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Clinical Trial Report

A randomized phase II trial of captem or folfiri as SEcond-line therapy in NEuroendocrine CArcinomas and exploratory analysis of predictive role of PET imaging and biological markers (SENECA study)	
Summary	
EudraCT number	2016-000767-17
Global end of trial date	28/02/2022
Results information	
Result version number	v.1.0 (current)
This version publication date	14/02/2024
Trial information	
Trial identification	A randomized phase II trial of captem or folfiri as SEcond-line therapy in NEuroendocrine CArcinomas and exploratory analysis of predictive role of PET imaging and biological markers (SENECA study)
Sponsor protocol code	IRST100.22
Additional study identifiers	L2P1246
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03387592
WHO universal trial number (UTN)	-
Notes	-
Sponsor	
Sponsor organization name	IRCCS Istituto Romagnolo per lo Studio dei Tumori "Dino Amadori" - IRST S.r.l.
Sponsor organization address	via Piero Maroncelli, 40 - 47014 Meldola (FC) - Italy
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Sponsor organization name	IRCCS Istituto Romagnolo per lo Studio dei Tumori "Dino Amadori" - IRST S.r.l.
Sponsor organization address	via Piero Maroncelli, 40 - 47014 Meldola (FC) - Italy
Notes	-
Pediatric regulatory details	
Is trial part of an agreed pediatric investigation plan (PIP). Does article 45 of REGULATION (EC) No I	No
19Q_I/2006 apply to this trial? Does article 46 of REGULATION (EC) No I?	No
1901/2006 apply to this trial?	No
Notes	-

Results analysis stage	
Analysis stage	Final
Date of final analysis	23 June 2022

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Primary completion date	11 February 2021
Global end of trial date	28 February 2022
Was the trial prematurely ended?	Yes (results from first step of a two steps Bryant and Day's design are shown)
Notes	-
General information about the trial	
Main objective of the trial The primary aim of this randomized phase II non-comparative trial is to assess the Disease Control Rate (DCR) of FOLFIRI or CAPTEM regimens in patients with metastatic NECs or different origin after failure of a first line treatment.	
This study is conducted in full conformity with the revision of the Declaration of Helsinki, the ICH Guidelines for Good Clinical Practice (CPMP/ICH/135/95) July 1996, the Directive 2001/20/EEC of the European Parliament and other relevant local legislation.	
The protocol, informed consent and any accompanying material provided to the patient has been submitted by the investigator to the Competent Ethics Committee for review. Approval from the committee has been obtained before starting the study. All patients signed an Informed consent to participate to the study before any study procedures	
Background therapy	-
Evidence for comparator	-
Actual start date of recruitment	06/03/2017 (first patient's randomization)
Long term follow-up planned	-
Independent data monitoring committee (IDMC) involvement?	No
Notes	-
Population of trial subjects	
Subjects enrolled per Country	
Country: Number of subjects enrolled	Italy: 53
Worldwide total number of subjects	53
EEA total number of subjects	53
Subjects enrolled per country	
Country: Number of subjects enrolled	Italy: 53
Notes	-
Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wks	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	33
From 65 to 84 years	20
85 years and over	0
Adults (18-64 years)	33
From 65 to 84 years	20

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85 years and over	0
Subject disposition	
Recruitment	
Recruitment details This was a multicenter, Italian study. 53 patients were recruited in 17 active centers:	

City - Center - ID	***N. of enrolled patients***
Meldola (FC) - IRCCS Istituto Romagnolo per lo Studio dei Tumori "Dino Amadori" - IRST S.r.l. - 01	16
Milano (MI) - Fondazione IRCCS Istituto Nazionale Tumori (INT) - 02	4
Modena (MO) - A.O.U. Policlinico di Modena - 05	4
Parma (PR) - A.O.U. di Parma - 08	1
Pisa (PI) - A.O.U. Pisana S. Chiara - 06	1
Roma (RM) - Policlinico Universitario Campus Biomedico - 13	1
Bari (BA) - A.O.U. Consorziale Policlinico di Bari "Giovanni XXIII" - 16	1
Faenza (RA) - Ospedale "Degli Infermi" - 04	2
Padova (PD) - IRCCS Istituto Oncologico Veneto (IOV) - 09	5
Lecce (LE) - P.O. "Vito Fazzi" - 10	5
Castellana Grotte (BA) - IRCCS "Saverio de Bellis" - 07	2
Bolzano (BZ) - Ospedale Centrale di Bolzano - 03	3
Ancona (AN) - A.O.U. Ospedali Riuniti di Ancona - 12	1
Palermo (PA) - A.O.U. Policlinico " Paolo Giaccone" - 17	1
Firenze (FI) - A.O.U. Careggi - 23	1
Milano (MI) - IRCCS Istituto Europeo di Oncologia (IEO) - 20	2
Orbassano (TO) - A.O.U. S. Luigi Gonzaga - 21	3

