Clinical trial results:
A phase I/II study of nab-paclitaxel (Abraxane®) and gemcitabine followed by modified FOLFOX (AG-mFOLFOX) in patients with previously untreated, metastatic pancreatic adenocarcinoma

Summary

EudraCT number	2014-005350-19
Trial protocol	ES
Global end of trial date	10 April 2021

Results information

Result version number	v1 (current)
This version publication date	22 June 2022
First version publication date	22 June 2022

Trial information

Trial identification

Sponsor protocol code	TTD-14-05

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02504333
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Spanish Cooperative for Digestive Tumour Therapy (TTD)
Sponsor organisation address	C/ Téllez no. 30 posterior, 1st floor, office 4-2/4-3, Madrid, Spain, 28007
Public contact	TTD, Spanish Cooperative for Digestive Tumour Therapy , 0034 91378 82 75, ttd@ttdgroup.org
Scientific contact	TTD, Spanish Cooperative for Digestive Tumour Therapy, 0034 91 378 82 75, ttd@ttdgroup.org

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	08 April 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 April 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Phase I:
- To determine the safety DLT for the AG-mFOLFOX combination.

Phase II:

Primary objective:
- Clinical efficacy of AG-mFOLFOX vs AG as measured as % of overall survival al 12 months after treatment initiation.

Secondary objective:
- Overall survival rate at 6 months (% OS 6 months).
- Overall survival rate at 24 months (% OS 24 months).
- Time to progression (TTP).
- Progression-free survival (PFS).
- Overall survival (OS).
- Objective radiographic response (ORR) according to RECIST.
- CA 19.9 marker response.
- Safety profile according to NCI-CTCAE version 4 criteria.
- Quality of life of the patients based on the EORTC QLQ-C30/PAN26 and EORTC QLQ-CIPN20 questionnaires, which are specific for neurological toxicity.

Protection of trial subjects:

This clinical study will be conducted in accordance with the protocol, the principles established in the latest version of the Declaration of Helsinki with regard to Good Clinical Practice, current regulations on clinical trials (Royal Decree 1090/2015 regulating clinical trials with medicinal products, the Ethics Committees for Research with medicinal products and the Spanish Clinical Studies Registry regulating clinical trials with medicinal products in Spain, and which incorporates in its entirety the regulations of European Directive 2001/20/EC regarding the provisions of the Member States on the implementation of Good Clinical Practice in the conduct of clinical trials with medicinal products for human use), as well as Act 14/2007, of 3 July on biomedical research, and Royal Decree 1716/2011, of 18 November, in all applicable aspects.

The investigator agrees, on signing the protocol, to comply with the instructions and procedures described therein and, thus, to follow the principles of Good Clinical Practice they entail, as well as the applicable regulations. Furthermore, the investigator will ensure that the staff of his/her team is qualified by education, training, and experience to assume responsibility for the proper conduction of the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 October 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	24 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 168
Worldwide total number of subjects	168
EEA total number of subjects	168

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)	79
From 65 to 84 years	89
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were included in the phase I study from 08-10-2015 to 09-09-2016 in some centers in Spain. A total of 12 patients were recruited but 1 was screening failure.
Patients were included in the phase II study from 27-7-2017 to 16-04-2019 in different centers in Spain. A total of 182 patients were recruited but 25 were screening failures.

Pre-assignment

Screening details:

Patients recruited were ≥ 18 years, had metastatic pancreatic adenocarcinoma (stage IV), a 0-1 ECOG score, a measurable disease according to RECIST criteria version 1.1, an adequate liver, kidney and bone marrow function, and haven't been previously treated with systemic or investigational therapy for metastatic pancreatic cancer.

Period 1

Period 1 title	Phase I/II trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Phase II, Arm A (Control): AG

Arm description:

Nab-paclitaxel (Abraxane®) 125 mg/m2 administered intravenously over 30 minutes followed by gemcitabine 1000 mg/m2 administered intravenously over 30 minutes on days 1, 8, and 15 every 28 days (4 weeks).

Arm type	Active comparator
Investigational medicinal product name	Nab-paclitaxel
Investigational medicinal product code	
Other name	Abraxane®
Pharmaceutical forms	Powder for dispersion for injection
Routes of administration	Intravenous use

Dosage and administration details:

Nab-paclitaxel (Abraxane®) 125 mg/m2 administered intravenously over 30 minutes on days 1, 8, and 15 every 28 days (4 weeks). This treatment will be repeated every 4 weeks (1 treatment cycle).
The dose of the drugs will be calculated based on patient weight. The patient weight used in dose calculation will always be a whole number, so fractions of kg will not be considered in the final weight; for this purpose, body weight will always be rounded to the nearest kg unit.

Investigational medicinal product name	gemcitabine
Investigational medicinal product code	
Other name	Gemzar®
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Gemcitabine 1000 mg/m2 administered intravenously over 30 minutes on days 1, 8, and 15 every 28 days (4 weeks). This treatment will be repeated every 4 weeks (1 treatment cycle).
The dose of the drugs will be calculated based on patient weight. The patient weight used in dose calculation will always be a whole number, so fractions of kg will not be considered in the final weight; for this purpose, body weight will always be rounded to the nearest kg unit.

Arm title	Phase II, Arm B: AG-mFOLFOX

Arm description:

- AG: Nab-paclitaxel (Abraxane®) will be administered intravenously over 30 minutes, followed by gemcitabine intravenously over 30 minutes on days 1, 8 and 15 every 42 days (6 weeks), according to

doses established in Phase I.
- Modified FOLFOX-6 (mFOLFOX-6) administered on day 29 every 42 days (6 weeks), according to doses established in Phase I.

Arm type	Experimental
Investigational medicinal product name	Nab-paclitaxel
Investigational medicinal product code	
Other name	Abraxane®
Pharmaceutical forms	Powder for dispersion for injection
Routes of administration	Intravenous use

Dosage and administration details:

Nab-paclitaxel (Abraxane®) was administered intravenously over 30 minutes on days 1, 8 and 15 every 42 days (6 weeks) according to doses established in Phase I detailed as follows: 125 mg/m2 i.v. 30’ administered on days 1, 8 and 15.
The dose of the drugs was calculated based on patient weight. The patient weight used in dose calculation will always be a whole number, so fractions of kg were not considered in the final weight; for this purpose, body weight was always rounded to the nearest kg unit.

Investigational medicinal product name	gemcitabine
Investigational medicinal product code	
Other name	Gemzar®
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Gemcitabine was administered intravenously over 30 minutes on days 1, 8 and 15 every 42 days (6 weeks) according to doses established in Phase I detailed as follows: 1000 mg/m2 i.v. 30’ administered on days 1, 8 and 15.
The dose of the drugs was calculated based on patient weight. The patient weight used in dose calculation will always be a whole number, so fractions of kg were not considered in the final weight; for this purpose, body weight was always rounded to the nearest kg unit.

Investigational medicinal product name	mFOLFOX-6
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion, Injection/infusion, Powder for solution for infusion
Routes of administration	Intravenous bolus use , Intravenous use

Dosage and administration details:

Modified FOLFOX-6 (mFOLFOX-6) administered on day 29 every 42 days (6 weeks), according to doses established in Phase I detailed below:
Oxaliplatin: 85 mg/m2 i.v. 2 h, day 1, followed by or concomitant to (according to the practice at each site) leucovorin calcium (LV): 400 mg/m2 (racemic) or 200 mg/m2 (L-form) i.v., followed by fluorouracil (5-FU): 400 mg/m2 i.v. as bolus, followed by 5-FU: 2400 mg/m2 administered over 46 h as continuous infusion.

Arm title	Phase I trial

Arm description:

Six patients were enrolled at the highest dose level and then a 3 + 3 dose de-escalation schema was carried out. The criterion for de-escalation was more than one out of six patients reporting dose-limiting toxicity (DLT). A patient was evaluable at a given dose level, if had completed two cycles of treatment, comprising the two sequential schemes repeated twice, or have withdrawn from the study as result of a DLT. Each treatment cycle consisted of a 42-day period with therapy administered as follows: 30-min intravenous IV nab-paclitaxel infusion (125 mg/m2) followed by 30-min IV GEM infusion (1000 mg/m2) on days 1, 8 and 15 and 120-min IV oxaliplatin infusion (85 mg/m2), followed or concomitant (according to clinical practice) to 120-min IV L-leucovorin (200 mg/m2) or racemic leucovorin (400 mg/m2) infusion, followed by IV bolus of 5-FU (400 mg/m2) and followed by 46-h IV 5-FU infusion (2400 mg/m2) on day 29.

Arm type	dose de-escalation

Investigational medicinal product name	Nab-paclitaxel
Investigational medicinal product code	
Other name	Abraxane®
Pharmaceutical forms	Powder for dispersion for injection
Routes of administration	Intravenous use

Dosage and administration details:

Nab-paclitaxel (Abraxane®) was administered intravenously over 30 minutes on days 1, 8 and 15 every 42 days (6 weeks) according to doses established in Phase I detailed as follows: 125 mg/m2 i.v. 30’ administered on days 1, 8 and 15.
The dose of the drugs was calculated based on patient weight. The patient weight used in dose calculation will always be a whole number, so fractions of kg were not considered in the final weight; for this purpose, body weight was always rounded to the nearest kg unit.

Investigational medicinal product name	gemcitabine
Investigational medicinal product code	
Other name	Gemzar®
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Gemcitabine was administered intravenously over 30 minutes on days 1, 8 and 15 every 42 days (6 weeks) according to doses established in Phase I detailed as follows: 1000 mg/m2 i.v. 30’ administered on days 1, 8 and 15.
The dose of the drugs was calculated based on patient weight. The patient weight used in dose calculation will always be a whole number, so fractions of kg were not considered in the final weight; for this purpose, body weight was always rounded to the nearest kg unit.

Investigational medicinal product name	mFOLFOX-6
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion, Injection/infusion, Powder for solution for infusion
Routes of administration	Intravenous bolus use , Intravenous use

Dosage and administration details:

Modified FOLFOX-6 (mFOLFOX-6) administered on day 29 every 42 days (6 weeks), according to doses established in Phase I detailed below:
Oxaliplatin: 85 mg/m2 i.v. 2 h, day 1, followed by or concomitant to (according to the practice at each site) leucovorin calcium (LV): 400 mg/m2 (racemic) or 200 mg/m2 (L-form) i.v., followed by fluorouracil (5-FU): 400 mg/m2 i.v. as bolus, followed by 5-FU: 2400 mg/m2 administered over 46 h as continuous infusion.

