Clinical trial results:
A RANDOMISED PHASE II TRIAL OF SECOND LINE THERAPY IN ADVANCED BILIARY TRACT CANCER: CAPECITABINE OR CAPECITABINE PLUS MITOMYCIN C (BIT-2)

Summary

EudraCT number	2011-002002-70
Trial protocol	IT
Global end of trial date	06 May 2015

Results information

Result version number	v1 (current)
This version publication date	26 May 2016
First version publication date	26 May 2016

Trial information

Trial identification

Sponsor protocol code	BIT-2

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01530503
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ospedale San Raffaele
Sponsor organisation address	Via Olgettina, 60, Milano, Italy, 20133
Public contact	Oncologia Medica, Ospedale San Raffaele , +39 02 26437644, cereda.stefano@hsr.it
Scientific contact	Oncologia Medica, Ospedale San Raffaele, +39 02 26437644, cereda.stefano@hsr.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	17 December 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 May 2015
Global end of trial reached?	Yes
Global end of trial date	06 May 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Assessment of the therapeutic activity of capecitabine alone or in combination with mitomycin C in terms of progression-free survival rate at 6 months from treatment start in patients with advanced/metastatic biliary adenocarcinoma in progression after gemcitabine and platinum compounds.

Protection of trial subjects:

Throughout the study, investigators prescribed any concomitant medication or treatment deemed necessary to provide adequate supportive care, as per protocol instructions, including therapeutic use of hematopoietic colony growth factors (granulocyte colony-stimulating factor [G-CSF]) and use of erythropoietin.
Dose adjustment and dose delay were foreseen in case of hematological and non hematological toxicity.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 October 2011
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: 57
Worldwide total number of subjects	57
EEA total number of subjects	57

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)	22
From 65 to 84 years	35

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between October 2011 and October 2013.

Pre-assignment

Screening details:

57 metastatic patients with progressive biliary tract adenocarcinoma (BTA) after gemcitabine and platinum analogs therapy were enrolled. Patients were stratified and randomized, by an online application based on baseline stage and site of primary tumor.

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
Arm title	Arm A

Arm description:

Patients were treated with Capecitabine 200mg/m2 alone, Day 1-14 of a 3-week cycle.
Patients remained on treatment until disease progression, patient refusal, consent withdrawal, medical decision or for a maximum of 6 months. The continuation of treatment after 6 months was decided on an individual basis, taking into account tolerability, toxicity and response, in the interest of the patient. Patients who discontinued the treatment in absence of disease progression were followed up until documentation of disease progression or start of another anticancer therapy.

Arm type	Experimental
Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

2000 mg/m2, Day 1-14 of a 3-week cycle divided in two doses taken with food.

Arm title	Arm B

Arm description:

Capecitabine 2000 mg m2, Day 1-14 in combination with Mytomicin C 6 mg/m2 Day 1 of a 3-week cycle.
Patients remained on treatment until disease progression, patient refusal, consent withdrawal, medical decision or for a maximum of 6 months. The continuation of treatment after 6 months was decided on an individual basis, taking into account tolerability, toxicity and response, in the interest of the patient. Patients who discontinued the treatment in absence of disease progression were followed up until documentation of disease progression or start of another anticancer therapy.

Arm type	Experimental
Investigational medicinal product name	Mytomicin C
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients were treated with IV infusion mitomycin C 6 mg/m2 on Day 1 of a 3-week cycle.

Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

2000 mg/m2, Day 1-14 of a 3-week cycle divided in two doses taken with food

Number of subjects in period 1	Arm A	Arm B
Started	28	29
Treated	26	29
Completed	1	0
Not completed	27	29
Adverse event, serious fatal	1	-
Consent withdrawn by subject	1	-
Physician decision	-	2
Lack of compliance with protocol requirements	1	2
Adverse event, non-fatal	-	9
Death	1	-
Patient refusal to continue the study treatment	1	1
Progression	20	15
Not treated	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Arm A
Reporting group description:	
Patients were treated with Capecitabine 200mg/m2 alone, Day 1-14 of a 3-week cycle. Patients remained on treatment until disease progression, patient refusal, consent withdrawal, medical decision or for a maximum of 6 months. The continuation of treatment after 6 months was decided on an individual basis, taking into account tolerability, toxicity and response, in the interest of the patient. Patients who discontinued the treatment in absence of disease progression were followed up until documentation of disease progression or start of another anticancer therapy.	
Reporting group title	Arm B
Reporting group description:	
Capecitabine 2000 mg m2, Day 1-14 in combination with Mytomicin C 6 mg/m2 Day 1 of a 3-week cycle. Patients remained on treatment until disease progression, patient refusal, consent withdrawal, medical decision or for a maximum of 6 months. The continuation of treatment after 6 months was decided on an individual basis, taking into account tolerability, toxicity and response, in the interest of the patient. Patients who discontinued the treatment in absence of disease progression were followed up until documentation of disease progression or start of another anticancer therapy.	