Pre-assignment	
Screening details A total of 67 patients were screened for eligibility; 14 patients resulted screen failure and were not randomized; a total of 53 patients were randomized (28 in arm A and 25 in arm B). Of these, all patients were evaluable for first step of the Bryant-Day design. They are evaluated in terms of efficacy and safety.	
Arms	
Are arms mutually exclusive?	Yes
Allocation method	Mixed block randomization
Blinding used	Not blinded
Arm title	
Arm A	**FOLFIRI administration**
Irinotecan (CPT-11)	180 mg/m^2 as 1hr. infusion
Calcium levofolinate (LV)	200 mg/m^2 as 2 hrs. infusion
(5-fluorouracil) FU	400 mg/m^2 as bolus then:
(5-fluorouracil) FU	2400 mg/m^2 as 48 hrs. continuous infusion
every 2 weeks until progression or for a maximum of 12 cycles.	
Arm type	Experimental
Investigational medicinal product name	Irinotecan, Calcium levofolinate, 5-fluorouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

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Dosage and administration details The recommended dose of irinotecan is 180 mg/m^2 administered as intravenous infusion of 30 to 90 minutes; the recommended dose of calcium levofolinate is 200 mg/m^2 as 2 hrs infusion. These drugs were followed 5-Fluorouracil 400 mg/m^2 given as bolus, and then 5-Fluorouracil 2400 mg/m^2 given as a 48 h continuous infusion on day 1, every 2 weeks, until progression or for a maximum of 12 cycles.	
Arm B	**CAPTEM administration**
Capecitabine	750 mg/m^2 orally twice a day on days 1-14
Temozolomide	200 mg/m^2 orally daily on days 10-14
every 4 weeks until progression or for a maximum of 6 cycles.	
Arm type	Experimental
Investigational medicinal product name	Capecitabine, Temozolomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details The recommended dose of capecitabine is 750 m/m2 orally twice a day on days 1-14, every 4 weeks, while the recommended dose of temozolomide is 200 mg/m2 daily on days 10-14, every 4 weeks, until progression or for a maximum of 6 cycles.	

Study population		
Baseline characteristics	**Arm A**	**Arm B**
Number of subjects	28	25
Age categorial		
Units	Subjects	
Adults (18-64 years)	17	16
From 65-84 years 85 years and over	11	9
Gender categorial		
Units	Subjects	
Male	15	17
Female	13	8
Subject analysis set		
Subject analysis set title	Intent-to-Treat (ITT) population	
Subject analysis set type	Intention-to-treat	
Subject analysis set description The Intention-to-treat (ITT) population is defined as the population of all enrolled patients.		
Subject analysis set title	Per protocol population	
Subject analysis set type	Per protocol	
Subject analysis set description The activity population (AP) is considered as all patients who received, in each treatment group, at least one cycle of treatment.		
Subject analysis set title	Safety population	
Subject analysis set type	Safety population	
Subject analysis set description The safety population (SP) is defined as all patients who received, in each treatment group, at least one cycle of treatment.		
Reporting group values		

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Number of subjects			
Age categorial			
Units: Subjects	***ITT***	***AP***	***SP***
Adults (18-64 years)	33	32	32
From 65-84 years 85 years and over	20	20	20
Gender categorial			
Units: Subjects	***ITT***	***AP***	***SP***
Male	32	31	31
Female	21	21	21