Number of subjects in period 1	Phase II, Arm A (Control): AG	Phase II, Arm B: AG-mFOLFOX	Phase I trial
Started	79	78	11
Completed	4	12	5
Not completed	75	66	6
Consent withdrawn by subject	-	1	-
death of the patient	75	64	6
Lost to follow-up	-	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Phase II, Arm A (Control): AG
Reporting group description:	
Nab-paclitaxel (Abraxane®) 125 mg/m2 administered intravenously over 30 minutes followed by gemcitabine 1000 mg/m2 administered intravenously over 30 minutes on days 1, 8, and 15 every 28 days (4 weeks).	
Reporting group title	Phase II, Arm B: AG-mFOLFOX
Reporting group description:	
- AG: Nab-paclitaxel (Abraxane®) will be administered intravenously over 30 minutes, followed by gemcitabine intravenously over 30 minutes on days 1, 8 and 15 every 42 days (6 weeks), according to doses established in Phase I. - Modified FOLFOX-6 (mFOLFOX-6) administered on day 29 every 42 days (6 weeks), according to doses established in Phase I.	
Reporting group title	Phase I trial
Reporting group description:	
Six patients were enrolled at the highest dose level and then a 3 + 3 dose de-escalation schema was carried out. The criterion for de-escalation was more than one out of six patients reporting dose-limiting toxicity (DLT). A patient was evaluable at a given dose level, if had completed two cycles of treatment, comprising the two sequential schemes repeated twice, or have withdrawn from the study as result of a DLT. Each treatment cycle consisted of a 42-day period with therapy administered as follows: 30-min intravenous IV nab-paclitaxel infusion (125 mg/m2) followed by 30-min IV GEM infusion (1000 mg/m2) on days 1, 8 and 15 and 120-min IV oxaliplatin infusion (85 mg/m2), followed or concomitant (according to clinical practice) to 120-min IV L-leucovorin (200 mg/m2) or racemic leucovorin (400 mg/m2) infusion, followed by IV bolus of 5-FU (400 mg/m2) and followed by 46-h IV 5-FU infusion (2400 mg/m2) on day 29.	

Reporting group values	Phase II, Arm A (Control): AG	Phase II, Arm B: AG-mFOLFOX	Phase I trial
Number of subjects	79	78	11
Age categorical Units: Subjects			
≤65 años	44	38	8
>65 años	35	40	3
Age continuous Units: years			
arithmetic mean	64.0	64.6	60.1
standard deviation	± 10.0	± 8.9	± 9.0
Gender categorical Units: Subjects			
Female	43	37	5
Male	36	41	6
ECOG scale			
The ECOG Performance Status Scale describes a patient's level of functioning in terms of their ability to care for themself, daily activity, and physical ability (walking, working, etc.). ECOG performance grade: • ECOG 0: The patient is completely asymptomatic and is able to perform normal work and activities of daily living. • ECOG 1: The patient has symptoms that prevent him/her from doing hard work, although he/she performs normally in daily activities and light work. The patient only stays in bed during night sleep.			
Units: Subjects			
ECOG 0	22	22	4
ECOG 1	57	56	7
Baseline medical history			

Does the patient present relevant past or active pathological history and/or symptoms related to the disease under study?			
Units: Subjects			
No	4	5	2
Yes	75	73	9
TNM grade at diagnosis			
Stage 0: Cancer in situ. Stage IA: Tumor is ≤ 2 cm in the pancreas. It has not spread to lymph nodes or other parts. Stage IB: Tumor is > 2 cm in the pancreas. It has not spread to lymph nodes or other parts. Stage IIA: Tumor is > 4 cm and extends beyond the pancreas. It has not spread to lymph nodes, or other parts. Stage IIB: Tumor of any size. It has spread to 1 to 3 regional lymph nodes but not to other parts Stage III: Tumor of any size. It has spread ≥ 4 regional lymph nodes but not to other parts, or has spread to nearby arteries and veins Stage IV: Tumor has spread along the body			
Units: Subjects			
IA	1	0	0
IB	1	0	0
IIA	2	0	0
IIB	1	3	1
III	4	3	0
IV	70	71	10
Unknown	0	1	0
Pancreatic tumour location: Head Units: Subjects			
No	47	48	6
Yes	32	30	5
Pancreatic tumour location: body Units: Subjects			
No	51	47	6
Yes	28	31	5
Pancreatic tumour location: tail Units: Subjects			
No	51	51	7
Yes	28	27	4
Pancreatic tumour location: Uncinate process Units: Subjects			
No	79	74	10
Yes	0	4	1
Pancreatic tumour location: unknown Units: Subjects			
No	79	76	10
Yes	0	2	1
Metastasis Units: Subjects			
Synchronous	75	74	9
Metachronous	4	4	2
Current location of tumors: liver Units: Subjects			
No	20	18	0
Yes	59	60	11
Current location of tumors: lungs			

Units: Subjects			
No	59	51	10
Yes	20	27	1
Current location of tumors: peritoneum Units: Subjects			
No	54	57	10
Yes	25	21	1
Current location of tumors: pancreas Units: Subjects			
No	8	11	1
Yes	71	67	10
Current location of tumors: regional lymph nodes Units: Subjects			
No	64	62	10
Yes	15	16	1
Current location of tumors: distant lymph nodes Units: Subjects			
No	66	63	11
Yes	13	15	0
Current location of tumors: stomach Units: Subjects			
No	79	77	11
Yes	0	1	0
Current location of tumors: large intestine Units: Subjects			
No	78	77	11
Yes	1	1	0
Current location of tumors: bones Units: Subjects			
No	78	73	10
Yes	1	5	1
Current location of tumors: other parts of the body Units: Subjects			
No	70	62	9
Yes	9	16	2
Number of organs involved Units: Subjects			
1 organ	3	2	1
2 organs	35	26	7
3 organs	27	31	2
4 organs	10	12	1
5 organs	4	5	0
6 organs	0	2	0
Patients with at least one previous surgery Units: Subjects			
No surgery	66	63	10
Surgery	13	15	1
Previous chemotherapy for pancreatic			

cancer Units: Subjects			
No	77	73	11
Yes	2	5	0
Previous radiotherapy			
The intention of radiotherapy has been adjuvant.			
Units: Subjects			
No	78	78	11
Yes	1	0	0
Weight Units: Kg			
arithmetic mean	68.7	67.5	71.4
standard deviation	± 15.4	± 13.2	± 14.4
Height Units: cm			
arithmetic mean	163.3	164.1	165.9
standard deviation	± 8.4	± 8.8	± 10.7
Body surface Units: m2			
arithmetic mean	1.7	1.7	1.8
standard deviation	± 0.2	± 0.2	± 0.2
Time since initial diagnosis of pancreatic cancer			
Time from initial diagnosis of pancreatic cancer to inclusion in the study (Inclusion date - Diagnosis date).			
Units: months			
arithmetic mean	2.0	2.6	1.1
standard deviation	± 4.7	± 6.0	± 0.9
Time since diagnosis of metastatic pancreatic cancer			
Time from diagnosis of metastatic pancreatic cancer to inclusion in the study (Date of inclusion - Date of diagnosis of metastatic cancer).			
Units: months			
arithmetic mean	0.9	1.3	1.0
standard deviation	± 0.7	± 3.1	± 0.9

Reporting group values	Total		
Number of subjects	168		
Age categorical Units: Subjects			
≤65 años	90		
>65 años	78		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	85		
Male	83		

ECOG scale			
The ECOG Performance Status Scale describes a patient's level of functioning in terms of their ability to care for themself, daily activity, and physical ability (walking, working, etc.). ECOG performance grade: • ECOG 0: The patient is completely asymptomatic and is able to perform normal work and activities of daily living. • ECOG 1: The patient has symptoms that prevent him/her from doing hard work, although he/she performs normally in daily activities and light work. The patient only stays in bed during night sleep.			
Units: Subjects			
ECOG 0	48		
ECOG 1	120		
Baseline medical history			
Does the patient present relevant past or active pathological history and/or symptoms related to the disease under study?			
Units: Subjects			
No	11		
Yes	157		
TNM grade at diagnosis			
Stage 0: Cancer in situ. Stage IA: Tumor is ≤ 2 cm in the pancreas. It has not spread to lymph nodes or other parts. Stage IB: Tumor is > 2 cm in the pancreas. It has not spread to lymph nodes or other parts. Stage IIA: Tumor is > 4 cm and extends beyond the pancreas. It has not spread to lymph nodes, or other parts. Stage IIB: Tumor of any size. It has spread to 1 to 3 regional lymph nodes but not to other parts Stage III: Tumor of any size. It has spread ≥ 4 regional lymph nodes but not to other parts, or has spread to nearby arteries and veins Stage IV: Tumor has spread along the body			
Units: Subjects			
IA	1		
IB	1		
IIA	2		
IIB	5		
III	7		
IV	151		
Unknown	1		
Pancreatic tumour location: Head Units: Subjects			
No	101		
Yes	67		
Pancreatic tumour location: body Units: Subjects			
No	104		
Yes	64		
Pancreatic tumour location: tail Units: Subjects			
No	109		
Yes	59		
Pancreatic tumour location: Uncinate process Units: Subjects			
No	163		
Yes	5		
Pancreatic tumour location: unknown Units: Subjects			
No	165		
Yes	3		

Metastasis Units: Subjects			
Synchronous	158		
Metachronous	10		
Current location of tumors: liver Units: Subjects			
No	38		
Yes	130		
Current location of tumors: lungs Units: Subjects			
No	120		
Yes	48		
Current location of tumors: peritoneum Units: Subjects			
No	121		
Yes	47		
Current location of tumors: pancreas Units: Subjects			
No	20		
Yes	148		
Current location of tumors: regional lymph nodes Units: Subjects			
No	136		
Yes	32		
Current location of tumors: distant lymph nodes Units: Subjects			
No	140		
Yes	28		
Current location of tumors: stomach Units: Subjects			
No	167		
Yes	1		
Current location of tumors: large intestine Units: Subjects			
No	166		
Yes	2		
Current location of tumors: bones Units: Subjects			
No	161		
Yes	7		
Current location of tumors: other parts of the body Units: Subjects			
No	141		
Yes	27		
Number of organs involved Units: Subjects			
1 organ	6		
2 organs	68		

3 organs	60		
4 organs	23		
5 organs	9		
6 organs	2		
Patients with at least one previous surgery Units: Subjects			
No surgery	139		
Surgery	29		
Previous chemotherapy for pancreatic cancer Units: Subjects			
No	161		
Yes	7		
Previous radiotherapy			
The intention of radiotherapy has been adjuvant.			
Units: Subjects			
No	167		
Yes	1		
Weight Units: Kg arithmetic mean standard deviation	- -		
Height Units: cm arithmetic mean standard deviation	- -		
Body surface Units: m2 arithmetic mean standard deviation	- -		
Time since initial diagnosis of pancreatic cancer			
Time from initial diagnosis of pancreatic cancer to inclusion in the study (Inclusion date - Diagnosis date).			
Units: months arithmetic mean standard deviation	- -		
Time since diagnosis of metastatic pancreatic cancer			
Time from diagnosis of metastatic pancreatic cancer to inclusion in the study (Date of inclusion - Date of diagnosis of metastatic cancer).			
Units: months arithmetic mean standard deviation	- -		

End points

End points reporting groups

Reporting group title	Phase II, Arm A (Control): AG

Reporting group description:

Nab-paclitaxel (Abraxane®) 125 mg/m2 administered intravenously over 30 minutes followed by gemcitabine 1000 mg/m2 administered intravenously over 30 minutes on days 1, 8, and 15 every 28 days (4 weeks).

