



Clinical trial results:

A multicentre, randomised, phase III trial of platinum-based chemotherapy versus non-platinum chemotherapy, after ERCC1 stratification, in patients with advanced/metastatic non-small cell lung cancer

Summary

EudraCT number	2007-007639-17
Trial protocol	GB
Global end of trial date	18 December 2014

Results information

Result version number	v1 (current)
This version publication date	02 September 2016
First version publication date	02 September 2016

Trial information

Trial identification

Sponsor protocol code	UCL/07/158
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Additional study identifiers

ISRCTN number	ISRCTN02370070
ClinicalTrials.gov id (NCT number)	NCT00801736
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University College London
Sponsor organisation address	Gower Street, London, United Kingdom, WC1E 6BT
Public contact	CR UK and UCL Cancer Trials Centre, University College London, ctc.et@ucl.ac.uk
Scientific contact	CR UK and UCL Cancer Trials Centre, University College London, ctc.et@ucl.ac.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	18 December 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 December 2014
Global end of trial reached?	Yes
Global end of trial date	18 December 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The trial will have two main objectives:

- 1) To detect an improvement in survival for ERCC1+ve patients treated with a non-platinum chemotherapy compared to platinum-based treatment.
- 2) To establish non-inferiority or improvement in survival for ERCC1-ve patients treated with a platinum-based chemotherapy compared to non-platinum treatment.

Squamous cell patients will receive gemcitabine with either cisplatin or paclitaxel. Non-squamous cell patients will receive pemetrexed with either cisplatin or paclitaxel.

Protection of trial subjects:

Patient safety was monitored using regular patient assessments, dose modifications for regular review of safety data by the Independent Data Monitoring Committee (IDMC) and Trial Management Group (TMG) and through strict eligibility criteria.

Patient data is stored in a secure manner and UCL CTC trials are registered in accordance with the Data Protection Act 1998 and the Data Protection Officer at UCL.

Background therapy:

All patients receiving the pemetrexed-containing regimens received 350-1000 micrograms oral folic acid throughout treatment and 1000 micrograms of intramuscular vitamin B12 every 9 weeks.

It was recommended that patients receiving cisplatin were given a 3-drug anti-emetic combination of a 5-HT3 serotonin receptor antagonist, dexamethasone and aprepitant.

It was recommended that patients receiving paclitaxel were given a 2-drug anti-emetic combination of a 5-HT3 serotonin receptor antagonist and dexamethasone.

Evidence for comparator:

For squamous patients the comparator was cisplatin/gemcitabine. For non-squamous patients the comparator was cisplatin/pemetrexed.

A meta-analysis of two large randomised trials demonstrated that patients with squamous histology have a lower survival than non-squamous patients. One trial randomised patients to cisplatin/pemetrexed or cisplatin/gemcitabine. Non-squamous patients receiving pemetrexed-based therapy had an improved outcome however squamous histology patient had a worse outcome. Based on these findings, together with the licensing indication of cisplatin/pemetrexed being restricted to non-squamous patients only, the ET trial used gemcitabine in the platinum/non-platinum doublets for squamous patients instead of pemetrexed.

Cisplatin/pemetrexed was chosen as the comparator for non-squamous patients as previous studies of pemetrexed have shown it to be well tolerated as a treatment for NSCLC when given alongside platinum chemotherapy. In the largest randomised study conducted for advanced NSCLC, cisplatin/pemetrexed was found to be non-inferior to cisplatin/gemcitabine, an effective widely-used reference regimen for the front-line treatment of advanced NSCLC. However patients treated with cisplatin/pemetrexed developed significantly less toxicity and those with non-squamous histology had a statistically superior overall survival.

Actual start date of recruitment	06 October 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: 637
Worldwide total number of subjects	637
EEA total number of subjects	637

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)	326
From 65 to 84 years	311
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were randomised into the trial between 07/10/09 and 24/07/13. 648 patients were randomised from NHS hospitals across the UK.