End points reporting group	
Primary endpoint: disease control date (DCR)	
Endpoint title	Disease control rate (DCR)
Endpoint description	The primary aim of this randomized phase II non-comparative trial is to assess the Disease Control Rate (DCR) of FOLFIRI or CAPTEM regimens in patients with metastatic NECs or different origin after failure of a first line treatment
Endpoint type	Primary
Endpoint timeframe	The timeframe between the date of randomization of the first patient (06/03/2017) and evaluation of the progression of disease of the last enrolled patient (11/02/2021) were about 4 years
Statistical analysis	
Statistical analysis title	DCR analysis

Analysis on primary objective will be performed on ITT and AP. Each patient will be assigned to one of the following categories: 1) complete response, 2) partial response, 3) stable disease for at least 12 weeks, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 8) unknown (not assessable, insufficient data). Patients in response categories 1-3 should be considered as disease controlled. 95% CI for DCR will be performed. Patients in response categories 4-8 should be considered as failing to respond to treatment.

We use Bryant and Day design in order to estimate a sample size who takes in account the activity but also the toxicity. Although randomization will be used to allocate patients in the 2 arms, no formal statistical comparisons between treatment regimens is planned. The purpose of randomization is to reduce bias due to patient selection into each treatment arm. We assume that:

Acceptable rates:

DCR rate ≥ 60%

Relevant- toxicity rate ≤ 20%

Inacceptable rates:

DCR rate ≤ 40%

Relevant-toxicity rate ≥ 40%

Type I error (α) = 0,10 both for toxicity and DCR

Power (1-β) 90%.

According to these hypotheses, the first step requires 25 patients, if ≥10 patients with a DCR will be observed and ≥15 patients will not have any relevant toxicity, the study will enroll patients in the next step. If the study will enter in the second step, a total of 53 patients will be enrolled. If ≥25 patients with DCR and ≥36 patients without any relevant toxicity will be observed, the treatment will be considered active and not toxic. This design is applied at each scheme of therapy and all the analysis will be done separately. If one of the schemes does not

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achieve the expected proportions of the first step, the arm will be closed and the patients will be enrolled in the other arm until target is reached; if the expected proportions will not be reached in any arms than the study will be prematurely closed. If no premature stop will occur, a total of 106 evaluable patients will be needed (53 patients in each arm). Taking account of 5% of dropouts rate will be enrolled in the study 56 patients in each arm for a total of 112 patients.		
Comparison group	Not applicable	
Number of subjects included in analysis	53	
First step analysis was conducted on 53 patients (28 patients in Folfiri ARM and 25 patients in Captem ARM). Twenty-eight patients instead of expected 25 were enrolled in Folfiri ARM, because the size of mixed block in the randomization list were slightly imbalanced, due to the number of stratification factors (disease and ki67 level) and the relatively small number of cases.		
Response to therapy		
Number of enrolled patients		
	Arm A	**Arm B**
Started treatment	28	25
Disease control rate (DCR)	9 (37.5%)	7 (28.0%)
95%CI for DCR percentage	18.8-59.4	12.1-49.4
Progression of disease	15 (60.9%)	18 (72.0%)
Not evaluable patients	4	0
Co-primary endpoint: safety		
Endpoint title	Safety	
Endpoint description	Acute and late toxicity will be evaluated; the late toxicity is the toxicity that occurred after 30 days from the last treatment cycle. The toxicity will be evaluated according to CTCAE Version 5.0.	
Endpoint type	Co-primary	
Endpoint timeframe	The timeframe between the date of randomization of the first patient (06/03/2017) and evaluation of the progression of disease of the last enrolled patient (11/02/2021) were about 4 years	
Statistical analysis		
Statistical analysis title	Safety analysis	
Definition of relevant-toxicity: G3-4 gastrointestinal toxicity, G4 thrombocytopenia, prolonged G3-G4 neutropenia for more 7 days and drug related hospitalization. The acute toxicity will be evaluated in the safety population.		
Comparison group	Not applicable	
Number of subjects included in analysis	53	
Number of patients with AEs relevant for study interruption		
Number of enrolled patients		
	Arm A	**Arm B**
Started treatment	28	25
Patients with G3-4 neutropenia and prolonged hospitalization for >7 days (%)	3 (10.7%)	0 (0.0%)
Patients with G3-4 Thrombocytopenia (%)	0 (0.0%)	0 (0.0%)
Patients with G3-4 Nausea/Vomiting (SAE) (%)	0 (0.0%)	1 (4.0%)
Patients with other G3-G4 AE with possible/certain/definite relation with treatment (%)	3 (10.7%)	2 (8.0%)