Reporting group title	Phase II, Arm B: AG-mFOLFOX

Reporting group description:

- AG: Nab-paclitaxel (Abraxane®) will be administered intravenously over 30 minutes, followed by gemcitabine intravenously over 30 minutes on days 1, 8 and 15 every 42 days (6 weeks), according to doses established in Phase I.
- Modified FOLFOX-6 (mFOLFOX-6) administered on day 29 every 42 days (6 weeks), according to doses established in Phase I.

Reporting group title	Phase I trial

Reporting group description:

Six patients were enrolled at the highest dose level and then a 3 + 3 dose de-escalation schema was carried out. The criterion for de-escalation was more than one out of six patients reporting dose-limiting toxicity (DLT). A patient was evaluable at a given dose level, if had completed two cycles of treatment, comprising the two sequential schemes repeated twice, or have withdrawn from the study as result of a DLT. Each treatment cycle consisted of a 42-day period with therapy administered as follows: 30-min intravenous IV nab-paclitaxel infusion (125 mg/m2) followed by 30-min IV GEM infusion (1000 mg/m2) on days 1, 8 and 15 and 120-min IV oxaliplatin infusion (85 mg/m2), followed or concomitant (according to clinical practice) to 120-min IV L-leucovorin (200 mg/m2) or racemic leucovorin (400 mg/m2) infusion, followed by IV bolus of 5-FU (400 mg/m2) and followed by 46-h IV 5-FU infusion (2400 mg/m2) on day 29.

Primary: Maximum-tolerated dose (MTD) evaluation

End point title	Maximum-tolerated dose (MTD) evaluation[1][2]

End point description:

Six patients were enrolled at the highest dose level and then a 3 + 3 dose de-escalation schema was carried out. The criterion for de-escalation was more than one out of six patients reporting dose-limiting toxicity (DLT). A patient was evaluable at a given dose level, if had completed two cycles of treatment, or have withdrawn from the study as result of a DLT.
Treatment continued until disease progression, unacceptable toxicity or consent withdrawal. New treatment cycle was not started until absolute neutrophil count ≥1500/mL, platelet count ≥100 000/mL, serum bilirubin level ≤1.5 x upper limit of normal, creatinine clearance level ≥40 mL/min and recovery from other clinically significant non-haematologic toxicities (except alopecia) <Grade 2. If the patient did not meet these
criteria, treatment was delayed until these requirements were met. Patients who required a treatment delay of >4 weeks were removed.
Note: there was no reduction in the dose of folinic acid.

End point type	Primary

End point timeframe:

Two cycles of treatment of 42 days

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This is a single-arm phase I clinical trial, therefore, no statistical analysis was performed for this endpoint.
[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The maximum-tolerated dose was only evaluated for patients in the Phase I part of the trial as defined in the study protocol.

End point values	Phase I trial			
Subject group type	Reporting group			
Number of subjects analysed	6[3]			
Units: mg/m2				
number (not applicable)				
Nab-paclitaxel	125			
Gemcitabine	1000			
mFOLFOX: Oxaliplatin	85			
mFOLFOX: 5-FU bolus	400			
mFOLFOX: 5-FU infusion	2400			

Notes:

[3] - Five patients were excluded for not completing two cycles of treatment.

Statistical analyses

No statistical analyses for this end point

Primary: Overall survival rate at 12 months

End point title	Overall survival rate at 12 months[4]

End point description:

Overall survival rate at 12 months is defined as the percentage of patients alive 12 months after inclusion in the study. To calculate this, an analysis will be made using the Kaplan-Meier method. The Kaplan-Meier plot, median survival and 95% confidence interval was calculated, and the number of events and censored events as well. The 12-month live patient rate and its 95% confidence interval is provided below.

End point type	Primary

End point timeframe:

12 months

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The overall survival rate at 12 months was only evaluated for patients in the Phase II part of the trial as defined in the study protocol.

End point values	Phase II, Arm A (Control): AG	Phase II, Arm B: AG-mFOLFOX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	78		
Units: Percentage (%)				
number (confidence interval 95%)	35.4 (24.9 to 46.0)	55.3 (44.2 to 66.5)		

Statistical analyses

Statistical analysis title	Fisher's exact test

Statistical analysis description:

Fisher's exact test is a statistical significance test used in the analysis of contingency tables to analyze whether two dichotomous variables are associated when the sample to be studied is too small.

Comparison groups	Phase II, Arm A (Control): AG v Phase II, Arm B: AG-mFOLFOX

Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.016 [5]
Method	Fisher exact

Notes:

[5] - Overall survival rate of AG-mFOLFOX-6 is significantly higher than AG (Control).

Secondary: Preliminary efficacy assessment

End point title	Preliminary efficacy assessment[6]

End point description:

The preliminary efficacy was assessed by the Objective Response Rate (ORR) and the Disease Control Rate (DCR). ORR is the percentage of patients with advanced or metastatic cancer in a clinical study who have a partial or complete response to the treatment according to RECIST 1.1 criteria within a certain period of time. A partial response (PR) is a decrease in the size of a tumor or in the amount of cancer in the body, and a complete response (CR) is the disappearance of all signs of cancer in the body. DCR is defined as the percentage of patients with advanced or metastatic cancer who have achieved complete response, partial response and stable disease (SD) to a therapeutic intervention in clinical trials of anticancer agents.

End point type	Secondary

End point timeframe:

October 2015- September 2016.

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The preliminary efficacy assessment was only evaluated for patients in the Phase I part of the trial as defined in the study protocol.

End point values	Phase I trial			
Subject group type	Reporting group			
Number of subjects analysed	10[7]			
Units: Percentage (%)				
number (confidence interval 95%)				
Objective response rate (CR=0; PR=5)	50 (20.1 to 79.9)			
Disease control rate (CR=0; PR=5; SD=3)	80 (44.2 to 96.5)			

Notes:

[7] - One patient died before the first CT.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival rate at 6 months

End point title	Overall survival rate at 6 months[8]

End point description:

Overall survival rate at 6 months is defined as the percentage of patients alive 6 months after inclusion in the study. To calculate this, an analysis will be made using the Kaplan-Meier method. The Kaplan-Meier plot, median survival and 95% confidence interval was calculated, and the number of events and censored events as well. The 6-month live patient rate and its 95% confidence interval is provided below.

End point type	Secondary

End point timeframe:

6 months

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The overall survival rate at 6 months was only evaluated for patients in the Phase II part of the trial as defined in the study protocol.

End point values	Phase II, Arm A (Control): AG	Phase II, Arm B: AG-mFOLFOX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	78		
Units: Percentage (%)				
number (confidence interval 95%)	69.6 (59.5 to 79.8)	73.8 (63.9 to 83.7)		

Statistical analyses

Statistical analysis title	Fisher's exact test
Comparison groups	Phase II, Arm A (Control): AG v Phase II, Arm B: AG-mFOLFOX
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.598 [9]
Method	Fisher exact

Notes:

[9] - No statistically significant

Secondary: Overall survival rate at 24 months

End point title	Overall survival rate at 24 months[10]

End point description:

Overall survival rate at 24 months is defined as the percentage of patients alive 24 months after inclusion in the study. To calculate this, an analysis will be made using the Kaplan-Meier method. The Kaplan-Meier plot, median survival and 95% confidence interval was calculated, and the number of events and censored events as well. The 24-month live patient rate and its 95% confidence interval is provided below.

End point type	Secondary

End point timeframe:

24 months

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The overall survival rate at 24 months was only evaluated for patients in the Phase II part of the trial as defined in the study protocol.

End point values	Phase II, Arm A (Control): AG	Phase II, Arm B: AG-mFOLFOX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	78		
Units: Percentage (%)				
number (confidence interval 95%)	7.6 (1.8 to 13.4)	22.4 (13.0 to 31.8)		

Statistical analyses

Statistical analysis title	Fisher's exact test
Comparison groups	Phase II, Arm A (Control): AG v Phase II, Arm B: AG-mFOLFOX
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.012
Method	Fisher exact

Secondary: Time to progression (TTP)

End point title	Time to progression (TTP)[11]

End point description:

TTP is the length of time from the date of diagnosis or the start of treatment for a disease until the disease starts to get worse or spread to other parts of the body. The analysis was made using the Kaplan-Meier method estimating median time to progression and 95% confidence interval. Patients who have not shown disease progression or death were censored at the date of the last response assessment. If a patient has several response evaluations showing disease progression, the first of these evaluations was used in the time to progression analysis.
Patients who are given a new treatment (radiotherapy or chemotherapy, other treatments) and have not progressed or have documented progression or death following the initiation of that new treatment have been censored at the date of initiation of that treatment, even if this is the treatment under study.
Patients in whom no tumor assessments are available after the baseline assessment have been censored on day 1.

End point type	Secondary

End point timeframe:

From the date of randomization/inclusion of treatment until the patient progresses or dies due to disease progression.

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Time to progression was only evaluated for patients in the Phase II part of the trial as defined in the study protocol.

End point values	Phase II, Arm A (Control): AG	Phase II, Arm B: AG-mFOLFOX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	78		
Units: month				
median (confidence interval 95%)	5.296 (3.285 to 7.307)	9.276 (5.840 to 12.713)		

Statistical analyses

Statistical analysis title	Log rank test

Statistical analysis description:

The log rank test is a statistical methodology for comparing the distribution of time until the occurrence of an event of interest in independent groups.

Comparison groups	Phase II, Arm A (Control): AG v Phase II, Arm B: AG-mFOLFOX
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [12]
Method	Logrank
Parameter estimate	Odds ratio (OR)

Notes:

[12] - Time to progression for AG-mFOLFOX regimen is statistically higher than for AG regimen.

Statistical analysis title	Cox regression

Statistical analysis description:

The Cox proportional-hazards model is essentially a regression model commonly used statistical in medical research for investigating the association between the survival time of patients and one or more predictor variables.

Comparison groups	Phase II, Arm A (Control): AG v Phase II, Arm B: AG-mFOLFOX
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [13]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.462
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.319
upper limit	0.669

Notes:

[13] - Time to progression for AG-mFOLFOX regimen is statistically higher than for AG regimen.

