



## Clinical trial results:

**A multicentre randomised phase II clinical study of UFT/leucovorin (LV), radiotherapy with or without cetuximab following induction gemcitabine plus capecitabine in patients with locally advanced pancreatic cancer**

### Summary

EudraCT number	2008-000517-30
Trial protocol	GB
Global end of trial date	20 July 2015

### Results information

Result version number	v1 (current)
This version publication date	07 August 2016
First version publication date	07 August 2016

### Trial information

#### Trial identification

Sponsor protocol code	3065
-----------------------	------

#### Additional study identifiers

ISRCTN number	ISRCTN65518365
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

### Sponsors

Sponsor organisation name	Royal Marsden NHS Foundation Trust
Sponsor organisation address	Downs Road, Sutton, London, United Kingdom,
Public contact	Khurum Khan, Royal Marsden NHS Foundation Trust, 0208 661 3279, khurum.khan@rmh.nhs.uk
Scientific contact	Dr Khurum Khan, Dr Chiara Braconi, 0208 661 3279, jacqui.oates@rmh.nhs.uk

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	20 July 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 July 2015
Global end of trial reached?	Yes
Global end of trial date	20 July 2015
Was the trial ended prematurely?	Yes

Notes:

---

## General information about the trial

Main objective of the trial:

One-year overall survival rate

Protection of trial subjects:

Regular IDMC

Background therapy:

Despite the recent advancements in diagnosis and management of solid malignancies, pancreatic ductal adenocarcinoma (PDAC) remains a highly lethal disease, with mortality to incidence ratio of nearly one and 5-year survival of 6% (1). Only 10-20% of patients with PDAC present with potentially resectable disease while the remaining either present with locally advanced unresectable (40-50%) or metastatic disease (40%) (2). Management of Locally advanced Pancreatic Cancer (LAPC) remains largely under-researched with lack of evidence both in terms of optimal treatment approach and biomarkers that could inform such an approach (3). Although previously conducted studies failed to demonstrate any definite survival advantage of chemo-radiotherapy (CRT) over chemotherapy (CT) alone (4, 5), retrospective analysis of 4 phase II-III studies demonstrated that patients without disease progression after 3 months of CT, followed by CRT had a longer survival than those continuing on CT alone (6). Moreover, a pooled meta-analysis of SAKK and UK studies showed survival advantage with gemcitabine and capecitabine (GEM-CAP) combination (HR 0.86, 95% CI 0.75-0.98, p=0.02) (7, 8); suggesting this could be considered as useful neo-adjuvant chemotherapy (NACT) approach. Recent evidence suggests that addition of epidermal growth factor receptor (EGFR) inhibition to CRT is feasible and promising in terms of efficacy (9). Furthermore, EGFR is known to be expressed or upregulated in up to 69-95% of advanced pancreatic cancer (10, 11) and the EGFR tyrosine kinase inhibitor (TKI), erlotinib combined with gemcitabine demonstrated modest survival benefit over gemcitabine alone (12). However, currently there are no convincing data on the combination of TKI and radiotherapy, whilst cetuximab, an anti-EGFR antibody has been safely combined with chemotherapy and radiotherapy in patients with LAPC and with other cancers (13-15).

Evidence for comparator:

References:

1. Siegel R et al, Cancer statistics, 2014. PubMed PMID: 24399786.
2. Willett CG et al, 2005. PubMed PMID: 16002845.
3. Yip D et al, 2006 (3):CD002093. PubMed PMID: 16855985.
4. Sultana A, et al. 2007 Apr 23;96(8):1183-90. PubMed PMID: 17406358.
5. Chauffert B, et al. 2008 Sep;19(9):1592-9. PubMed PMID: 18467316.
6. Huguet F, 2007 Jan 20;25(3):326-31. PubMed PMID: 17235048.
7. Herrmann R, et al. 2007 Jun 1;25(16):2212-7. PubMed PMID: 17538165
8. Cunningham D, et al. 2009 Nov 20;27(33):5513-8. PubMed PMID: 19858379.
9. Van Zweenen AA, et al. 2015 Jun 8. PubMed PMID: 26056353.
10. Xiong HQ, et al. 2004 Jul 1;22(13):2610-6. PubMed PMID: 15226328.
11. Bloomston M, 2006;23(1-2):74-9. PubMed PMID: 16717472.
12. Moore MJ, et al. 2007 May 20;25(15):1960-6. PubMed PMID: 17452677.
13. Crane CH, et al. 011 Aug 1;29(22):3037-43. PubMed PMID: 21709185.
14. Bonner JA, et al. 2006 Feb 9;354(6):567-78. PubMed PMID: 16467544.
15. Hofheinz RD, et al. 2006 Dec 1;66(5):1384-90. PubMed PMID: 16979839.

Actual start date of recruitment	17 December 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

---

### Population of trial subjects

---

#### Subjects enrolled per country

---

Country: Number of subjects enrolled	United Kingdom: 17
Worldwide total number of subjects	17
EEA total number of subjects	17

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)	9
From 65 to 84 years	8
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Patients screened according to the following inclusion criteria: Inclusion criteria:

- Histologically or cytologically proven adenocarcinoma or poorly differentiated carcinoma of pancreas
- Considered to be unresectable based on one of the following:
- extensive peri-pancreatic lymph node involvement
- encasement or occlusion of the superior me

### Period 1

Period 1 title	Registration
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

### Arms

Arm title	All Patients
-----------	--------------

Arm description:

all patients recieved GEM-CAP prior to randmisation

Arm type	GEM-CAP
Investigational medicinal product name	GEM-CAP
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

GEM-CAP × 4 cycles

Gemcitabine 1000mg/m<sup>2</sup> Days 1, 8 + 15

Capecitabine 1660mg/m<sup>2</sup>/day Days 1-21 q 4 weeks

<b>Number of subjects in period 1</b>	All Patients
Started	17
Completed	13
Not completed	4
Patients ineligible for randomisation	4

### Period 2

Period 2 title	Randomisation
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

**Arms**

Are arms mutually exclusive?	Yes
<b>Arm title</b>	RT alone
Arm description: -	
Arm type	No intervention
No investigational medicinal product assigned in this arm	
<b>Arm title</b>	RT + Cetux
Arm description:	
Radiotherapy plus cetuximab	
Arm type	Experimental
Investigational medicinal product name	CETUXIMAB
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravascular use
Dosage and administration details:	
Cetuximab 400mg/m2 week 1, thereafter 250mg/m2 weeks 2-6	

<b>Number of subjects in period 2</b>	RT alone	RT + Cetux
Started	7	6
Completed	4	5
Not completed	3	1
Consent withdrawn by subject	1	-
Adverse event, non-fatal	1	-
Lack of efficacy	1	1

## Baseline characteristics

### Reporting groups

Reporting group title	Registration
-----------------------	--------------

Reporting group description: -

Reporting group values	Registration	Total	
Number of subjects	17	17	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	9	9	
From 65-84 years	8	8	
85 years and over	0	0	
Gender categorical			
Units: Subjects			
Female	6	6	
Male	11	11	

## End points

### End points reporting groups

Reporting group title	All Patients
Reporting group description: all patients recieved GEM-CAP prior to randmisation	
Reporting group title	RT alone
Reporting group description: -	
Reporting group title	RT + Cetux
Reporting group description: Radiotherapy plus cetuximab	

### Primary: 1 year Overall Survival

End point title	1 year Overall Survival
End point description: Overall survival at 1 year as defined as time from registration to death, or censored at last follow-up if still alive at time of analysis.	
End point type	Primary
End point timeframe: 1 year post last patient registered	

End point values	RT alone	RT + Cetux		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	6		
Units: survival percent alive				
number (confidence interval 95%)	100 (100 to 100)	66.7 (29.1 to 100)		

### Statistical analyses

Statistical analysis title	Overall survival
Statistical analysis description: Overall survival was calculated using Kaplan Meier methods.	
Comparison groups	RT alone v RT + Cetux
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.801
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.17

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.35
upper limit	3.92



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From randomisation to 30 days post last treatment

Adverse event reporting additional description:

Grade 3 - 5 only

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

### Dictionary used

Dictionary name	No dictionary
-----------------	---------------

Dictionary version	0
--------------------	---

### Reporting groups

Reporting group title	RT alone
-----------------------	----------

Reporting group description: -

Reporting group title	RT + Cetux
-----------------------	------------

Reporting group description: -

Serious adverse events	RT alone	RT + Cetux	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 7 (42.86%)	2 / 6 (33.33%)	
number of deaths (all causes)	5	6	
number of deaths resulting from adverse events	0	0	
General disorders and administration site conditions			
Allergic Reaction			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RIBCAGE AND UPPER ABDO PAIN			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Neutropenia			

subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Gastrointestinal disorders</b>			
Diarrhoea			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Infections and infestations</b>			
Non Neutropenic infection			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	RT alone	RT + Cetux	
<b>Total subjects affected by non-serious adverse events</b>			
subjects affected / exposed	5 / 7 (71.43%)	5 / 6 (83.33%)	
<b>General disorders and administration site conditions</b>			
Fatigue			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
<b>Blood and lymphatic system disorders</b>			
Thrombocytopenia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	2	
Neutropenia			
subjects affected / exposed	2 / 7 (28.57%)	5 / 6 (83.33%)	
occurrences (all)	2	7	
<b>Gastrointestinal disorders</b>			
MALAENA			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Abdominal pain			

subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 6 (0.00%) 0	
Skin and subcutaneous tissue disorders			
Dyspnoea			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Hand Foot Syndrome			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	5	0	
Hyperglycaemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	6	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 October 2013	Emergent data from the LAP-07 study failed to demonstrate any meaningful survival advantage (either progression free survival or overall survival) with the use of chemo-radiotherapy following first-line chemotherapy in locally advanced pancreatic cancer. These results were presented at the ASCO 2013 annual meeting and thus the study was closed on recommendation of IDMC.

Notes:

---

### 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.

The study closed prematurely resulting in recruitment of only 17 patients, therefore data obtained from the study need to be interpreted with caution. The molecular data obtained from the study on utility of micro-RNA21 is however extremely valuable

Notes:

---

### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/26862857>