Reporting group values	Arm A	Arm B	Total
Number of subjects	28	29	57
Age categorical Units: Subjects			
Adults (18-64 years)	8	14	22
From 65-84 years	20	15	35
Age continuous			
Data for Age continuous were reported for treated (55) patecipants only.			
Units: years			
median	66	65	
full range (min-max)	45 to 74	30 to 78	-
Gender categorical Units: Subjects			
Female	19	12	31
Male	9	17	26
Race Units: Subjects			
White	28	28	56
Missing	0	1	1
Primary Disease Site Units: Subjects			
Gallbladder Cancer	5	6	11
Ampulla of Vater	3	3	6
Inthrahepatic Bile Ducts	17	17	34
Extrahepatic bile Ducts	3	3	6
Disease Extent at Study Entry Units: Subjects			
Metastatic	28	29	57
Hystopathological Grade Units: Subjects			
Grade 2	8	5	13

Grade 3	8	11	19
Not assessable	12	13	25
Karnofsky Performance Status Units: Subjects			
0-69	0	0	0
70-79	5	7	12
80-89	1	0	1
90-100	22	22	44

End points

End points reporting groups

Reporting group title	Arm A

Reporting group description:

Patients were treated with Capecitabine 200mg/m2 alone, Day 1-14 of a 3-week cycle.
Patients remained on treatment until disease progression, patient refusal, consent withdrawal, medical decision or for a maximum of 6 months. The continuation of treatment after 6 months was decided on an individual basis, taking into account tolerability, toxicity and response, in the interest of the patient.
Patients who discontinued the treatment in absence of disease progression were followed up until documentation of disease progression or start of another anticancer therapy.

Reporting group title	Arm B

Reporting group description:

Capecitabine 2000 mg m2, Day 1-14 in combination with Mytomicin C 6 mg/m2 Day 1 of a 3-week cycle.
Patients remained on treatment until disease progression, patient refusal, consent withdrawal, medical decision or for a maximum of 6 months. The continuation of treatment after 6 months was decided on an individual basis, taking into account tolerability, toxicity and response, in the interest of the patient.
Patients who discontinued the treatment in absence of disease progression were followed up until documentation of disease progression or start of another anticancer therapy.

Subject analysis set title	Patients Evaluable for Efficacy Analysis
Subject analysis set type	Full analysis

Subject analysis set description:

This is the patient population for the primary efficacy analysis of PFS-6 rate and consists of all eligible and treated patients who fulfil the following additional conditions:
• The patient has baseline tumor/oncologic assessment.
• The patient has received at least the first treatment cycle.
• The patient doesn’t die within the first 3 weeks of treatment, thus preventing any benefit from the therapy.
In case that the patient has not progressed or died before the 6 month tumour assessment and missed it, s/he will be classified as
• failure, if at the following assessment s/he is rated as PD or there is no further information or dies without a re-assessment.
• response, if at the following assessment s/he is SD or better
If deemed of clinical interest, patient disposition, baseline characteristics and treatment exposure will be presented also in this population.

Primary: Progression-free survival rate at 6 months from treatment start (PFS-6)

End point title	Progression-free survival rate at 6 months from treatment start (PFS-6)[1]

End point description:

The PFS-6 rate, is calculated as the proportion of evaluable patients known to be alive and progression-free at ≥ 6 months since study treatment start out of the total number of evaluable patients.
If 8 or more responses is achieved out of first 26 evaluable patients it is concluded that the regimen(s) deserve further exploration.
Supportive analyses of the primary endpoint include the estimation of the PFS-6 rate together with its exact, two-tail, 95% confidence interval and the estimation of the PFS curve by the Kaplan-Meier method in both the evaluable and the treated patient population.

End point type	Primary

End point timeframe:

At six months from treatment start.

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: No formal comparison between the two arms was to be performed. The main goal of the study was to assess whether either of the regimens or both were worth being explored further in a confirmatory trial in the indication.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	29		
Units: percent				
number (confidence interval 95%)	8 (0.98 to 26.03)	10.34 (2.19 to 27.35)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival

End point title	Progression free survival

End point description:

Progression-free survival is calculated as the time from the treatment start to the date of first documentation of objective progression or of death due to any cause, whichever comes first. Subjects who have not progressed while on study and have not died while on study are censored at the last evaluable radiographic assessment date.

End point type	Secondary

End point timeframe:

From treatment start to progression disease or death.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	29		
Units: months				
median (confidence interval 95%)	2.1 (1.94 to 2.89)	2.33 (2.07 to 4.53)		

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate

End point title	Objective Response Rate

End point description:

Objective Response Rate is the relative frequency of either a complete or partial response while on study; subjects prematurely discontinuing without a post-baseline tumour response assessment or subjects with an observed complete or partial response that is not confirmed are considered non-responders. Point and 95% confidence interval estimates are calculated for the objective tumor response rate. The analysis is performed in the evaluable and in the treated patient populations. The estimates of the rates of unconfirmed tumor objective responses ia also provided and considered as supportive.