Secondary: Progression-free survival (PFS)

End point title	Progression-free survival (PFS)[14]

End point description:

PFS is the length of time during and after the treatment of a disease that a patient lives with the disease but it does not get worse. The analysis was made using the Kaplan-Meier method estimating median progression-free survival and 95% confidence interval. Patients who have not shown disease progression or death were censored at the date of the last response assessment. If a patient has several response evaluations showing disease progression, the first of these evaluations was used in the time to progression analysis.
Patients who are given a new treatment (radiotherapy or chemotherapy, other treatments) and have not progressed or have documented progression or death following the initiation of that new treatment have been censored at the date of initiation of that treatment, even if this is the treatment under study.
Patients in whom no tumor assessments are available after the baseline assessment have been censored on day 1.

End point type	Secondary

End point timeframe:

From the date of randomization/inclusion of treatment until the patient progresses or dies of any cause.

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Progression-free survival was only evaluated for patients in the Phase II part of the trial as defined in the study protocol.

End point values	Phase II, Arm A (Control): AG	Phase II, Arm B: AG-mFOLFOX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	78		
Units: months				
median (confidence interval 95%)	5.164 (3.278 to 7.051)	7.895 (6.207 to 9.583)		

Statistical analyses

Statistical analysis title	Log rank test
Comparison groups	Phase II, Arm A (Control): AG v Phase II, Arm B: AG-mFOLFOX
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [15]
Method	Logrank
Parameter estimate	Odds ratio (OR)

Notes:

[15] - Free-progression survival for AG-mFOLFOX regimen is statistically higher than for AG regimen.

Statistical analysis title	Cox regression
Comparison groups	Phase II, Arm A (Control): AG v Phase II, Arm B: AG-mFOLFOX
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [16]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.516
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.363
upper limit	0.734

Notes:

[16] - Free-progression survival for AG-mFOLFOX regimen is statistically higher than for AG regimen.

Secondary: Overall survival (OS)

End point title	Overall survival (OS)[17]

End point description:

Overall survival is the time elapsed from the date of randomization/inclusion until the patient dies of any

cause. In the rest of the patients, the last available follow-up was taken as the last control. The analysis was made using the Kaplan-Meier method estimating median overall survival and 95% confidence interval.

End point type	Secondary

End point timeframe:

From the date of randomization/inclusion until the patient dies of any cause.

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The overall survival was only evaluated for patients in the Phase II part of the trial as defined in the study protocol.

End point values	Phase II, Arm A (Control): AG	Phase II, Arm B: AG-mFOLFOX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	78		
Units: months				
median (confidence interval 95%)	9.737 (7.477 to 11.997)	13.158 (10.072 to 16.243)		

Statistical analyses

Statistical analysis title	Log rank test
Comparison groups	Phase II, Arm A (Control): AG v Phase II, Arm B: AG-mFOLFOX
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.022 [18]
Method	Logrank
Parameter estimate	Odds ratio (OR)

Notes:

[18] - Overall survival for AG-mFOLFOX regimen is statistically higher than for AG regimen.

Statistical analysis title	Cox regression
Comparison groups	Phase II, Arm A (Control): AG v Phase II, Arm B: AG-mFOLFOX
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.023 [19]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.676
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.483
upper limit	0.947

Notes:

[19] - Overall survival for AG-mFOLFOX regimen is statistically higher than for AG regimen.

Secondary: Best overall response

End point title	Best overall response[20]

End point description:

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence according to RECIST criteria:
- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or
non-target) must have reduction in short axis to <10 mm.
- Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate
an absolute increase of at least 5 mm.
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as
reference the smallest sum diameters while on study.
- NE: not evaluated.

End point type	Secondary

End point timeframe:

36 months

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only Phase II subjects were analyzed in this endpoint.

End point values	Phase II, Arm A (Control): AG	Phase II, Arm B: AG-mFOLFOX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	78		
Units: patients				
Complete response (CR)	0	4		
Partial response (PR)	22	36		
Stable disease (SD)	32	22		
Progressive disease (PD)	17	7		
NE	8	9		

Statistical analyses

Statistical analysis title	Fisher's exact test
Comparison groups	Phase II, Arm A (Control): AG v Phase II, Arm B: AG-mFOLFOX
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.008
Method	Fisher exact

Secondary: Objective response rate (ORR)

End point title	Objective response rate (ORR)[21]

End point description:

ORR is the percentage of patients with advanced or metastatic cancer in a clinical study who have a partial or complete response to the treatment according to RECIST 1.1 criteria within a certain period of time. A partial response (PR) is a decrease in the size of a tumor or in the amount of cancer in the body, and a complete response (CR) is the disappearance of all signs of cancer in the body.

End point type	Secondary

End point timeframe:

36 months

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only Phase II subjects were analyzed in this endpoint.

End point values	Phase II, Arm A (Control): AG	Phase II, Arm B: AG-mFOLFOX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	78		
Units: percentage (%)				
number (confidence interval 95%)	27.8 (18.4 to 39.1)	51.3 (39.7 to 62.8)		

Statistical analyses

Statistical analysis title	Fisher's exact test
Comparison groups	Phase II, Arm A (Control): AG v Phase II, Arm B: AG-mFOLFOX
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003 [22]
Method	Fisher exact

Notes:

[22] - ORR of AG-mFOLFOX regimen is significantly higher than ORR of AG regimen (control).

Secondary: Confirmed best overall response

End point title	Confirmed best overall response[23]

End point description:

The best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation according to RECIST criteria.

End point type	Secondary

End point timeframe:

36 months

Notes:

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only Phase II subjects were analyzed in this endpoint.

End point values	Phase II, Arm A (Control): AG	Phase II, Arm B: AG-mFOLFOX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	78		
Units: patients				
Complete response (CR)	0	3		
Partial response (PR)	16	28		
Stable disease (SD)	38	31		
Progressive response (PR)	17	7		
Not evaluated (NE)	8	9		

Statistical analyses

Statistical analysis title	Fisher's exact test
Comparison groups	Phase II, Arm A (Control): AG v Phase II, Arm B: AG-mFOLFOX
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.022
Method	Fisher exact

Secondary: Confirmed ORR

End point title	Confirmed ORR[24]

End point description:

ORR is the percentage of patients with advanced or metastatic cancer in a clinical study who have a partial or complete response to the treatment according to RECIST 1.1 criteria within a certain period of time. Confirmation of CR and PR es required.

End point type	Secondary

End point timeframe:

36 months

Notes:

[24] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only Phase II subjects were analyzed in this endpoint.

End point values	Phase II, Arm A (Control): AG	Phase II, Arm B: AG-mFOLFOX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	78		
Units: percentage (%)				
median (confidence interval 95%)	20.3 (12.4 to 30.8)	39.7 (28.8 to 51.5)		

Statistical analyses

Statistical analysis title	Fisher's exact test
Comparison groups	Phase II, Arm B: AG-mFOLFOX v Phase II, Arm A (Control): AG
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.009 [25]
Method	Fisher exact

Notes:

[25] - Confirmed ORR of AG-mFOLFOX regimen is significantly higher than ORR of AG regimen (control).

Secondary: CA 19-9 levels

End point title	CA 19-9 levels[26]

End point description:

This test measures the amount of a protein called CA 19-9 (cancer antigen 19-9) in the blood. CA 19-9 is a type of tumor marker. CA 19-9 was analyzed at baseline visit (within 14 days prior to study inclusion/randomization) and at each evaluation visit (every 8 ± 2 weeks regardless of delays and/or cycles administered).

End point type	Secondary

End point timeframe:

36 months

Notes:

[26] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only Phase II subjects were analyzed in this endpoint.

End point values	Phase II, Arm A (Control): AG	Phase II, Arm B: AG-mFOLFOX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79[27]	78[28]		
Units: U/mL				
median (inter-quartile range (Q1-Q3))				
Baseline visit (NA=75; NB= 73)	398.2 (28.4 to 2918.0)	861.0 (92.2 to 10634.1)		
Evaluation visit 1 (NA=68; NB=64)	170.5 (16.3 to 982.3)	228.7 (21.1 to 3841.3)		
Evaluation visit 2 (NA=49; NB=55)	117.3 (19.3 to 564.3)	83.4 (13.6 to 1308.0)		
Evaluation visit 3 (NA=32; NB=47)	48.1 (6.4 to 772.0)	50.0 (8.8 to 558.5)		

Evaluation visit 4 (NA=23; NB=37)	117.8 (12.0 to 1315.0)	39.6 (8.0 to 385.1)		
Evaluation visit 5 (NA=15; NB=35)	30.9 (5.2 to 1586.5)	25.3 (8.9 to 450.3)		
Evaluation visit 6 (NA=9; NB=24)	21.2 (8.2 to 168.6)	21.1 (7.5 to 61.4)		
Evaluation visit 7 (NA=8; NB=23)	42.9 (8.1 to 101.6)	47.4 (9.0 to 215.0)		
Evaluation visit 8 (NA=4; NB=18)	47.8 (8.2 to 705.0)	19.3 (8.4 to 122.8)		
Evaluation visit 9 (NA=1; NB=17)	11.3 (11.3 to 11.3)	66.0 (16.0 to 714.7)		
Evaluation visit 10 (NA=1; NB=11)	19.1 (19.1 to 19.1)	49.4 (15.0 to 249.9)		
Evaluation visit 11 (NA=1; NB=9)	14.9 (14.9 to 14.9)	30.3 (14.6 to 429.7)		
Evaluation visit 12 (NA=1; NB=8)	14.9 (14.9 to 14.9)	174.7 (14.3 to 1081.6)		
Evaluation visit 13 (NA=0; NB=4)	0 (0 to 0)	246.3 (14.0 to 1667.5)		
Evaluation visit 14 (NA=0; NB=4)	0 (0 to 0)	16.2 (12.6 to 934.7)		
Evaluation visit 15 (NA=0; NB=3)	0 (0 to 0)	19.9 (13.8 to 1221.4)		
Evaluation visit 16 (NA=0; NB=3)	0 (0 to 0)	22.9 (18.5 to 1257.2)		

Notes:

[27] - NA indicates the number of patients analyzed in arm A at each visit

[28] - NB indicates the number of patients analyzed in arm B at each visit.