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Secondary endpoint: Progression-free survival (PFS) analysis		
Endpoint title	PFS analysis	
Endpoint description	Progression free survival is defined as the time from the start treatment date to the date of first observation of documented disease progression or death due to any cause. Patients without tumor progression at the time of analysis will be censored at their last date of tumor evaluation	
Endpoint type	Secondary	
Endpoint timeframe	The timeframe between the date of randomization of the first patient (06/03/2017) and evaluation of the progression of disease of the last enrolled patient (11/02/2021) were about 4 years.	
Statistical analysis		
Statistical analysis title	Analysis of PFS	
Comparison group	Not applicable	
Number of subjects included in analysis	53	
Number of enrolled patients	52 (1 patient not evaluable)	
	Arm A	**Arm B**
Median PFS (95%CI)	3.0 (2.8-7.9)	2.7 (1.9-4.1)
Secondary endpoint: Overall survival (OS) analisys		
Endpoint title	OS analysis	
Endpoint description	Overall Survival (OS) is defined as the time from treatment start to the time of death from any cause. Subjects who are alive at the time of the final analysis or who have become lost to follow-up will be censored at their last known alive date.	
Endpoint type	Secondary	
Endpoint timeframe	The timeframe between the date of randomization of the first patient (06/03/2017) and end of trial (28/02/2022) is about 5 years.	
Statistical analysis		
Statistical analysis title	Analysis of OS	
Comparison group	Not applicable	
Number of subjects included in analysis	53	
Number of enrolled patients	52 (1 patient not evaluable)	
	Arm A	**Arm B**
Median OS (95%CI)	6.4 (4.1-11.3)	7.4 (3.7-12.5)
Secondary endpoint: Quality of life		
Endpoint title	Quality of life (QoL)	
Endpoint description	It will be evaluated through validated standardized data collection forms from the EORTC QLQ-C30 questionnaire. QoL will be collected at baseline, every 3 months since treatment start and at EOT.	
Endpoint type	Secondary	
Endpoint timeframe	The timeframe between the date of randomization of the first patient (06/03/2017) and evaluation of the	

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	progression of disease of the last enrolled patient (11/02/2021) were about 4 years	
Statistical analysis		
Statistical analysis title	Analysis of QoL	
Descriptive statistics were carried out		
Comparison group	Not applicable	
Number of subjects included in analysis	24 patients who had data on both screening and three months evaluation questionnaires	
	Screening evaluation (n=24)	**3-months evaluation ((n=24)**
Functional scales		
Physical functioning, mean score ±SD	78.3 ± 18.9	66.7 ± 24.6
Role functioning, mean score ±SD	75.0 ± 27.4	64.6 ± 36.6
Emotional functioning, mean score ±SD	72.9 ± 19.7	73.3 ± 22.9
Cognitive functioning, mean score ±SD	89.6 ± 12.8	83.3 ± 24.1
Social functioning, mean score ±SD	81.9 ± 25.5	78.5 ± 29.3
Symptoms scales		
Fatigue, mean score ±SD	29.6 ± 19.8	40.7 ± 25.3
Nausea and vomiting, mean score ±SD	9.7 ± 16.9	13.2 ± 24.6
Pain, mean score ±SD	22.9 ± 27.3	22.9 ± 27.3
Dyspnea, mean score ±SD	15.3 ± 19.6	18.1 ± 19.6
Sleeplessness, mean score ±SD	30.6 ± 31.0	37.5 ± 38.4
Loss of appetite, mean score ±SD	18.1 ± 25.9	18.1 ± 29.5
Constipation, mean score ±SD	22.2 ± 30.6	23.6 ± 30.2
Diarrhea, mean score ±SD	2.8 ± 9.4	15.3 ± 21.9
Financial problems, mean score ±SD	18.1 ± 32.6	19.4 ± 29.4
Global health status, mean score ±SD	80.5 ± 15.2	75.2 ± 16.9
Secondary endpoint: Efficacy and safety for patients who underwent to further treatment (OS)		
Endpoint title	Efficacy and safety of further treatment	
Endpoint description	OS and PFS time were calculated from the evidence of progressive disease for II line until death (or last follow up contact) or progressive disease (or death or last follow up contact) respectively.	
Endpoint type	Secondary	
Endpoint timeframe	The timeframe between the date of randomization of the first patient (06/03/2017) and trial (28/02/2022) is about 5 years.	
Statistical analysis		
Statistical analysis title	OS and PFS of further lines	
Third line drugs wasn't study objective evaluation. Only information on PD was collected but not TE and RECIST evaluation. For this reason, only descriptive analysis was carried out.		
Comparison group	Not applicable	
Number of subjects included in analysis	47 patients with information on further lines	