End point type	Secondary

End point timeframe:

From randomization to first documentation of objective progression.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	29		
Units: percent				
number (confidence interval 95%)				
Confirmed CR plus PR	0 (0 to 0)	3.4 (0.1 to 17.8)		
Unconfirmed CR plus PR	4 (0.1 to 20.4)	3.4 (0.1 to 17.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall Survival (OS) is the time from the date of randomization to the date of death from any cause. Subjects who are known to be alive or for whom a date of death is unknown, are censored on the later of the date of the last study assessment or last known telephone contact.

End point type	Secondary

End point timeframe:

From the randomization to death from any cause.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	29		
Units: months				
median (confidence interval 95%)	10.09 (4.47 to 14.06)	8.11 (5.06 to 15.08)		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate

End point title	Disease Control Rate

End point description:

Disease Control Rate is the relative frequency of confirmed objective responses and long lasting (SD≥ 6 months) stabilizations measured from the date of randomization to the date of first documentation of objective progression. Point and 95% confidence interval estimates are calculated for the disease control rate (confirmed CRs / PRs and SD >= 6 weeks). The analysis are performed in the evaluable and in the

treated patient populations.

End point type	Secondary

End point timeframe:

From randomization to first documentation of objective progression.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	29		
Units: percent				
number (confidence interval 95%)	28 (12.1 to 49.4)	37.9 (20.7 to 57.7)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Before treatment administration at baseline (baseline signs and symptoms), on treatment until the safety follow up visit (42 days after the last dose of study drug administration).

Adverse event reporting additional description:

The adverse events (AEs) are coded by the Medical Dictionary for Regulatory Activities (MedDRA) and their severity graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. All SAEs and non-serious AEs are collected.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	5.1

Reporting groups

Reporting group title	Arm A

Reporting group description:

Patients treated with oral capecitabine 2000 mg/m2 day 1-14 in two divided doses taken with food.

Reporting group title	Arm B

Reporting group description:

Patients treated with oral capecitabine 2000 mg/m2 day 1-14 in two divided doses taken with food plus bolus IV infusion mitomycin C 6 mg/m2 dissolved in sterile water for injection with a ratio of 10 mg/20ml or 40 mg/80 ml respectively on day 1

Serious adverse events	Arm A	Arm B	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 26 (7.69%)	7 / 29 (24.14%)	
number of deaths (all causes)	23	21	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Stent Occlusion			
subjects affected / exposed	0 / 26 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Progression Disease			
subjects affected / exposed	1 / 26 (3.85%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Asthenia			

subjects affected / exposed	1 / 26 (3.85%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	1 / 26 (3.85%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 26 (0.00%)	3 / 29 (10.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Abdominal pain			
subjects affected / exposed	0 / 26 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 26 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	1 / 26 (3.85%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal infection			
subjects affected / exposed	0 / 26 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Anorexia			

subjects affected / exposed	1 / 26 (3.85%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Arm A	Arm B	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 26 (80.77%)	19 / 29 (65.52%)	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 26 (11.54%)	6 / 29 (20.69%)	
occurrences (all)	5	8	
Fatigue			
subjects affected / exposed	0 / 26 (0.00%)	3 / 29 (10.34%)	
occurrences (all)	0	5	
Pyrexia			
subjects affected / exposed	0 / 26 (0.00%)	7 / 29 (24.14%)	
occurrences (all)	0	15	
Disease progression			
subjects affected / exposed	2 / 26 (7.69%)	2 / 29 (6.90%)	
occurrences (all)	2	2	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	2 / 26 (7.69%)	14 / 29 (48.28%)	
occurrences (all)	4	21	
Anaemia			
subjects affected / exposed	1 / 26 (3.85%)	3 / 29 (10.34%)	
occurrences (all)	2	3	
Leukopenia			
subjects affected / exposed	0 / 26 (0.00%)	2 / 29 (6.90%)	
occurrences (all)	0	2	
Neutropenia			
subjects affected / exposed	0 / 26 (0.00%)	2 / 29 (6.90%)	
occurrences (all)	0	2	
Gastrointestinal disorders			

Nausea subjects affected / exposed occurrences (all)	5 / 26 (19.23%) 8	5 / 29 (17.24%) 6	
Abdominal Pain subjects affected / exposed occurrences (all)	3 / 26 (11.54%) 4	8 / 29 (27.59%) 10	
Diarrhoea subjects affected / exposed occurrences (all)	3 / 26 (11.54%) 3	4 / 29 (13.79%) 5	
Constipation subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2	2 / 29 (6.90%) 2	
Vomiting subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 3	4 / 29 (13.79%) 5	
Stomatitis subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1	2 / 29 (6.90%) 2	
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2	1 / 29 (3.45%) 1	
Skin and subcutaneous tissue disorders Palmar-plantar erythrodysaesthesia syndrome subjects affected / exposed occurrences (all)	5 / 26 (19.23%) 9	6 / 29 (20.69%) 8	
Musculoskeletal and connective tissue disorders Pain in limb subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2	0 / 29 (0.00%) 0	
Metabolism and nutrition disorders Anorexia subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2	3 / 29 (10.34%) 3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Not Applicable

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/26659366