Statistical analyses

Statistical analysis title	Evaluation 3 (aprox. 6 months)
Comparison groups	Phase II, Arm A (Control): AG v Phase II, Arm B: AG-mFOLFOX
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.795
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Evaluation 6 (aprox. 12 months)
Comparison groups	Phase II, Arm A (Control): AG v Phase II, Arm B: AG-mFOLFOX
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.919
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Evaluation 12 (aprox. 24 months)
Comparison groups	Phase II, Arm A (Control): AG v Phase II, Arm B: AG-mFOLFOX

Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.439
Method	Wilcoxon (Mann-Whitney)

Secondary: EORTC QLQ-C30 scale (cycle 1)

End point title	EORTC QLQ-C30 scale (cycle 1)[29]

End point description:

Quality of life questionnaire specific for neurological toxicity. The scores for each dimension have been calculated according to the scoring algorithms (QLQ C30 SCmanual/ ISBN 2-9300 64-22-6 /Third edition, 2001).

End point type	Secondary

End point timeframe:

First cycle (day 1)

Notes:

[29] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only Phase II subjects were analyzed in this endpoint.

End point values	Phase II, Arm A (Control): AG	Phase II, Arm B: AG-mFOLFOX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79[30]	78[31]		
Units: score				
arithmetic mean (standard deviation)				
Global health status/Qol (NA=67; NB=61)	47.5 (± 22.5)	54.4 (± 25.7)		
Physical functioning (NA=67; NB=60)	74.0 (± 24.0)	80.4 (± 19.0)		
Role functioning (NA=67; NB=61)	60.7 (± 33.9)	73.2 (± 30.0)		
Emotional functioning (NA=66; NB=61)	67.2 (± 20.9)	68.3 (± 22.2)		
Cognitive functioning (NA=67; NB=61)	85.3 (± 22.2)	88.0 (± 19.5)		
Social functioning (NA=64; NB=60)	69.5 (± 28.1)	74.2 (± 26.6)		
Fatigue (NA=67; NB=61)	40.9 (± 28.0)	34.8 (± 29.4)		
Nausea and vomiting (NA=67; NB=61)	9.7 (± 17.4)	11.2 (± 22.3)		
Pain (NA=67; NB=61)	44.8 (± 30.3)	35.0 (± 29.5)		
Dyspnoea (NA=65; NB=60)	13.8 (± 25.6)	13.9 (± 28.3)		
Insomnia (NA=67; NB=60)	67.2 (± 28.7)	66.1 (± 31.6)		
Appetite loss (NA=67; NB=61)	44.8 (± 37.9)	31.7 (± 34.1)		
Constipation (NA=66; NB=61)	36.9 (± 36.1)	31.1 (± 35.4)		
Diarrhoea (NA=67; NB=61)	10.9 (± 23.5)	12.6 (± 23.7)		
Financial difficulties (NA=65; NB=61)	15.9 (± 26.4)	20.8 (± 27.3)		

Notes:

[30] - NA indicates number of patients analyzed in arm A for every item at cycle 1

[31] - NB indicates the number of patients analyzed in arm B for every item at cycle 1

Statistical analyses

Statistical analysis title	Role functioning

Statistical analysis description:

There are no statistical differences in the other items.

Comparison groups	Phase II, Arm A (Control): AG v Phase II, Arm B: AG-mFOLFOX
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.028
Method	Wilcoxon (Mann-Whitney)

Secondary: EORTC QLQ-C30 scale (cycle 2)

End point title	EORTC QLQ-C30 scale (cycle 2)[32]

End point description:

End point type	Secondary

End point timeframe:

Second cycle (day 1)

Notes:

[32] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only Phase II subjects were analyzed in this endpoint.

End point values	Phase II, Arm A (Control): AG	Phase II, Arm B: AG-mFOLFOX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79[33]	78[34]		
Units: score				
arithmetic mean (standard deviation)				
Global health status/Qol (NA=60; NB=53)	54.6 (± 17.9)	62.1 (± 20.3)		
Physical functioning (NA=61; NB=53)	70.7 (± 24.8)	80.5 (± 17.6)		
Role functioning (NA=61; NB=53)	60.9 (± 34.8)	71.1 (± 28.3)		
Emotional functioning (NA=59; NB=52)	65.8 (± 25.7)	78.2 (± 17.9)		
Cognitive functioning (NA=59; NB= 53)	85.9 (± 19.8)	92.1 (± 12.1)		
Social functioning (NA= 59; NB=53)	65.5 (± 27.1)	68.6 (± 24.6)		
Fatigue (NA=61; NB=53)	43.9 (± 29.4)	37.7 (± 24.3)		
Nausea and vomiting (NA=61; NB=53)	10.4 (± 16.4)	10.1 (± 20.0)		
Pain (NA=61; NB=53)	27.3 (± 25.3)	22.3 (± 23.8)		
Dyspnoea (NA=59; NB=53)	10.7 (± 19.0)	10.7 (± 25.5)		
Insomnia (NA=61; NB=53)	57.9 (± 27.1)	54.7 (± 22.7)		
Appetite loss (NA=60; NB=53)	31.7 (± 32.7)	22.6 (± 29.8)		
Constipation (NA=61; NB=53)	18.6 (± 30.1)	26.4 (± 31.6)		
Diarrhoea (NA=59; NB=52)	22.6 (± 31.2)	21.8 (± 32.9)		
Financial difficulties (NA=59; NB=53)	17.5 (± 27.2)	25.2 (± 30.6)		

Notes:

[33] - NA indicates the number of patients analyzed in arm A for every item at cycle 2

[34] - NB indicates the number of patients analyzed in arm B for every item at cycle 2

Statistical analyses

Statistical analysis title	Global health status/QoI
Statistical analysis description:	
We only display analysis of those items with statistical differences	
Comparison groups	Phase II, Arm A (Control): AG v Phase II, Arm B: AG-mFOLFOX
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Physical functioning
Statistical analysis description:	
We only display analysis of those items with statistical differences	
Comparison groups	Phase II, Arm A (Control): AG v Phase II, Arm B: AG-mFOLFOX
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.048
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Emotional functioning
Statistical analysis description:	
We only display analysis of those items with statistical differences	
Comparison groups	Phase II, Arm A (Control): AG v Phase II, Arm B: AG-mFOLFOX
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.011
Method	Wilcoxon (Mann-Whitney)

Secondary: EORTC QLQ-C30 scale (end of treatment)

End point title	EORTC QLQ-C30 scale (end of treatment)[35]
End point description:	

End point type	Secondary
End point timeframe:	
visit at end of treatment	

Notes:

[35] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only Phase II subjects were analyzed in this endpoint.

End point values	Phase II, Arm A (Control): AG	Phase II, Arm B: AG-mFOLFOX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79[36]	78[37]		
Units: score				
arithmetic mean (standard deviation)				
Global health status/Qol (NA=39; NB=29)	51.7 (± 22.5)	52.0 (± 26.2)		
Physical functioning (NA=39; NB=30)	65.1 (± 29.8)	70.4 (± 24.2)		
Role functioning (NA=39; NB=30)	58.1 (± 35.6)	61.1 (± 32.9)		
Emotional functioning (NA=39; NB=29)	63.9 (± 30.2)	65.8 (± 24.7)		
Cognitive functioning (NA=39; NB= 29)	79.5 (± 25.8)	81.0 (± 23.9)		
Social functioning (NA= 39; NB=29)	59.0 (± 34.8)	63.8 (± 31.5)		
Fatigue (NA=39; NB=30)	47.9 (± 29.6)	42.2 (± 32.0)		
Nausea and vomiting (NA=39; NB=29)	8.5 (± 17.5)	10.9 (± 16.8)		
Pain (NA=39; NB=29)	32.5 (± 33.5)	29.9 (± 27.2)		
Dyspnoea (NA=39; NB=30)	19.7 (± 28.3)	16.7 (± 28.7)		
Insomnia (NA=39; NB=29)	53.0 (± 28.3)	54.0 (± 28.7)		
Appetite loss (NA=39; NB=29)	30.8 (± 32.8)	26.4 (± 32.6)		
Constipation (NA=39; NB=30)	21.4 (± 31.1)	22.2 (± 28.1)		
Diarrhoea (NA=39; NB=29)	11.1 (± 23.4)	12.6 (± 20.7)		
Financial difficulties (NA=39; NB=29)	24.8 (± 34.8)	25.3 (± 27.7)		

Notes:

[36] - NA indicates the number of patients analyzed in arm A for every item at end of treatment.

[37] - NB indicates the number of patients analyzed in arm B for every item at end of treatment

Statistical analyses

Statistical analysis title	EORTC QLQ-C30 at end of treatment
Comparison groups	Phase II, Arm A (Control): AG v Phase II, Arm B: AG-mFOLFOX
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [38]
Method	Wilcoxon (Mann-Whitney)

Notes:

[38] - No significantly differences among items of this questionnaire at end of treatment

Secondary: EORTC QLQ-PAN26 scale (Cycle 1)

End point title	EORTC QLQ-PAN26 scale (Cycle 1)[39]

End point description:

The QLQ-PAN26 consists of seven hypothesized scales to assess pancreatic pain, digestive symptoms, altered bowel habit, hepatic, body image, satisfaction with health care, and sexuality. In addition, ten single items measure other issues related to pancreatic cancer. Users should be aware though that the scaling structure is still preliminary. All of the scales and single item measures range in score from 0 to 100.

End point type	Secondary

End point timeframe:

First cycle (day 1)

Notes:

[39] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only Phase II subjects were analyzed in this endpoint.

End point values	Phase II, Arm A (Control): AG	Phase II, Arm B: AG-mFOLFOX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79[40]	78[41]		
Units: score				
arithmetic mean (standard deviation)				
Pancreatic pain (NA=66; NB=61)	38.6 (± 28.6)	33.2 (± 25.8)		
Bloating (NA=66; NB=61)	32.3 (± 33.6)	31.1 (± 34.4)		
Digestive symptoms (NA=65; NB=61)	41.0 (± 32.6)	28.7 (± 29.0)		
Taste (NA=66; NB=60)	23.7 (± 31.9)	19.4 (± 29.0)		
Indigestion (NA=65; NB=60)	19.0 (± 26.3)	9.4 (± 17.5)		
Flatulence (NA=66; NB=61)	42.9 (± 34.0)	44.3 (± 33.2)		
Weight loss (NA=64; NB=61)	42.2 (± 37.2)	37.7 (± 33.0)		
Weakness arms and legs (NA=66; NB=61)	35.9 (± 34.2)	29.0 (± 28.9)		
Dry mouth (NA=66; NB=61)	44.9 (± 37.2)	30.6 (± 35.1)		
Hepatic symptoms (NA=65; NB=61)	13.1 (± 21.1)	10.9 (± 16.9)		
Troubled with side-effects (NA=59; NB=45)	22.0 (± 31.3)	18.5 (± 28.9)		
Future Worries (NA=65; NB=61)	70.8 (± 31.5)	66.1 (± 31.3)		
Planning of activities (NA=63; NB=58)	29.6 (± 34.4)	36.2 (± 33.8)		
Satisfaction with health care (NA=65; NB=61)	56.2 (± 23.7)	61.5 (± 22.7)		
Sexuality (NA=57; NB=52)	45.6 (± 40.9)	44.6 (± 37.9)		
Altered bowel habit (NA=65; NB=60)	19.2 (± 26.2)	15.8 (± 22.4)		
Body image (NA=65; NB=61)	26.9 (± 34.6)	15.3 (± 19.3)		

Notes:

[40] - NA indicates the number of patients of arm A analyzed for every item at day 1 of cycle 1.