Pre-assignment

Screening details:

- Staging scans performed no more than 28 days prior to registration or randomisation
- Adequate bone marrow, liver and renal function assessed within 14 days of registration
- Other pre-registration assessments to be performed within 21 days of registration (inc physical examination, assessment of adverse events, quality of life questionnaires)

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	Control Arm

Arm description:

Squamous patients: cisplatin/gemcitabine

Non-squamous patients: cisplatin/pemetrexed

Arm type	Active comparator
Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

75mg/m² on Day 1 of 21 day cycles. Up to 6 cycles given in total.

Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1250mg/m² on Day 1 and Day 8 of 21 day cycles. Up to 6 cycles in total.

Investigational medicinal product name	Pemetrexed
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

500mg/m² on Day 1 of 21 day cycles. Up to 6 cycles in total.

Arm title	Investigational Arm
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Arm description:

Squamous patients: paclitaxel/gemcitabine

Non-squamous patients: paclitaxel/pemetrexed

Arm type	Experimental
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Investigational medicinal product name	Pemetrexed
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

500mg/m2 on Day 1 of 21 day cycles. Up to 6 cycles in total.

Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

175mg/m2 on Day 1 of 21 day cycle. Up to 6 cycles in total.

Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1250mg/m2 on Day 1 and Day 8 of 21 day cycles. Up to 6 cycles in total.

Number of subjects in period 1	Control Arm	Investigational Arm
Started	314	323
Completed	314	323

Baseline characteristics

Reporting groups

Reporting group title

Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	637	637	
Age categorical			
Units: Subjects			
Adults (18-64 years)	326	326	
From 65-84 years	311	311	
Gender categorical			
Units: Subjects			
Female	244	244	
Male	393	393	
ECOG Performance Status			
Units: Subjects			
PS 0	275	275	
PS 1	362	362	
Disease Stage			
Units: Subjects			
IIIb	148	148	
IV	489	489	
Smoking Status			
Units: Subjects			
Never	52	52	
Former	270	270	
Current	315	315	
ERCC1 Status			
Units: Subjects			
Negative	251	251	
Positive	386	386	
XFP Status			
Units: Subjects			
Negative	142	142	
Positive	333	333	
Unavailable	162	162	

End points

End points reporting groups

Reporting group title	Control Arm
Reporting group description:	
Squamous patients: cisplatin/gemcitabine	
Non-squamous patients: cisplatin/pemetrexed	
Reporting group title	Investigational Arm
Reporting group description:	
Squamous patients: paclitaxel/gemcitabine	
Non-squamous patients: paclitaxel/pemetrexed	

Primary: Overall survival

End point title	Overall survival ^[1]
End point description:	

End point type	Primary
End point timeframe:	
From start of randomisation until primary completion date.	

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: Overall survival

HR (95% CI)

Nonsquamous

ERCC1 negative 0.98 (0.72-1.34)

ERCC1 positive 1.15 (0.88-1.51)

Squamous

ERCC1 negative 1.56 (0.79-3.08)

ERCC1 positive 1.40 (0.97-2.03)

End point values	Control Arm	Investigational Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	314	323		
Units: Months				
median (confidence interval 95%)				
Overall Survival for Squamous Patients	11.4 (7 to 19.6)	8.7 (4.1 to 15.4)		
Overall Survival for Non-Squamous Patients	10.9 (6.1 to 16.8)	9.5 (4.8 to 17.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival

End point title	Progression Free Survival
End point description:	
End point type	Secondary
End point timeframe:	
From randomisation to primary completion date	

End point values	Control Arm	Investigational Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	314	323		
Units: Months				
median (confidence interval 95%)				
Squamous Patients	7.8 (3.7 to 12.6)	5 (2.6 to 8.8)		
Non-Squamous Patients	6.9 (2.9 to 10.7)	5.5 (2.2 to 9.7)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From informed consent until 24 months post randomisation