III line therapy	**Median OS (95%CI)**	**Median PFS (95%CI)**

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Captem (n=11 patients)	5.07 (1.94-8.22)	3.13 (2.00-4.87)
Folfiri (n=13 patients)	10.49 (3.19-NE)	3.68 (1.74-8.06)
Best supportive care (BSC) (n=14 pts)	0.32 (0.03-0.92)	-
Other treatments* (n=9 pts)	5.33 (1.15-9.54)	2.47 (1.15-NE)
NE→ not estimable from statistical software		

*Patients with other treatments→2 pts with radiotherapy, 2 pts with Temozolomide, 1 pt with 177-Lu, 1 pt carbo+eto, 1 pt folfox, 1 pt docetaxel, 1 pt cisplatin. Patients with BSC were patients who didn't any treatment after SENECA study. Of patients who underwent to CAPTEM, 3 had G3/G4 AEs (one patient without information on further AEs); Of patients who underwent to FOLFIRI, 4 had G3/G4 AEs (one patient without information on further AEs). For six patients no information on further treatment were collected.

Explorative endpoint: when available, as explorative objective: to assess the impact of PET with gallium on PFS	
Endpoint title	PET impact
Endpoint description	Will be calculated the PFS stratified on PET result as explorative aim.
Endpoint type	Explorative
Endpoint timeframe	The timeframe between the date of randomization of the first patient (06/03/2017) and evaluation of the progression of disease of the last enrolled patient (11/02/2021) were about 4 years.
Statistical analysis	
Statistical analysis title	PFS PET
Twelve patients underwent to Gallium PET while 13 patients underwent to 18-FDG PET: of these, 10 ant 13 patients respectively were positive.	
Comparison group	Not applicable
Number of subjects included in analysis	Not done due to low number of cases
Explorative endpoint (biological substudy): Identification of novel biomarker for neuroendocrine carcinoma	
Endpoint title	Circulating miRNA
Endpoint description	To identify circulating biomarkers, the circulating miRNA profile will be assessed at baseline in the first 20 patients (explorative study). Serum miRNAs resulting from this first screening will be assessed at baseline in all patients who agree to participate to this biologic part of the trial. In these patients the serum miRNAs resulting from the explorative study will be assessed also at the first patient re-evaluation (after 3 months from the first treatment) and at the time of progression and will be correlated to DCR, OS and PFS.
Endpoint type	Explorative
Endpoint timeframe	The timeframe between the date of randomization of the first patient (06/03/2017) and evaluation of the progression of disease of the last enrolled patient (11/02/2021) were about 4 years.
Statistical analysis	
Statistical analysis title	PFS PET
From the bioinformatic view, DESeq2 and EdgeR R packages were used to identify deregulated microRNA: nineteen miRNA were identified from both two methods. These miRNA were analyzed corrected by age	

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comparing patients and healthy donors. In patient's subgroup three of these were prognostic in terms of best overall response, OS and PFS. Further analysis on RT-PCR will be needed for validation.		
Comparison group	Not applicable	
Number of subjects included in analysis	20 patients + 20 healthy donors	
	Healthy donor Median values (min-max) N=20	Patients Median values (min-max) N=18
hsa-miR-1246 (P-value based on Wilcoxon rank-sum test:<0.001)	206.6 (61.3-522.5)	2596.1 (57.5-45681.5)
hsa-miR-1290 (P-value based on Wilcoxon rank-sum test:<0.001)	38.6 (18.4-156.8)	415.6 (11.9-9019.8)
hsa-miR-320c (P-value based on Wilcoxon rank-sum test:<0.001)	383.6 (178.1-1306.3)	2884.8 (209.7-37222.5)
Progression-free survival		
Cut of for specific hsa-miR	Median PFS (95%CI)	p-value from log rank test
hsa-miR-1246		
<690	7.9 (7.7-NE)	0.029
≥690	2.9 (2.0-7.8)	
hsa-miR-1290		
<241	7.9 (4.1-NE)	0.025
≥241	2.8 (1.0-7.9)	
hsa-miR-320c		
<4242	7.9 (2.8-9.4)	0.016
≥4242	2.7 (1.0-4.1)	
Overall survival		
Cut of for specific hsa-miR	Median PFS (95%CI)	p-value from log rank test
hsa-miR-1246		
<3407	10.7 (7.4-NE)	0.096
≥3407	3.8 (1.1-NE)	
hsa-miR-1290		
<1734	13.2 (9.2-23.9)	0.010
≥1734	3.7 (1.2-NE)	
hsa-miR-320c		
<4954	13.2 (9.8-NE)	0.005
≥4954	3.8 (2.8-NE)	
NE→ not evaluable from statistical software.		

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Adverse Events	
Adverse events information	
Timeframe for reporting adverse events	All AE occurring during the treatment period, from informed consent sign to the end of treatment. After that, every three months until disease progression.
Assessment type	Systematic
Dictionary used	
Dictionary name	NCI CTCAE
Dictionary version	5
Reporting groups	
Reporting group title	Enrolled patients
Reporting group description	Treatment toxicity: the maximum toxicity per patient was evaluated over all cycles of therapy based on the two different scheme of therapy, FOLFIRI and CAPTEM. SP was considered for the analysis of SAE and AE. The main toxicity events linked to treatment registered were: Neutropenia, Febrile neutropenia, leukopenia, Thrombocytopenia, Asthenia/fatigue, Nausea, Vomiting, Diarrhea, loss of appetite, Erythema/rush, fever, anorexia, mucositis, liver toxicity, renal toxicity, Nervous system disorder, Hand-foot syndrome and Peripheral edema.

Serious adverse events	**FOLFIRI ARM (n=27)**	**CAPTEM ARM (n=25)**
Total subjects affected by serious adverse events	5	7
Subject affected/exposed	5/27	7/25
Number of deaths (all causes)	23	19
Number of deaths resulting from adverse event	0	0
Febrile Neutropenia		
Subjects affected/exposed	1/27	0/25
Occurrences causally related to treatment/all	1/27	0/25
Deaths causally related to treatment/all	0/27	0/25
Anemia		
Subjects affected/exposed	1/27	0/25
Occurrences causally related to treatment/all	1/27	0/25
Deaths causally related to treatment/all	0/27	0/25
Thrombocytopenia		
Subjects affected/exposed	0/27	1/25
Occurrences causally related to treatment/all	0/27	1/25
Deaths causally related to treatment/all	0/27	0/25
Nausea		
Subjects affected/exposed	0/27	1/25
Occurrences causally related to treatment/all	0/27	1/25
Deaths causally related to treatment/all	0/27	0/25
Vomiting		
Subjects affected/exposed	0/27	1/25
Occurrences causally related to treatment/all	0/27	1/25

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Deaths causally related to treatment/all	0/27	0/25
Fever		
Subjects affected/exposed	1/27	0/25
Occurrences causally related to treatment/all	1/27	0/25
Deaths causally related to treatment/all	0/27	0/25
Catheter Related Infection		
Subjects affected/exposed	0/27	1/25
Occurrences causally related to treatment/all	0/27	0/25
Deaths causally related to treatment/all	0/27	0/25
Bronchopolmonitis		
Subjects affected/exposed	1/27	0/25
Occurrences causally related to treatment/all	0/27	0/25
Deaths causally related to treatment/all	0/27	0/25
Acute renal fail		
Subjects affected/exposed	1/27	0/25
Occurrences causally related to treatment/all	0/27	0/25
Deaths causally related to treatment/all	0/27	0/25
Pneumonitis		
Subjects affected/exposed	2/27	0/25
Occurrences causally related to treatment/all	2/27	0/25
Deaths causally related to treatment/all	0/27	0/25
Lipotimic episode		
Subjects affected/exposed	1/27	0/25
Occurrences causally related to treatment/all	0/27	0/25
Deaths causally related to treatment/all	0/27	0/25
Herpes Zoster		
Subjects affected/exposed	1/27	0/25
Occurrences causally related to treatment/all	1/27	0/25
Deaths causally related to treatment/all	0/27	0/25
Hyperkaliemia		
Subjects affected/exposed	1/27	0/25
Occurrences causally related to treatment/all	0/27	0/25
Deaths causally related to treatment/all	0/27	0/25
Pulmonary Embolism		
Subjects affected/exposed	0/27	1/25
Occurrences causally related to treatment/all	0/27	0/25
Deaths causally related to treatment/all	0/27	0/25
Peripheral Edema		
Subjects affected/exposed	0/27	1/25
Occurrences causally related to treatment/all	0/27	0/25
Deaths causally related to treatment/all	0/27	0/25
Worsening of physical condition		
Subjects affected/exposed	0/27	2/25
Occurrences causally related to treatment/all	0/27	0/25
Deaths causally related to treatment/all	0/27	0/25
Dysphagia		

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Subjects affected/exposed	0/27	1/25
Occurrences causally related to treatment/all	0/27	0/25
Deaths causally related to treatment/all	0/27	0/25
Brain metastasis		
Subjects affected/exposed	0/27	1/25
Occurrences causally related to treatment/all	0/27	0/25
Deaths causally related to treatment/all	0/27	0/25
Oliguria		
Subjects affected/exposed	0/27	1/25
Occurrences causally related to treatment/all	0/27	0/25
Deaths causally related to treatment/all	0/27	0/25
Treatment related non-Serious adverse events*	**FOLFIRI ARM (n=27)**	**CAPTEM ARM (n=25)**
Neutropenia		
Subjects affected/exposed	12/27	3/25
Occurrences (all)	17	5
Leukopenia		
Subjects affected/exposed	1/27	1/25
Occurrences (all)	1	1
Anemia		
Subjects affected/exposed	8/27	3/25
Occurrences (all)	11	4
Thrombocytopenia		
Subjects affected/exposed	2/27	5/25
Occurrences (all)	6	9
Asthenia/fatigue		
Subjects affected/exposed	9/27	6/25
Occurrences (all)	13	8
Nausea		
Subjects affected/exposed	8/27	5/25
Occurrences (all)	16	5
Vomiting		
Subjects affected/exposed	6/27	5/25
Occurrences (all)	6	5
Diarrhea		
Subjects affected/exposed	8/27	1/25
Occurrences (all)	14	1
Loss of appetite		
Subjects affected/exposed	2/27	0/25
Occurrences (all)	2	0
Erythema/rush		
Subjects affected/exposed	1/27	1/25
Occurrences (all)	1	1
Fever		
Subjects affected/exposed	1/27	0/25
Occurrences (all)	2	0
Anorexia		

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Subjects affected/exposed	0/27	2/25
Occurrences (all)	0	2
Mucositis		
Subjects affected/exposed	3/27	0/25
Occurrences (all)	4	0
Liver toxicity		
Subjects affected/exposed	4/27	7/25
Occurrences (all)	5	12
Renal toxicity		
Subjects affected/exposed	0/27	1/25
Occurrences (all)	0	1
Nervous system disorder		
Subjects affected/exposed	1/27	0/25
Occurrences (all)	1	0
Hand-food syndrome		
Subjects affected/exposed	1/27	0/25
Occurrences (all)	1	0
Peripheral edema		
Subjects affected/exposed	0/27	2/25
Occurrences (all)	0	2
Other		
Subjects affected/exposed	9/27	6/25
Occurrences (all)	10	8
*only certain, probable or possible relation with treatment of each grade.		

More information	
Substantial protocol amendments (globally)	
Were there any global substantial amendments to the protocol?	Yes
Date	**Amendment**
2019	The study protocol was amended for the following reasons: - Study duration: was updated to a total of 60 months (including 48 months of enrollment), so as to allow completion of the study procedures and achievement of the target. - Secondary objectives/endpoints: an exploratory objective was introduced to collect and evaluate data on the outcome and toxicity of subsequent treatment after progression from experimental therapy. Disease Control Rate (DCR) and relevant toxicities (G3-G4) will be evaluated for the secondary endpoint analysis. This data will allow assessments to be made about the safety of the investigational drugs to detect any late toxicities, and will provide insight into whether overall survival may be related to treatment in the SENECA protocol or will affect subsequent treatments. - Eligibility criteria: have been updated, allowing the inclusion of patients with asymptomatic encephalic metastases, so that the efficacy of the experimental

	treatment (both irinotecan and temozolomide cross the blood-brain barrier) can also be evaluated in this category of patients who, at the same time, will benefit from a therapeutic opportunity they would not otherwise have. Exclusion was maintained for patients with uncontrolled or symptomatic brain metastases, as these patients, who already have a bleak prognosis per se, require additional treatments (such as regional loco-regional RT treatment for palliative purposes) that may delay the initiation of treatment. In addition, the reported symptoms may invalidate the efficacy/safety data. In addition, rare histologic forms of neuroendocrine carcinomas of different origins such as those of the uro-gynecologic tract and forms with unknown primaries were also included, which, however, represent a small percentage of the total number of cases. The amended protocol will also allow patients who have performed previous treatment with everolimus and immunotherapy to enter the study since clinical trials, especially in the NET G3 subcategory, have been investigating the role of immunotherapy and biologic drugs in this patient setting in recent years. - Stratification criteria: through the amendment, the aim was to make the clinical study more current and more adherent to clinical practice through the modification of the stratification criteria, in accordance with the 2017 WHO classification that divides pancreatic neuroendocrine carcinomas into two groups (NET G3 and NEC G3) based on the morphology of the tumor itself (well-differentiated vs poorly differentiated). This approach will also be used for neuroendocrine carcinomas of the intestinal tract. - Study procedures: the study procedures were updated to make them adhere to the changes described above; in particular, a description of follow-up following progression was introduced, which will consist of visits, laboratory and instrumental examinations as per clinical practice, which will allow data to be collected on the efficacy and safety of post-protocol treatment until new progression. - the bibliographic references: this section has been updated, adding scientific papers published in recent years related to the classification of neuroendocrine carcinomas. - the references of the criteria for evaluation of adverse events: they have been updated to version 5.0.
2020	An urgent amendment has been notified due to COVID-19 pandemic. In compliance with the enunciation of AIFA of 12/03/2020 on the management of clinical trials during COVID-19 emergency, the Promoter authorized the trial centers to the supply of sufficient oral investigational drugs for "CAPTEM treatment" for more than the 4 weeks foreseen in the protocol for a single cycle of therapy. The Promoter also authorized the performance of "pre-cycle" hematological examinations close to the patient's home: these examinations should be performed in public facilities, as recommended by AIFA. These measures have been taken on the basis of a careful assessment of the risk related to the COVID-19 outbreak for the protection of the investigational patient and in view of the urgent need to minimize contact between the patient and the investigational staff, in order also not to overburden healthcare facilities.

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	The study protocol was amended to replace the principal investigator of the Coodinating center of Meldola
Interruption (globally)	
Enrollment was stopped when 53 patients were enrolled, according to the Bryant and Day's two step design for the time necessary for data cleaning and subsequent conduct of the planned first step analysis. This analysis showed that, in relation to the evaluation of the primary objective, a statistically significant result was achieved. In view of this result, enrolment was considered concluded.	
Limitations and caveats	
Non reported.	

Conclusion
Despite the fact that we did not reach the primary end-point and the trial was stopped prematurely due to futility, some considerations could be extrapolated by the results presented: in fact, to date, there is no truly effective second-line chemotherapy for patients with NEC. Our study confirms the poor prognosis of these rare and aggressive tumors, even if fails to identify an effective regimen for their second-line treatment.

	Date	**Signature**
Flavia Foca Trial Statistician	08/03/2024	Flavia Foca
Sponsor's representative	12/03/24	