[41] - NB indicates the number of patients of arm B analyzed for every item at day 1 of cycle 1.

Statistical analyses

Statistical analysis title	Digestive symptoms
Statistical analysis description:	
We only display analysis of those items with statistical differences	
Comparison groups	Phase II, Arm A (Control): AG v Phase II, Arm B: AG-mFOLFOX
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.033
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Indigestion
Comparison groups	Phase II, Arm A (Control): AG v Phase II, Arm B: AG-mFOLFOX

Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.033
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Dry mouth
Comparison groups	Phase II, Arm A (Control): AG v Phase II, Arm B: AG-mFOLFOX
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.026
Method	Wilcoxon (Mann-Whitney)

Secondary: EORTC QLQ-PAN26 scale (Cycle 4)

End point title	EORTC QLQ-PAN26 scale (Cycle 4)[42]

End point description:

The QLQ-PAN26 consists of seven hypothesized scales to assess pancreatic pain, digestive symptoms, altered bowel habit, hepatic, body image, satisfaction with health care, and sexuality. In addition, ten single items measure other issues related to pancreatic cancer. Users should be aware though that the scaling structure is still preliminary. All of the scales and single item measures range in score from 0 to 100.

End point type	Secondary

End point timeframe:

Day 1 of cycle 4

Notes:

[42] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only Phase II subjects were analyzed in this endpoint.

End point values	Phase II, Arm A (Control): AG	Phase II, Arm B: AG-mFOLFOX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79[43]	78[44]		
Units: score				
arithmetic mean (standard deviation)				
Pancreatic pain (NA=37; NB=44)	14.3 (± 18.2)	11.9 (± 13.6)		
Bloating (NA=36; NB=44)	19.4 (± 24.4)	16.7 (± 21.0)		
Digestive symptoms (NA=37; NB=44)	22.5 (± 24.9)	18.6 (± 23.1)		
Taste (NA=36; NB=44)	46.3 (± 35.9)	34.8 (± 27.8)		
Indigestion (NA=35; NB=44)	8.6 (± 21.9)	6.8 (± 15.4)		
Flatulence (NA=37; NB=43)	40.5 (± 29.5)	41.9 (± 32.6)		
Weight loss (NA=36; NB=44)	41.7 (± 35.1)	27.3 (± 29.9)		
Weakness arms and legs (NA=37; NB=44)	36.9 (± 35.8)	25.8 (± 24.8)		
Dry mouth (NA=36; NB=44)	43.5 (± 37.2)	24.2 (± 25.3)		
Hepatic symptoms (NA=37; NB=44)	11.7 (± 16.1)	6.1 (± 14.4)		

Altered bowel habit (NA=37; NB=44)	22.1 (± 29.4)	17.0 (± 22.9)		
Body image (NA=34; NB=44)	31.9 (± 32.1)	23.5 (± 23.4)		
Troubled with side-effects (NA=33; NB=44)	43.4 (± 30.6)	31.1 (± 23.2)		
Future Worries (NA=35; NB=43)	61.9 (± 33.5)	45.7 (± 29.1)		
Planning of activities (NA=35; NB=43)	30.5 (± 32.7)	48.8 (± 32.0)		
Satisfaction with health care (NA=35; NB=44)	54.3 (± 21.1)	68.9 (± 17.8)		
Sexuality (NA=27; NB=34)	25.9 (± 34.7)	48.0 (± 37.8)		

Notes:

[43] - NA indicates the number of patients of arm A analyzed for every item at day 1 of cycle 4.

[44] - NB indicates the number of patients of arm B analyzed for every item at day 1 of cycle 4.

Statistical analyses

Statistical analysis title	Dry mouth
Statistical analysis description:	
We only display those items with statistical differences.	
Comparison groups	Phase II, Arm A (Control): AG v Phase II, Arm B: AG-mFOLFOX
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.021
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Hepatic symptoms
Comparison groups	Phase II, Arm A (Control): AG v Phase II, Arm B: AG-mFOLFOX
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.034
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Future worries
Comparison groups	Phase II, Arm A (Control): AG v Phase II, Arm B: AG-mFOLFOX
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.023
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Planning of activities
Comparison groups	Phase II, Arm A (Control): AG v Phase II, Arm B: AG-mFOLFOX

Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.015
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Satisfaction with health care
Comparison groups	Phase II, Arm A (Control): AG v Phase II, Arm B: AG-mFOLFOX
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Sexuality
Comparison groups	Phase II, Arm A (Control): AG v Phase II, Arm B: AG-mFOLFOX
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.02
Method	Wilcoxon (Mann-Whitney)

Secondary: EORTC QLQ-PAN26 scale (end of treatment)

End point title	EORTC QLQ-PAN26 scale (end of treatment)[45]

End point description:

The QLQ-PAN26 consists of seven hypothesized scales to assess pancreatic pain, digestive symptoms, altered bowel habit, hepatic, body image, satisfaction with health care, and sexuality. In addition, ten single items measure other issues related to pancreatic cancer. Users should be aware though that the scaling structure is still preliminary. All of the scales and single item measures range in score from 0 to 100.

End point type	Secondary

End point timeframe:

End of treatment

Notes:

[45] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only Phase II subjects were analyzed in this endpoint.

End point values	Phase II, Arm A (Control): AG	Phase II, Arm B: AG-mFOLFOX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	78		
Units: score				
arithmetic mean (standard deviation)				

Pancreatic pain (NA=39; NB=29)	27.1 (± 27.4)	27.3 (± 25.2)		
Bloating (NA=39; NB=29)	25.6 (± 34.6)	26.4 (± 34.9)		
Digestive symptoms (NA=39; NB=30)	29.5 (± 30.2)	25.0 (± 24.7)		
Taste (NA=39; NB=30)	35.9 (± 33.7)	34.4 (± 30.9)		
Indigestion (NA=39; NB=29)	15.4 (± 26.3)	16.1 (± 26.2)		
Flatulence (NA=38; NB=30)	41.2 (± 34.2)	43.3 (± 29.2)		
Weight loss (NA=39; NB=29)	37.6 (± 36.8)	28.7 (± 35.3)		
Weakness arms and legs (NA=39; NB=30)	41.9 (± 31.3)	35.6 (± 33.8)		
Dry mouth (NA=37; NB=30)	41.4 (± 38.0)	37.8 (± 33.6)		
Hepatic symptoms (NA=39; NB=30)	9.4 (± 17.4)	15.6 (± 27.7)		
Altered bowel habit (NA=39; NB=30)	14.1 (± 22.1)	25.6 (± 25.8)		
Body image (NA=38; NB=29)	38.6 (± 35.3)	28.7 (± 31.1)		
Troubled with side-effects (NA=37; NB=29)	47.7 (± 31.0)	46.0 (± 33.8)		
Future Worries (NA=38; NB=29)	62.3 (± 33.0)	63.2 (± 33.7)		
Planning of activities (NA=36; NB=28)	36.1 (± 35.1)	27.4 (± 28.8)		
Satisfaction with health care (NA=37; NB=29)	58.6 (± 21.7)	55.2 (± 20.9)		
Sexuality (NA=28; NB=23)	32.7 (± 40.2)	47.8 (± 39.7)		

Statistical analyses

Statistical analysis title	Altered bowel habit
Statistical analysis description: We only show those items with statistically differences	
Comparison groups	Phase II, Arm B: AG-mFOLFOX v Phase II, Arm A (Control): AG
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.029
Method	Wilcoxon (Mann-Whitney)

Secondary: EORTC QLQ-CIPN20 scale (Cycle 1)

End point title	EORTC QLQ-CIPN20 scale (Cycle 1)[46]
End point description: The CIPN20 module includes 20 items, conceptualised as consisting of 3 scales: 1. Sensory scale: Items 1-6, 9, 10 and 18 address sensory symptoms and problems. It is hypothesized that these items will form a multi-item scale. The individual items and the multi-item scale should be scored such that higher scores represent more symptoms/problems (i.e., higher score = worse). 2. Motor scale: Items 7, 8, 11-15 and 19 address motor symptoms and problems. It is hypothesized that these items, excluding item 19, will form a multi-item scale. Item 19 is conditional on driving a car, and thus is not relevant to all patients. Thus, it should be treated as a separate item. 3. Autonomic scale: Items 16, 17 and 20 assess autonomic symptoms and problems. Items 16 and 17 are hypothesized to form a two-item scale. Item 20 is relevant only for men, and thus should be treated as a separate item.	
End point type	Secondary
End point timeframe: First cycle (day 1)	

Notes:

[46] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only Phase II subjects were analyzed in this endpoint.

End point values	Phase II, Arm A (Control): AG	Phase II, Arm B: AG-mFOLFOX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79[47]	78[48]		
Units: score				
arithmetic mean (standard deviation)				
Sensory Scale (NA=63; NB=57)	92.6 (± 11.8)	96.3 (± 5.1)		
Motor scale (NA=63; NB=57)	89.9 (± 14.8)	95.5 (± 5.6)		
Item 19 (NA=27; NB=32)	96.3 (± 14.1)	99.0 (± 5.9)		
Automatic scale (NA=63; NB=57)	90.2 (± 16.6)	93.0 (± 14.1)		
Item 20 (NA=22; NB=25)	54.5 (± 41.8)	57.3 (± 42.5)		

Notes:

[47] - NA indicates number of patients analyzed in arm A for every item at cycle 1

[48] - NB indicates number of patients analyzed in arm B for every item at cycle 1

Statistical analyses

Statistical analysis title	Motor scale

Statistical analysis description:

There are no statistical differences in the other items.

Comparison groups	Phase II, Arm A (Control): AG v Phase II, Arm B: AG-mFOLFOX
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.026
Method	Wilcoxon (Mann-Whitney)

Secondary: EORTC QLQ-CIPN20 scale (Cycle 2)

End point title	EORTC QLQ-CIPN20 scale (Cycle 2)[49]

End point description:

The CIPN20 module includes 20 items, conceptualised as consisting of 3 scales:
1. Sensory scale: Items 1-6, 9, 10 and 18 address sensory symptoms and problems. It is hypothesized that these items will form a multi-item scale. The individual items and the multi-item scale should be scored such that higher scores represent more symptoms/problems (i.e., higher score = worse).
2. Motor scale: Items 7, 8, 11-15 and 19 address motor symptoms and problems. It is hypothesized that these items, excluding item 19, will form a multi-item scale. Item 19 is conditional on driving a car, and thus is not relevant to all patients. Thus, it should be treated as a separate item.
3. Autonomic scale: Items 16, 17 and 20 assess autonomic symptoms and problems. Items 16 and 17 are hypothesized to form a two-item scale. Item 20 is relevant only for men, and thus should be treated as a separate item.

End point type	Secondary

End point timeframe:

Second cycle (day 1)

Notes:

[49] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only Phase II subjects were analyzed in this endpoint.

End point values	Phase II, Arm A (Control): AG	Phase II, Arm B: AG-mFOLFOX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79[50]	78[51]		
Units: Score				
arithmetic mean (standard deviation)				
Sensory Scale (NA=57; NB=49)	94.1 (± 7.3)	86.1 (± 11.4)		
Motor scale (NA=57; NB=49)	92.8 (± 8.5)	87.7 (± 11.3)		
Item 19 (NA=23; NB=24)	100.0 (± 0.0)	93.1 (± 24.0)		
Automatic scale (NA=57; NB=49)	85.7 (± 18.8)	85.0 (± 19.6)		
Item 20 (NA=23; NB=18)	55.1 (± 41.0)	61.1 (± 41.6)		

Notes:

[50] - NA indicates number of patients analyzed in arm A for every item at cycle 2

[51] - NB indicates number of patients analyzed in arm B for every item at cycle 2

Statistical analyses

Statistical analysis title	Sensory scale

Statistical analysis description:

We only display analysis of those items with statistical differences

Comparison groups	Phase II, Arm A (Control): AG v Phase II, Arm B: AG-mFOLFOX
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Motor scale
Comparison groups	Phase II, Arm A (Control): AG v Phase II, Arm B: AG-mFOLFOX
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.015
Method	Wilcoxon (Mann-Whitney)

Secondary: EORTC QLQ-CIPN20 scale (end of treatment)

End point title	EORTC QLQ-CIPN20 scale (end of treatment)[52]

End point description:

The CIPN20 module includes 20 items, conceptualised as consisting of 3 scales:
1. Sensory scale: Items 1-6, 9, 10 and 18 address sensory symptoms and problems. It is hypothesized that these items will form a multi-item scale. The individual items and the multi-item scale should be scored such that higher scores represent more symptoms/problems (i.e., higher score = worse).

2. Motor scale: Items 7, 8, 11-15 and 19 address motor symptoms and problems. It is hypothesized that these items, excluding item 19, will form a multi-item scale. Item 19 is conditional on driving a car, and thus is not relevant to all patients. Thus, it should be treated as a separate item.
3. Autonomic scale: Items 16, 17 and 20 assess autonomic symptoms and problems. Items 16 and 17 are hypothesized to form a two-item scale. Item 20 is relevant only for men, and thus should be treated as a separate item.

End point type	Secondary

End point timeframe:

End of treatment

Notes:

[52] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only Phase II subjects were analyzed in this endpoint.

End point values	Phase II, Arm A (Control): AG	Phase II, Arm B: AG-mFOLFOX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79[53]	78[54]		
Units: Score				
arithmetic mean (standard deviation)				
Sensory Scale (NA=38; NB=29)	76.8 (± 24.5)	82.2 (± 18.1)		
Motor scale (NA=38; NB=29)	78.7 (± 22.8)	84.7 (± 18.6)		
Item 19 (NA=13; NB=16)	82.1 (± 32.2)	97.9 (± 8.3)		
Automatic scale (NA=37; NB=29)	80.6 (± 20.6)	82.8 (± 21.1)		
Item 20 (NA=14; NB=13)	33.3 (± 41.3)	46.2 (± 42.0)		

Notes:

[53] - NA indicates number of patients analyzed in arm A for every item at end of treatment

[54] - NB indicates number of patients analyzed in arm B for every item at end of treatment

Statistical analyses

Statistical analysis title	EORTC QLQ-CIPN20 scale at end of treatment
Comparison groups	Phase II, Arm A (Control): AG v Phase II, Arm B: AG-mFOLFOX
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [55]
Method	Wilcoxon (Mann-Whitney)

Notes:

[55] - There are no statistical differences for any item.

Secondary: Disease Control Rate (DCR)

End point title	Disease Control Rate (DCR)[56]

End point description:

DCR is defined as the percentage of patients with advanced or metastatic cancer who have achieved complete response, partial response and stable disease to a therapeutic intervention in clinical trials according to Recist 1.1

End point type	Secondary

End point timeframe:

36 months

Notes:

[56] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only Phase II subjects were analyzed in this endpoint.

End point values	Phase II, Arm A (Control): AG	Phase II, Arm B: AG-mFOLFOX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	78		
Units: percentage (%)				
number (confidence interval 95%)	68.4 (56.9 to 78.4)	79.5 (68.8 to 87.8)		

Statistical analyses

Statistical analysis title	Fisher's exact test
Comparison groups	Phase II, Arm A (Control): AG v Phase II, Arm B: AG-mFOLFOX
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.146
Method	Fisher exact

Secondary: Confirmed DCR

End point title	Confirmed DCR[57]

End point description:

DCR is defined as the percentage of patients with advanced or metastatic cancer who have achieved complete response, partial response and stable disease to a therapeutic intervention in clinical trials according to Recist 1.1

End point type	Secondary

End point timeframe:

36 months

Notes:

[57] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only Phase II subjects were analyzed in this endpoint.

End point values	Phase II, Arm A (Control): AG	Phase II, Arm B: AG-mFOLFOX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	78		
Units: Percentage (%)				
number (confidence interval 95%)	68.4 (56.9 to 78.4)	79.5 (68.8 to 87.8)		

Statistical analyses

Statistical analysis title	Fisher's exact test
Comparison groups	Phase II, Arm A (Control): AG v Phase II, Arm B: AG-mFOLFOX
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.146
Method	Fisher exact

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From 8/10/15 to 10/04/21.	
Adverse event reporting additional description:	
The investigator must record all AEs occurring from the time the patient signs the informed consent until 28 days after the last dose of the investigational medicinal product. Adverse events, especially those whose relationship with the investigational drug is "suspicious", will be monitored until they have resolved or returned to baseline values.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups	
Reporting group title	Phase I safety population
Reporting group description:	
It's defined as all patients who have received at least one administration of the study drugs	
Reporting group title	Phase II arm A safety population
Reporting group description:	
The safety analysis includes all patients who have received at least one administration of the study drugs.	
Reporting group title	Phase II arm B safety population
Reporting group description:	
The safety analysis includes all patients who have received at least one administration of the study drugs.	

Serious adverse events	Phase I safety population	Phase II arm A safety population	Phase II arm B safety population
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 11 (45.45%)	47 / 79 (59.49%)	41 / 76 (53.95%)
number of deaths (all causes)	6	75	62
number of deaths resulting from adverse events	2	12	7
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour associated fever			
subjects affected / exposed	0 / 11 (0.00%)	0 / 79 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour pain			
subjects affected / exposed	0 / 11 (0.00%)	1 / 79 (1.27%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Vascular disorders			

Deep vein thrombosis			
subjects affected / exposed	1 / 11 (9.09%)	2 / 79 (2.53%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombophlebitis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 79 (1.27%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 79 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Condition aggravated			
subjects affected / exposed	0 / 11 (0.00%)	1 / 79 (1.27%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
General physical health deterioration			
subjects affected / exposed	0 / 11 (0.00%)	3 / 79 (3.80%)	2 / 76 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 3	0 / 1
Pain			
subjects affected / exposed	0 / 11 (0.00%)	1 / 79 (1.27%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 11 (0.00%)	2 / 79 (2.53%)	3 / 76 (3.95%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic shock			
subjects affected / exposed	0 / 11 (0.00%)	0 / 79 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 11 (0.00%)	0 / 79 (0.00%)	2 / 76 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	0 / 11 (0.00%)	1 / 79 (1.27%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 79 (1.27%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 11 (0.00%)	0 / 79 (0.00%)	3 / 76 (3.95%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 11 (0.00%)	1 / 79 (1.27%)	2 / 76 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Completed suicide			
subjects affected / exposed	0 / 11 (0.00%)	1 / 79 (1.27%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Confusional state			
subjects affected / exposed	0 / 11 (0.00%)	0 / 79 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood bilirubin increased			

subjects affected / exposed	0 / 11 (0.00%)	1 / 79 (1.27%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Gastrointestinal toxicity			
subjects affected / exposed	0 / 11 (0.00%)	0 / 79 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Patella fracture			
subjects affected / exposed	0 / 11 (0.00%)	1 / 79 (1.27%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	0 / 11 (0.00%)	0 / 79 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal fracture			
subjects affected / exposed	0 / 11 (0.00%)	1 / 79 (1.27%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 11 (9.09%)	0 / 79 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 11 (0.00%)	0 / 79 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Ischaemic cerebral infarction			
subjects affected / exposed	0 / 11 (0.00%)	1 / 79 (1.27%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

Radiculopathy			
subjects affected / exposed	0 / 11 (0.00%)	0 / 79 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 11 (0.00%)	2 / 79 (2.53%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone marrow failure			
subjects affected / exposed	0 / 11 (0.00%)	0 / 79 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 11 (0.00%)	2 / 79 (2.53%)	5 / 76 (6.58%)
occurrences causally related to treatment / all	0 / 0	2 / 2	4 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Splenic infarction			
subjects affected / exposed	0 / 11 (0.00%)	1 / 79 (1.27%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 11 (0.00%)	1 / 79 (1.27%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	0 / 11 (0.00%)	0 / 79 (0.00%)	2 / 76 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Diarrhoea			
subjects affected / exposed	0 / 11 (0.00%)	1 / 79 (1.27%)	7 / 76 (9.21%)
occurrences causally related to treatment / all	0 / 0	1 / 1	7 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Enteritis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 79 (1.27%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer			
subjects affected / exposed	0 / 11 (0.00%)	0 / 79 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 11 (9.09%)	2 / 79 (2.53%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 1	0 / 2	1 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Gastrointestinal toxicity			
subjects affected / exposed	0 / 11 (0.00%)	1 / 79 (1.27%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematemesis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 79 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Intestinal obstruction			
subjects affected / exposed	0 / 11 (0.00%)	4 / 79 (5.06%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Intra-abdominal fluid collection			
subjects affected / exposed	0 / 11 (0.00%)	1 / 79 (1.27%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 11 (9.09%)	0 / 79 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Vomiting			

subjects affected / exposed	0 / 11 (0.00%)	1 / 79 (1.27%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	0 / 11 (0.00%)	2 / 79 (2.53%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis acute			
subjects affected / exposed	1 / 11 (9.09%)	0 / 79 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	0 / 11 (0.00%)	0 / 79 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic failure			
subjects affected / exposed	0 / 11 (0.00%)	2 / 79 (2.53%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Jaundice cholestatic			
subjects affected / exposed	0 / 11 (0.00%)	2 / 79 (2.53%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 11 (0.00%)	1 / 79 (1.27%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal colic			
subjects affected / exposed	0 / 11 (0.00%)	0 / 79 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue			

disorders			
Arthralgia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 79 (1.27%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Infections and infestations			
Abdominal infection			
subjects affected / exposed	0 / 11 (0.00%)	1 / 79 (1.27%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess limb			
subjects affected / exposed	0 / 11 (0.00%)	0 / 79 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 79 (1.27%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Biliary tract infection			
subjects affected / exposed	1 / 11 (9.09%)	0 / 79 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 11 (0.00%)	3 / 79 (3.80%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 4	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
COVID-19			
subjects affected / exposed	0 / 11 (0.00%)	0 / 79 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	0 / 11 (0.00%)	0 / 79 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Influenza			
subjects affected / exposed	0 / 11 (0.00%)	0 / 79 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 11 (0.00%)	6 / 79 (7.59%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 6	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pneumonia bacterial			
subjects affected / exposed	0 / 11 (0.00%)	1 / 79 (1.27%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 11 (0.00%)	5 / 79 (6.33%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	1 / 5	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 11 (0.00%)	3 / 79 (3.80%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	1 / 1
Septic shock			
subjects affected / exposed	0 / 11 (0.00%)	1 / 79 (1.27%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 11 (0.00%)	4 / 79 (5.06%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 6	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 79 (1.27%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			

Hypocalcaemia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 79 (1.27%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypomagnesaemia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 79 (1.27%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Phase I safety population	Phase II arm A safety population	Phase II arm B safety population
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 11 (100.00%)	79 / 79 (100.00%)	76 / 76 (100.00%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 11 (0.00%)	13 / 79 (16.46%)	6 / 76 (7.89%)
occurrences (all)	0	21	7
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 11 (0.00%)	6 / 79 (7.59%)	5 / 76 (6.58%)
occurrences (all)	0	8	5
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 11 (0.00%)	6 / 79 (7.59%)	1 / 76 (1.32%)
occurrences (all)	0	8	1
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 11 (0.00%)	7 / 79 (8.86%)	5 / 76 (6.58%)
occurrences (all)	0	8	7
Transaminases increased			
subjects affected / exposed	0 / 11 (0.00%)	3 / 79 (3.80%)	9 / 76 (11.84%)
occurrences (all)	0	3	12
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 11 (9.09%)	6 / 79 (7.59%)	1 / 76 (1.32%)
occurrences (all)	1	7	1
Nervous system disorders			

Dizziness			
subjects affected / exposed	0 / 11 (0.00%)	3 / 79 (3.80%)	4 / 76 (5.26%)
occurrences (all)	0	3	4
Dysaesthesia			
subjects affected / exposed	3 / 11 (27.27%)	2 / 79 (2.53%)	9 / 76 (11.84%)
occurrences (all)	4	2	20
Dysgeusia			
subjects affected / exposed	0 / 11 (0.00%)	12 / 79 (15.19%)	12 / 76 (15.79%)
occurrences (all)	0	14	15
Paraesthesia			
subjects affected / exposed	5 / 11 (45.45%)	5 / 79 (6.33%)	18 / 76 (23.68%)
occurrences (all)	12	5	27
Peripheral sensory neuropathy			
subjects affected / exposed	2 / 11 (18.18%)	30 / 79 (37.97%)	43 / 76 (56.58%)
occurrences (all)	3	91	173
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 11 (54.55%)	37 / 79 (46.84%)	42 / 76 (55.26%)
occurrences (all)	22	63	108
Febrile neutropenia			
subjects affected / exposed	0 / 11 (0.00%)	4 / 79 (5.06%)	6 / 76 (7.89%)
occurrences (all)	0	4	6
Leukopenia			
subjects affected / exposed	3 / 11 (27.27%)	4 / 79 (5.06%)	18 / 76 (23.68%)
occurrences (all)	9	5	39
Neutropenia			
subjects affected / exposed	8 / 11 (72.73%)	33 / 79 (41.77%)	50 / 76 (65.79%)
occurrences (all)	30	77	248
Thrombocytopenia			
subjects affected / exposed	6 / 11 (54.55%)	27 / 79 (34.18%)	50 / 76 (65.79%)
occurrences (all)	18	85	239
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	9 / 11 (81.82%)	53 / 79 (67.09%)	62 / 76 (81.58%)
occurrences (all)	14	154	233
Fatigue			

subjects affected / exposed	0 / 11 (0.00%)	5 / 79 (6.33%)	2 / 76 (2.63%)
occurrences (all)	0	6	2
General physical health deterioration			
subjects affected / exposed	0 / 11 (0.00%)	4 / 79 (5.06%)	2 / 76 (2.63%)
occurrences (all)	0	5	2
Mucosal inflammation			
subjects affected / exposed	2 / 11 (18.18%)	10 / 79 (12.66%)	15 / 76 (19.74%)
occurrences (all)	3	15	26
Oedema			
subjects affected / exposed	0 / 11 (0.00%)	5 / 79 (6.33%)	1 / 76 (1.32%)
occurrences (all)	0	5	1
Oedema peripheral			
subjects affected / exposed	0 / 11 (0.00%)	20 / 79 (25.32%)	11 / 76 (14.47%)
occurrences (all)	0	28	17
Pain			
subjects affected / exposed	0 / 11 (0.00%)	5 / 79 (6.33%)	3 / 76 (3.95%)
occurrences (all)	0	5	3
Pyrexia			
subjects affected / exposed	6 / 11 (54.55%)	22 / 79 (27.85%)	24 / 76 (31.58%)
occurrences (all)	8	55	52
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 11 (9.09%)	2 / 79 (2.53%)	4 / 76 (5.26%)
occurrences (all)	1	4	6
Abdominal pain			
subjects affected / exposed	1 / 11 (9.09%)	21 / 79 (26.58%)	16 / 76 (21.05%)
occurrences (all)	1	30	23
Abdominal pain upper			
subjects affected / exposed	1 / 11 (9.09%)	5 / 79 (6.33%)	9 / 76 (11.84%)
occurrences (all)	1	5	9
Constipation			
subjects affected / exposed	3 / 11 (27.27%)	20 / 79 (25.32%)	18 / 76 (23.68%)
occurrences (all)	3	25	30
Diarrhoea			
subjects affected / exposed	4 / 11 (36.36%)	33 / 79 (41.77%)	42 / 76 (55.26%)
occurrences (all)	5	72	98

Nausea			
subjects affected / exposed	4 / 11 (36.36%)	29 / 79 (36.71%)	35 / 76 (46.05%)
occurrences (all)	5	44	74
Stomatitis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 79 (1.27%)	10 / 76 (13.16%)
occurrences (all)	0	3	23
Vomiting			
subjects affected / exposed	2 / 11 (18.18%)	24 / 79 (30.38%)	23 / 76 (30.26%)
occurrences (all)	2	31	30
Respiratory, thoracic and mediastinal disorders			
Catarrh			
subjects affected / exposed	0 / 11 (0.00%)	3 / 79 (3.80%)	6 / 76 (7.89%)
occurrences (all)	0	4	12
Cough			
subjects affected / exposed	0 / 11 (0.00%)	4 / 79 (5.06%)	3 / 76 (3.95%)
occurrences (all)	0	4	4
Dyspnoea			
subjects affected / exposed	0 / 11 (0.00%)	4 / 79 (5.06%)	4 / 76 (5.26%)
occurrences (all)	0	5	7
Epistaxis			
subjects affected / exposed	0 / 11 (0.00%)	4 / 79 (5.06%)	8 / 76 (10.53%)
occurrences (all)	0	5	11
Pneumothorax			
subjects affected / exposed	0 / 11 (0.00%)	0 / 79 (0.00%)	4 / 76 (5.26%)
occurrences (all)	0	0	5
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	2 / 11 (18.18%)	21 / 79 (26.58%)	23 / 76 (30.26%)
occurrences (all)	3	21	31
Erythema			
subjects affected / exposed	0 / 11 (0.00%)	5 / 79 (6.33%)	6 / 76 (7.89%)
occurrences (all)	0	6	6
Pruritus			
subjects affected / exposed	0 / 11 (0.00%)	5 / 79 (6.33%)	5 / 76 (6.58%)
occurrences (all)	0	7	5
Rash			

subjects affected / exposed	0 / 11 (0.00%)	7 / 79 (8.86%)	9 / 76 (11.84%)
occurrences (all)	0	8	10
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 11 (0.00%)	5 / 79 (6.33%)	9 / 76 (11.84%)
occurrences (all)	0	5	13
Back pain			
subjects affected / exposed	1 / 11 (9.09%)	5 / 79 (6.33%)	10 / 76 (13.16%)
occurrences (all)	1	5	11
Musculoskeletal pain			
subjects affected / exposed	2 / 11 (18.18%)	1 / 79 (1.27%)	8 / 76 (10.53%)
occurrences (all)	5	1	8
Myalgia			
subjects affected / exposed	1 / 11 (9.09%)	3 / 79 (3.80%)	5 / 76 (6.58%)
occurrences (all)	1	3	8
Pain in extremity			
subjects affected / exposed	0 / 11 (0.00%)	6 / 79 (7.59%)	3 / 76 (3.95%)
occurrences (all)	0	6	3
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 11 (0.00%)	6 / 79 (7.59%)	4 / 76 (5.26%)
occurrences (all)	0	9	4
Pneumonia			
subjects affected / exposed	0 / 11 (0.00%)	6 / 79 (7.59%)	1 / 76 (1.32%)
occurrences (all)	0	6	1
Respiratory tract infection			
subjects affected / exposed	0 / 11 (0.00%)	10 / 79 (12.66%)	8 / 76 (10.53%)
occurrences (all)	0	13	9
Urinary tract infection			
subjects affected / exposed	0 / 11 (0.00%)	10 / 79 (12.66%)	5 / 76 (6.58%)
occurrences (all)	0	13	5
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 11 (18.18%)	30 / 79 (37.97%)	29 / 76 (38.16%)
occurrences (all)	2	48	48

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 January 2016	Version 2 of 4 January 2016
17 March 2017	Addition of sites. Amendments not applicable to the protocol, and therefore no new version is generated.
11 July 2017	Update of sites. Amendments not applicable to the protocol, and therefore no new version is generated.
16 February 2018	Change of investigator. Amendments not applicable to the protocol, and therefore no new version is generated.
21 January 2019	Amendments not applicable to the protocol, and therefore no new version is generated.
04 December 2019	Version 3 of 4 December 2019

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/32977220