Assessment type	Systematic
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Dictionary used

Dictionary name	CTCAE
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Dictionary version	4
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Reporting groups

Reporting group title	All Patients
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Reporting group description: -

Serious adverse events	All Patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	275 / 637 (43.17%)		
number of deaths (all causes)	563		
number of deaths resulting from adverse events	4		
Investigations			
Platelet count abnormal			
subjects affected / exposed	8 / 637 (1.26%)		
occurrences causally related to treatment / all	7 / 8		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Thrombosis			
subjects affected / exposed	19 / 637 (2.98%)		
occurrences causally related to treatment / all	10 / 19		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Heart			
subjects affected / exposed	25 / 637 (3.92%)		
occurrences causally related to treatment / all	9 / 25		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	17 / 637 (2.67%)		
occurrences causally related to treatment / all	15 / 17		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	40 / 637 (6.28%)		
occurrences causally related to treatment / all	37 / 40		
deaths causally related to treatment / all	1 / 1		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	8 / 637 (1.26%)		
occurrences causally related to treatment / all	6 / 8		
deaths causally related to treatment / all	0 / 0		
Fever			
subjects affected / exposed	26 / 637 (4.08%)		
occurrences causally related to treatment / all	19 / 26		
deaths causally related to treatment / all	0 / 0		
Pain			
subjects affected / exposed	26 / 637 (4.08%)		
occurrences causally related to treatment / all	3 / 26		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Anaphylaxis			
subjects affected / exposed	9 / 637 (1.41%)		
occurrences causally related to treatment / all	8 / 9		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	25 / 637 (3.92%)		
occurrences causally related to treatment / all	20 / 25		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	22 / 637 (3.45%)		
occurrences causally related to treatment / all	18 / 22		
deaths causally related to treatment / all	0 / 0		

Vomiting			
subjects affected / exposed	29 / 637 (4.55%)		
occurrences causally related to treatment / all	24 / 29		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Chest pain			
subjects affected / exposed	15 / 637 (2.35%)		
occurrences causally related to treatment / all	5 / 15		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	33 / 637 (5.18%)		
occurrences causally related to treatment / all	3 / 33		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	10 / 637 (1.57%)		
occurrences causally related to treatment / all	5 / 10		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Infection			
subjects affected / exposed	87 / 637 (13.66%)		
occurrences causally related to treatment / all	40 / 87		
deaths causally related to treatment / all	3 / 3		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	8 / 637 (1.26%)		
occurrences causally related to treatment / all	3 / 8		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	All Patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	472 / 637 (74.10%)		
Investigations			

Alkaline Phosphatase Raised subjects affected / exposed occurrences (all)	7 / 637 (1.10%) 7		
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	15 / 637 (2.35%) 15		
Gamma-glutamyltransferase abnormal subjects affected / exposed occurrences (all)	13 / 637 (2.04%) 13		
Vascular disorders Thrombosis subjects affected / exposed occurrences (all)	31 / 637 (4.87%) 31		
Cardiac disorders Heart Problems subjects affected / exposed occurrences (all)	37 / 637 (5.81%) 37		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	10 / 637 (1.57%) 10		
Neuropathy subjects affected / exposed occurrences (all)	22 / 637 (3.45%) 22		
General disorders and administration site conditions Alopecia subjects affected / exposed occurrences (all)	13 / 637 (2.04%) 13		
Appetite disorder subjects affected / exposed occurrences (all)	20 / 637 (3.14%) 20		
Fatigue subjects affected / exposed occurrences (all)	117 / 637 (18.37%) 117		
Pyrexia			

subjects affected / exposed occurrences (all)	29 / 637 (4.55%) 29		
Pain subjects affected / exposed occurrences (all)	86 / 637 (13.50%) 86		
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	44 / 637 (6.91%) 44		
Neutropenia subjects affected / exposed occurrences (all)	91 / 637 (14.29%) 91		
Platelet count decreased subjects affected / exposed occurrences (all)	24 / 637 (3.77%) 24		
White blood cell count decreased subjects affected / exposed occurrences (all)	31 / 637 (4.87%) 31		
Immune system disorders			
Anaphylaxis subjects affected / exposed occurrences (all)	10 / 637 (1.57%) 10		
Gastrointestinal disorders			
Constipation subjects affected / exposed occurrences (all)	11 / 637 (1.73%) 11		
Diarrhoea subjects affected / exposed occurrences (all)	37 / 637 (5.81%) 37		
Mucositis Oral subjects affected / exposed occurrences (all)	13 / 637 (2.04%) 13		
Nausea subjects affected / exposed occurrences (all)	46 / 637 (7.22%) 46		
Vomiting			

subjects affected / exposed occurrences (all)	45 / 637 (7.06%) 45		
Respiratory, thoracic and mediastinal disorders			
Chest pain			
subjects affected / exposed	30 / 637 (4.71%)		
occurrences (all)	30		
Cough			
subjects affected / exposed	7 / 637 (1.10%)		
occurrences (all)	7		
Dyspnoea			
subjects affected / exposed	80 / 637 (12.56%)		
occurrences (all)	80		
Pulmonary embolism			
subjects affected / exposed	35 / 637 (5.49%)		
occurrences (all)	35		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	5 / 637 (0.78%)		
occurrences (all)	5		
Infections and infestations			
Infection			
subjects affected / exposed	136 / 637 (21.35%)		
occurrences (all)	136		
Sepsis			
subjects affected / exposed	7 / 637 (1.10%)		
occurrences (all)	7		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	10 / 637 (1.57%)		
occurrences (all)	10		
Hypoalbuminaemia			
subjects affected / exposed	8 / 637 (1.26%)		
occurrences (all)	8		
Hypokalaemia			
subjects affected / exposed	7 / 637 (1.10%)		
occurrences (all)	7		

Hyponatraemia			
subjects affected / exposed	19 / 637 (2.98%)		
occurrences (all)	19		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 October 2008	Changes to protocol: - Changes to members of the TMG - Clarification that assessments should be made in relation to trial registration not trial randomisation - Pre-chemotherapy blood requirements modified in line with drug modification guidelines - List of trial CRFs modified to include Adverse Event Form
29 April 2009	Changes to protocol, patient information sheet, consent form, gp letter and patient cards: - Addition of two new treatment arms for squamous patients (gemcitabine/cisplatin and gemcitabine/paclitaxel) - Amendments to the rationale of the trial as well as inclusion of rationale for including new treatment arms for squamous group - Gemcitabine/Cisplatin and Gemcitabine/Paclitaxel chemotherapy regimens added - All dose modification tables amended according to guidelines on SmPC for Pemetrexed and new dose modification tables added for Gemcitabine doublets - Statistical considerations section updated to include data on Gemcitabine/Cisplatin and Gemcitabine/Paclitaxel in squamous patients - Inclusion of 4 new references - Addition of uncommon adverse events listed in Appendix 7 from the updated SmPC for Pemetrexed and the SmPC for Gemcitabine - Biological trial summary updated to include testing for resistance to gemcitabine - Addition of excluding patients who have recently received a yellow fever vaccination - Changes to patient information sheet, consent form, gp letter and patient cards to reflect new trial design
19 August 2009	Changes to the protocol, patient information sheet and consent form: - Platelet count for inclusion in the trial changed to $>100 \times 10^9/L$ - Changes to the stratification factors for randomisation - Dose modification tables have been amended according to guidelines in the SmPC for Pemetrexed and Gemcitabine - The number of x-rays required for the trial has been reduced, i.e. at chemotherapy cycles 1, 3 and 5, as is standard practice in several centres. Having x-rays at cycles 2, 4 and 6 is now optional. - Adequate renal function is now defined as $>60\text{ml/min}$ by EDTA or C&G. - Common toxicology criteria for adverse events (CTCAE) version 3.0 is now replaced by CTCAE version 4.0 - Clarification in the patient information sheet on what treatment non-squamous patients will receive inc. administration of vitamin B12 injections.

09 March 2010	Amendment to protocol, patient information sheet and consent form: • Addition of 24 hour urine collection as a method of determining patient GFR value • Clarification of two exclusion criteria's which apply to non-squamous patients only • Clarification that all trial drugs can be dose banded • Clarification that vitamin b12 and folic acid should be started 7 days before trial treatment • Addition of dose modifications for Gemcitabine arms of the trial in the presence of febrile neutropenia • Pharmacovigilance section of the protocol updated to reflect the CTC template protocol • Removal of choice to do PET-CT scanning rather than CT scanning • Maximum number of hours for fixation of patient tissue samples amended from 48 to 72
28 October 2010	Amendment to labels for all IMPs and NIMPs.
06 April 2011	Amendment to protocol, patient information sheet, pregnancy monitoring information sheet and consent form: • Further clarification of the end of trial timepoint • Section added clarifying trial activation process for sponsor • Guidance added to inclusion criteria regarding contraception and to exclusion criteria regarding renal function • Documents to be given to randomised patients added • Terminology revised in Pharmacovigilance section • Updated information in relation to SAE processing at the UCL CTC and clinical reviewing • Addition of a section covering incident reporting and serious breaches • Addition of a section covering trial monitoring and oversight • Addition of a section covering withdrawal of patients • Addition of a section covering trial closure • Clarifying which patient identifiable information will be collected by the UCL CTC • Patient information sheet updated with advice on pregnancy and contraception
26 July 2011	Amendment to protocol: • Inclusion criteria amendment: Previous palliative radiotherapy to non-target lesions is allowed for pain relief prior to starting chemotherapy (in version 8.0 and previous protocol versions it could not be given in the 28 days prior to starting chemotherapy) • Addition that tumour samples obtained by EBUS cores and EBUS FNA cell blocks are allowed provided that the tumour cells are well preserved • Clarifications to wording to section 5.0 – Pharmacovigilance • Section 5.6 rewritten to refer to DSURs instead of ASRs • Update to pemetrexed secondary label and addition of a primary label

03 October 2012	Amendment to protocol, PIS, consent form, GP letter and patient card in line with Urgent Safety Measure undertaken 07/09/2012: - Protocol: clarification EBUS FNA and FNA are examples of cytology; the following amended for consistency across protocol: provision of prescription to CTC prior to site activation and use of ALT or AST in incl/excl; procedure for reporting temp excursions added; update to DM section; insurance section clarified to reflect it is insurers decision to compensate and not UCL; list of expected AEs added for pem/cis and pem/pac. - PIS: ERCC1 amended to provide clarity and easier understanding for patients; duration of treatment corrected from 3 months to 4.5months; removal of AEs associated with gemcitabine; number of CTs corrected in section entitled 'Risk associated with the CT scan'. The risk factor is correct for 4 scans; wording updated to reflect pem/cisp is now licensed for first line treatment; insurance section updated in line with above protocol change. - Consent form: updated to reflect the change in version of the PIS - GP letter: correction to GP letter to indicate a new biopsy is not required for participation in the trial - Label Change for Pemetrexed: removal of primary label. Commercial stock to be over labelled for the outer packaging only. The outer and inner package will stay together at all times.
16 October 2014	Submission of results summary for patients and results summary cover letter for PI's.

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.

Trial stopped early in July 2013. Patients with squamous histology were excluded from September 2012. Only grade 3, 4 and 5 adverse events recorded. Relatedness of adverse events refers to number of patients not number of occurrences.

Notes: