOLFOX6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115	65		
Units: Patients				
Yes	68	46		
No	47	19		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety and Tolerability of mFOLFOX6 +/- Aflibercept Followed Chemoradiation

End point title	Safety and Tolerability of mFOLFOX6 +/- Aflibercept Followed Chemoradiation
End point description:	
The safety and tolerability of the study therapy will be assessed by means of AEs and changes in laboratory data. AEs will be coded and evaluated using the NCI-CTCAE v4.0 toxicity criteria (if NCI-CTCAE are not applicable, MedDRA will be used).	

End point type	Secondary
End point timeframe:	
Until 2 years and 2 months	

End point values	mFOLFOX6 + Aflibercept	mFOLFOX6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115 ^[1]	65 ^[2]		
Units: Patients				
At least one AE	115	65		
At least one Grade 3-4 AE	83	31		
At least one AE that lead to treatment discontinua	20	4		
At least one AE that lead to death	3	0		
At least one Serious Adverse Event (SAE)	45	16		
At least one treatment-related AE	105	59		
At least one treatment-related AE Grade 3-4	64	17		
At least one treatment-related AE that led to deat	0	0		
At least one treatment-related AE that led to perm	17	3		
At least one treatment-related Serious Adverse Eve	25	3		

Notes:

[1] - Each row is independent (one patient may suffer more than one event on the row list)

[2] - Each row is independent (one patient may suffer more than one event on the row list)

Statistical analyses

No statistical analyses for this end point

Secondary: To Determine the Rate of 30 Days Surgical Complications (Assessed by Means of AEs Reported)

End point title	To Determine the Rate of 30 Days Surgical Complications (Assessed by Means of AEs Reported)
End point description:	
Surgical complications will be assessed by means of AEs reported during 30 days post surgery.	
End point type	Secondary
End point timeframe:	
Until 2 years and 2 months	

End point values	mFOLFOX6 + Aflibercept	mFOLFOX6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115 ^[3]	65 ^[4]		
Units: Patients				
Postoperative AEs	3	1		
Postoperative AEs Grade 3-4	2	0		
Complications	60	30		
Anastomosis fistula	4	1		
wound infection	5	5		
intraabdominal infection	10	1		
Stoma complications	2	0		
Reoperation	9	5		

Notes:

[3] - Each row is independent (one patient may suffer more than one event and count in several rows)

[4] - Each row is independent (one patient may suffer more than one event and count in several rows)

Statistical analyses

No statistical analyses for this end point

Secondary: To Evaluate the 3 Years Local Recurrence and DFS

End point title	To Evaluate the 3 Years Local Recurrence and DFS
End point description:	To determine the rate of local recurrence and DFS at 3-years after completing the Study treatment.
End point type	Secondary
End point timeframe:	Until 5 years and two months

End point values	mFOLFOX6 + Aflibercept	mFOLFOX6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115	65		
Units: Percentage of patients				
arithmetic mean (confidence interval 95%)	75.2 (66.1 to 82.2)	81.5 (69.8 to 89.1)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Throughout the study. Approximately 3 years

Adverse event reporting additional description:

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.

Grade 3 or higher AEs were reported as serious. All the grade 1 and 2 as non serious.

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	20.1
--------------------	------

Reporting groups

Reporting group title	mFOLFOX6 + Aflibercept
-----------------------	------------------------

Reporting group description:

- mFOLFOX-6 scheme: 5-Fluoruracil [5-FU], oxaliplatin and leucovorin will be administered intravenously once every 14 days according to mFOLFOX-6 scheme:

Day 1: Oxaliplatin 85 mg/m² IV infusion in 250-500 mL and leucovorin 200 mg/m² IV, both over two hours, followed by 5-FU 400 mg/m² IV bolus and a 46 h infusion of 5-FU 2400 mg/m².

- Aflibercept, will be administered intravenously (I.V.) at doses of 4 mg/Kg on Day 1 every 14 days. Aflibercept will be supplied to sites by the study Sponsor as 4 ml vials at a concentration of 25 mg/ml. Treatment will continue until six cycles are administered unless unacceptable toxicity or progression occurs.

Aflibercept: Administered I.V. at doses of 4 mg/Kg on Day 1 every 14 days. It will be supplied to sites by Sponsor as 4 ml vials at a concentration of 25 mg/ml

5-Fluoruracil: Once every 14 days. Day 1: 400 mg/m² I.V. bolus and a 46 h infusion of 5-FU 2400 mg/m²

Oxaliplatin: Once every 14 days. Day 1: 85 mg/m² I.V. infusión in 250-500 mL, ove

Reporting group title	mFOLFOX6
-----------------------	----------

Reporting group description:

- mFOLFOX-6 scheme: 5-Fluoruracil [5-FU], oxaliplatin and leucovorin will be administered intravenously once every 14 days according to mFOLFOX-6 scheme:

Day 1: Oxaliplatin 85 mg/m² IV infusion in 250-500 mL and leucovorin 200 mg/m² IV, both over two hours, followed by 5-FU 400 mg/m² IV bolus and a 46 h infusion of 5-FU 2400 mg/m².

Treatment will continue until six cycles are administered unless unacceptable toxicity or progression occurs.

5-Fluoruracil: Once every 14 days. Day 1: 400 mg/m² I.V. bolus and a 46 h infusion of 5-FU 2400 mg/m²

Oxaliplatin: Once every 14 days. Day 1: 85 mg/m² I.V. infusión in 250-500 mL, over two hours, followed by 5-FU

Leucovorin: Once every 14 days. Day 1: 200 mg/m² I.V., over two hours, followed by 5-FU

Serious adverse events	mFOLFOX6 + Aflibercept	mFOLFOX6	
Total subjects affected by serious adverse events			
subjects affected / exposed	45 / 115 (39.13%)	16 / 65 (24.62%)	
number of deaths (all causes)	12	7	
number of deaths resulting from adverse events			
Vascular disorders			
Hypertension			

subjects affected / exposed	0 / 115 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Peripheral neuropathy			
subjects affected / exposed	2 / 115 (1.74%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 115 (1.74%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	4 / 115 (3.48%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 115 (0.87%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphonia			
subjects affected / exposed	1 / 115 (0.87%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 115 (0.87%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	1 / 115 (0.87%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	34 / 115 (29.57%)	2 / 65 (3.08%)	
occurrences causally related to treatment / all	34 / 34	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 115 (0.87%)	2 / 65 (3.08%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	1 / 115 (0.87%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	8 / 115 (6.96%)	4 / 65 (6.15%)	
occurrences causally related to treatment / all	8 / 8	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctalgia			
subjects affected / exposed	1 / 115 (0.87%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	2 / 115 (1.74%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	4 / 115 (3.48%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Palmar-plantar erythrodysaesthesia syndrome			

subjects affected / exposed	3 / 115 (2.61%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Stomatitis			
subjects affected / exposed	0 / 115 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	mFOLFOX6 + Aflibercept	mFOLFOX6	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	115 / 115 (100.00%)	65 / 65 (100.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	22 / 115 (19.13%)	3 / 65 (4.62%)	
occurrences (all)	22	3	
Epistaxis			
subjects affected / exposed	17 / 115 (14.78%)	1 / 65 (1.54%)	
occurrences (all)	17	1	
Nervous system disorders			
Peripheral neuropathy			
subjects affected / exposed	48 / 115 (41.74%)	30 / 65 (46.15%)	
occurrences (all)	48	30	
Dysaesthesia			
subjects affected / exposed	15 / 115 (13.04%)	10 / 65 (15.38%)	
occurrences (all)	15	10	
Paraesthesia			
subjects affected / exposed	11 / 115 (9.57%)	11 / 65 (16.92%)	
occurrences (all)	11	11	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	65 / 115 (56.52%)	38 / 65 (58.46%)	
occurrences (all)	65	38	

Nausea			
subjects affected / exposed	37 / 115 (32.17%)	23 / 65 (35.38%)	
occurrences (all)	37	23	
Abdominal pain			
subjects affected / exposed	16 / 115 (13.91%)	5 / 65 (7.69%)	
occurrences (all)	16	5	
Dysphonia			
subjects affected / exposed	19 / 115 (16.52%)	1 / 65 (1.54%)	
occurrences (all)	19	1	
Pyrexia			
subjects affected / exposed	14 / 115 (12.17%)	4 / 65 (6.15%)	
occurrences (all)	14	4	
Dysgeusia			
subjects affected / exposed	11 / 115 (9.57%)	8 / 65 (12.31%)	
occurrences (all)	11	8	
Musculoskeletal pain			
subjects affected / exposed	11 / 115 (9.57%)	7 / 65 (10.77%)	
occurrences (all)	11	7	
Aphonia			
subjects affected / exposed	14 / 115 (12.17%)	0 / 65 (0.00%)	
occurrences (all)	14	0	
Abdominal pain upper			
subjects affected / exposed	10 / 115 (8.70%)	3 / 65 (4.62%)	
occurrences (all)	10	3	
Fatigue			
subjects affected / exposed	7 / 115 (6.09%)	5 / 65 (7.69%)	
occurrences (all)	7	5	
Headache			
subjects affected / exposed	8 / 115 (6.96%)	1 / 65 (1.54%)	
occurrences (all)	8	1	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	14 / 115 (12.17%)	4 / 65 (6.15%)	
occurrences (all)	14	4	
Thrombocytopenia			

subjects affected / exposed occurrences (all)	9 / 115 (7.83%) 9	7 / 65 (10.77%) 7	
Anaemia subjects affected / exposed occurrences (all)	6 / 115 (5.22%) 6	7 / 65 (10.77%) 7	
Gastrointestinal disorders			
Diarrhoea subjects affected / exposed occurrences (all)	42 / 115 (36.52%) 42	22 / 65 (33.85%) 22	
Mucosal inflammation subjects affected / exposed occurrences (all)	48 / 115 (41.74%) 48	14 / 65 (21.54%) 14	
Vomiting subjects affected / exposed occurrences (all)	21 / 115 (18.26%) 21	13 / 65 (20.00%) 13	
Decreased appetite subjects affected / exposed occurrences (all)	25 / 115 (21.74%) 25	9 / 65 (13.85%) 9	
Constipation subjects affected / exposed occurrences (all)	13 / 115 (11.30%) 13	9 / 65 (13.85%) 9	
Proctalgia subjects affected / exposed occurrences (all)	11 / 115 (9.57%) 11	6 / 65 (9.23%) 6	
Rectal haemorrhage subjects affected / exposed occurrences (all)	14 / 115 (12.17%) 14	3 / 65 (4.62%) 3	
Anal inflammation subjects affected / exposed occurrences (all)	10 / 115 (8.70%) 10	0 / 65 (0.00%) 0	
Rectal tenesmus subjects affected / exposed occurrences (all)	8 / 115 (6.96%) 8	1 / 65 (1.54%) 1	
Skin and subcutaneous tissue disorders Palmar-plantar erythrodysaesthesia syndrome			

subjects affected / exposed occurrences (all)	13 / 115 (11.30%) 13	8 / 65 (12.31%) 8	
Infections and infestations			
Stomatitis			
subjects affected / exposed	14 / 115 (12.17%)	3 / 65 (4.62%)	
occurrences (all)	14	3	
Cystitis			
subjects affected / exposed	9 / 115 (7.83%)	7 / 65 (10.77%)	
occurrences (all)	9	7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported