



## Clinical trial results:

**An open-label, randomized, multicenter, phase II trial designed to estimate the activity of CAPTEM combination versus FOLFIRI as second line treatment in patients who have progressed on or after first-line oxaliplatin - containing chemotherapy for advanced, MGMT methylated, RAS mutated colorectal cancer**

### Summary

EudraCT number	2014-002417-36
Trial protocol	IT
Global end of trial date	16 July 2019

### Results information

Result version number	v1 (current)
This version publication date	13 December 2021
First version publication date	13 December 2021

### Trial information

#### Trial identification

Sponsor protocol code	CAPTEM
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02414009
WHO universal trial number (UTN)	-

Notes:

### Sponsors

Sponsor organisation name	Fondazione IRCCS Istituto Nazionale Tumori
Sponsor organisation address	via Venezian, 1, Milan, Italy, 20133
Public contact	trialcenter, trialcenter, trialcenter@istitutotumori.mi.it
Scientific contact	trialcenter, trialcenter, trialcenter@istitutotumori.mi.it

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	30 July 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 July 2019
Global end of trial reached?	Yes
Global end of trial date	16 July 2019
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

Progression free survival

Protection of trial subjects:

laboratory test and clinical visit before every drugs subministrations

Each patient had a direct contact to inform physicians about possible symptoms due to site effects of the experimental drugs and he received consultation about the optimal management.

Background therapy: -

Evidence for comparator: -

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

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 86
Worldwide total number of subjects	86
EEA total number of subjects	86

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)	31
From 65 to 84 years	55
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

18 Italian centers. Between November 6, 2014 and May 10, 2019, a total of 155 patients were pre-screened for MGMT methylation status and 86 molecularly eligible patients were randomized

### Pre-assignment

Screening details:

Inclusion criteria: age of 18 years or more; ECOG PS 0–1; RAS-mutated status and MGMT methylation; PD after previous oxaliplatin based regimen (no more than 1 prior treatment line); measurable lesion; adequate bone marrow, liver, and renal function. Exclusion: deficiency DPD; Gilbert S.; relevant cardiovascular disease; active malignancies; pregnancy

### Pre-assignment period milestones

Number of subjects started	86
Number of subjects completed	86

### Period 1

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

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	CAPTEM

Arm description:

The schedule of CAPTEM regimen consisted of oral capecitabine 750 mg/sqm twice daily from days 1 to 14 every 28 days plus temozolomide 75 mg/sqm twice daily from days 10 to 14 every 28 days.

Arm type	Experimental
Investigational medicinal product name	CAPECITABINE
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

750 mg/sqm twice daily from days 1 to 14 every 28 days

Investigational medicinal product name	TEMOZOLOMIDE
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

75mg/sqm twice daily from days 10 to 14 every 28 days

<b>Arm title</b>	FOLFIRI
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Arm description:

The schedule of FOLFIRI regimen consisted of irinotecan 180 mg/sqm i.v. over 60 minutes on day 1, leucovorin 200 mg/sqm i.v. over 120 minutes on days 1 and 2, followed by 5-fluorouracil (5-FU) 400 mg/sqm i.v. bolus and then 5-FU 600 mg/sqm administered as a continuous intravenous infusion over 22 +/- 2 hours, both on days 1 and 2, every two weeks.

Arm type	Active comparator
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Investigational medicinal product name	IRINOTECAN
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use
Dosage and administration details:	
180 mg/sqm i.v. over 60 minutes on day 1	
Investigational medicinal product name	LEUCOVORIN
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
200 mg/sqm i.v. over 120 minutes on days 1 and 2	
Investigational medicinal product name	5-FLUORURACIL (5-FU)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
5-fluorouracil (5-FU) 400 mg/sqm i.v. bolus on day 1 and 2	
Investigational medicinal product name	5-FLUORURACIL (5-FU)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
600 mg/sqm administered as a continuous intravenous infusion over 22 2 hours, both on days 1 and 2, every two weeks	

<b>Number of subjects in period 1</b>	CAPTEM	FOLFIRI
Started	43	43
Completed	43	43

## Baseline characteristics

### Reporting groups

Reporting group title	CAPTEM
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Reporting group description:

The schedule of CAPTEM regimen consisted of oral capecitabine 750 mg/sqm twice daily from days 1 to 14 every 28 days plus temozolomide 75 mg/sqm twice daily from days 10 to 14 every 28 days.

Reporting group title	FOLFIRI
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Reporting group description:

The schedule of FOLFIRI regimen consisted of irinotecan 180 mg/sqm i.v. over 60 minutes on day 1, leucovorin 200 mg/sqm i.v. over 120 minutes on days 1 and 2, followed by 5-fluorouracil (5-FU) 400 mg/sqm i.v. bolus and then 5-FU 600 mg/sqm administered as a continuous intravenous infusion over 22 +/- 2 hours, both on days 1 and 2, every two weeks.

Reporting group values	CAPTEM	FOLFIRI	Total
Number of subjects	43	43	86
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	11	20	31
From 65-84 years	32	23	55
85 years and over	0	0	0
Age continuous			
Units: years			
median	70.0	67.0	
full range (min-max)	63.0 to 74.5	61.0 to 73.0	-
Gender categorical			
Units: Subjects			
Female	25	19	44
Male	18	24	42
ECOG performance status			
Units: Subjects			
ECOG PS 0	24	22	46
ECOG PS1	19	21	40
Primary tumor location			
Units: Subjects			
Right	15	17	32
Left	28	26	54
Primary tumor resected			
Units: Subjects			
YES	30	31	61
NO	13	12	25
Prior adjuvant treatment			

Units: Subjects			
YES	10	11	21
NO	33	32	65
Number of metastatic sites			
Units: Subjects			
ONE	18	15	33
MORE THAN ONE	25	28	53
Liver-limited disease			
Units: Subjects			
YES	11	7	18
NO	32	36	68
Synchronous metastases			
Units: Subjects			
YES	31	29	60
NO	12	14	26
First-line PFS			
Units: Subjects			
LESS THAN NINE MONTHS	20	19	39
NINE MONTHS OR MORE	23	24	47
Prior bevacizumab			
Units: Subjects			
YES	30	29	59
NO	13	14	27

## End points

### End points reporting groups

Reporting group title	CAPTEM
Reporting group description:	
The schedule of CAPTEM regimen consisted of oral capecitabine 750 mg/sqm twice daily from days 1 to 14 every 28 days plus temozolomide 75 mg/sqm twice daily from days 10 to 14 every 28 days.	
Reporting group title	FOLFIRI
Reporting group description:	
The schedule of FOLFIRI regimen consisted of irinotecan 180 mg/sqm i.v. over 60 minutes on day 1, leucovorin 200 mg/sqm i.v. over 120 minutes on days 1 and 2, followed by 5-fluorouracil (5-FU) 400 mg/sqm i.v. bolus and then 5-FU 600 mg/sqm administered as a continuous intravenous infusion over 22 +/- 2 hours, both on days 1 and 2, every two weeks.	

### Primary: Progression-free survival

End point title	Progression-free survival
End point description:	
End point type	Primary
End point timeframe:	
Between November 2014 and May 2019,	

End point values	CAPTEM	FOLFIRI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	43		
Units: month				
median (full range (min-max))	3.5 (2.0 to 5.0)	3.5 (2.3 to 6.1)		

### Statistical analyses

Statistical analysis title	PFS
Comparison groups	CAPTEM v FOLFIRI
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.05
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	95
Confidence interval	
level	95 %
sides	1-sided
upper limit	95

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**Secondary: overall survival**

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End point title	overall survival
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End point description:

End point type	Secondary
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End point timeframe:

Between November 2014 and May 2019.

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End point values	CAPTEM	FOLFIRI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	43		
Units: month				
median (full range (min-max))	9.5 (8.2 to 25.8)	10.6 (8.5 to 20.8)		

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**Statistical analyses**

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Statistical analysis title	OS
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Comparison groups	CAPTEM v FOLFIRI
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Number of subjects included in analysis	86
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Analysis specification	Pre-specified
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Analysis type	other
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P-value	= 0.05
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Method	Logrank
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Parameter estimate	Cox proportional hazard
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Point estimate	95
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Confidence interval

level	95 %
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sides	2-sided
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lower limit	0
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upper limit	100
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**Secondary: disease control rate (DCR)**

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End point title	disease control rate (DCR)
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End point description:

End point type	Secondary
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End point timeframe:

Between November 2014 and May 2019

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End point values	CAPTEM	FOLFIRI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	43		
Units: percentage protection				
number (not applicable)	53.5	53.5		

### Statistical analyses

Statistical analysis title	DCR
Comparison groups	FOLFIRI v CAPTEM
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.05
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	100

### Secondary: ORR

End point title	ORR
End point description:	
End point type	Secondary
End point timeframe:	
Between November 2014 and May 2019	

End point values	CAPTEM	FOLFIRI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	43		
Units: NUMBER				
median (confidence interval 95%)	11.6 (3.9 to 25.1)	11.6 (3.9 to 25.1)		

**Statistical analyses**

<b>Statistical analysis title</b>	ORR
Comparison groups	CAPTEM v FOLFIRI
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.05
Method	t-test, 2-sided
Confidence interval	
level	95 %
sides	2-sided

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

The data cut-off date for the analyses was July 30, 2019.

Assessment type	Systematic
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### Dictionary used

Dictionary name	NCI CTCAE
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Dictionary version	4.0
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### Reporting groups

Reporting group title	CAPTEM
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Reporting group description: -

Reporting group title	FOLFIRI
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Reporting group description: -

Serious adverse events	CAPTEM	FOLFIRI	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 43 (0.00%)	0 / 43 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	CAPTEM	FOLFIRI	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 43 (32.56%)	23 / 43 (53.49%)	
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	7 / 43 (16.28%)	23 / 43 (53.49%)	
occurrences (all)	1	1	
Neutropenia			
subjects affected / exposed	2 / 43 (4.65%)	19 / 43 (44.19%)	
occurrences (all)	1	1	
Thrombocytopenia			
subjects affected / exposed <sup>[1]</sup>	10 / 14 (71.43%)	3 / 23 (13.04%)	
occurrences (all)	1	1	
AST increased			

subjects affected / exposed <sup>[2]</sup> occurrences (all)	1 / 14 (7.14%) 1	5 / 23 (21.74%) 1	
ALT increased subjects affected / exposed <sup>[3]</sup> occurrences (all)	3 / 14 (21.43%) 1	4 / 23 (17.39%) 1	
Blood bilirubin increased subjects affected / exposed <sup>[4]</sup> occurrences (all)	4 / 14 (28.57%) 1	0 / 23 (0.00%) 1	
General disorders and administration site conditions			
Hand-foot syndrome subjects affected / exposed <sup>[5]</sup> occurrences (all)	4 / 14 (28.57%) 1	1 / 23 (4.35%) 1	
Fatigue subjects affected / exposed <sup>[6]</sup> occurrences (all)	14 / 14 (100.00%) 1	18 / 23 (78.26%) 1	
Gastrointestinal disorders			
Diarrhea subjects affected / exposed <sup>[7]</sup> occurrences (all)	6 / 14 (42.86%) 1	19 / 23 (82.61%) 1	
Nausea subjects affected / exposed <sup>[8]</sup> occurrences (all)	11 / 14 (78.57%) 1	14 / 23 (60.87%) 1	
Vomiting subjects affected / exposed <sup>[9]</sup> occurrences (all)	12 / 14 (85.71%) 1	8 / 23 (34.78%) 1	
Stomatitis subjects affected / exposed <sup>[10]</sup> occurrences (all)	1 / 14 (7.14%) 1	6 / 23 (26.09%) 1	

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: not equal because not all the patients showed the same AEs

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: not equal because not all the patients showed the same AEs

[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: not equal because not all the patients showed the same AEs

[4] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: not equal because not all the patients showed the same AEs

[5] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: not equal because not all the patients showed the same AEs

[6] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: not equal because not all the patients showed the same AEs

[7] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: not equal because not all the patients showed the same AEs

[8] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: not equal because not all the patients showed the same AEs

[9] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: not equal because not all the patients showed the same AEs

[10] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: not equal because not all the patients showed the same AEs

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/31740551>