



## Clinical trial results:

### A Novel Single Arm Phase II Study for Relapsed Germ Cell Tumours with Poor Prognosis

#### Summary

EudraCT number	2010-022795-31
Trial protocol	GB
Global end of trial date	05 May 2021

#### Results information

Result version number	v1
This version publication date	19 May 2024
First version publication date	19 May 2024

#### Trial information

##### Trial identification

Sponsor protocol code	TE 2010-12
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##### Additional study identifiers

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

Notes:

#### Sponsors

Sponsor organisation name	Barts Health NHS Trust
Sponsor organisation address	Joint Research and Management Office, 5 Walden Street, London, United Kingdom, E1 2EF
Public contact	Dr Jonathan Shamash, Barts Health NHS Trust, +44 02078827260, sponsorrep@bartshealth.nhs.net
Scientific contact	Dr Jonathan Shamash, Barts Health NHS Trust, +44 2078827260, sponsorrep@bartshealth.nhs.net

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	05 May 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 May 2021
Global end of trial reached?	Yes
Global end of trial date	05 May 2021
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To determine objective response rate (ORR). ORR is defined as the number of patients with an objective response (OR) divided by the number of patients analysed.

Objective response (OR) is defined as the number of patients with either (1) a complete response (CR) or partial response marker negative (PRm-) using the end of treatment overall response data, or (2) marker negative at screening who are operable with a post-surgery outcome of CR or PR, or (3) marker negative at screening who are not operable but survive and remain radiologically progression-free for one year from the date of enrolment.

Protection of trial subjects:

Since both the combination of oxaliplatin and paclitaxel or of oxaliplatin and irinotecan have similar activity in relapsed patients in the phase two setting [3] [6], this protocol was designed using pegylated filgrastim, actinomycin D, high dose methotrexate and weekly paclitaxel.

Patients received combination therapy for four cycles of 21 days each with weekly paclitaxel on days 8 and 15. The substitution was expected to lead to benefits in terms of toxicity reduction.

Sadeghi et al observed improved overall survival with acceptable neurotoxicity with an increase in oxaliplatin dose [10]. In the GAMMA trial oxaliplatin was initially administered at 100 mg/m<sup>2</sup> on day 3 of each cycle with acceptable toxicity observed. To optimise the treatment the oxaliplatin dose was then increased to 170mg/m<sup>2</sup> per 3 week cycle delivered as 85mg/m<sup>2</sup> on day 4 and 85/g/m<sup>2</sup> on day 8. Splitting the dose in to two gives greater control and avoids any theoretical increase in nephrotoxicity following methotrexate compared to giving the whole dose on day 3 (immediately after the methotrexate).

For this trial we assessed response using FDG-PET scans. FDG-PET scanning has a predictive role in several tumour types and has been used to demonstrate a rapid normalisation in metastatic germ cell tumours [2]. The additional radiation over diagnostic CT (as standard care) is minimal. A PET-CT scan was carried out before cycle two (between day 15-21 of cycle 1) and the results look to see whether early changes in glucose activity proved superior to early tumour marker decline to predict eventual outcome.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 November 2012
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: 44
Worldwide total number of subjects	44
EEA total number of subjects	0

Notes:

<b>Subjects enrolled per age group</b>	
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)	44
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

45 patients were enrolled between 14Nov2012 and 18Feb2020. 44 patients received study medication.

### Pre-assignment

Screening details:

45 patients with relapsed GCT (germ cell tumours) were enrolled between 14Nov2012 and 18Feb2020.

### Period 1

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

### Arms

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

This is a single arm phase II clinical study in patients with relapsed GCT. Patients received combination therapy for four cycles of 21 days each with weekly paclitaxel on days 8 and 15.

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

Dosage and administration details:

Paclitaxel 80mg/m<sup>2</sup> will be given on Day 1, Day 8 and Day 15 of 21 day cycles for 4 cycles.

Investigational medicinal product name	Actinomycin D
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Actinomycin D 1mg/m<sup>2</sup> on Day1 of 21day cycle for 4 cycles

Investigational medicinal product name	Methotrexate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Methotrexate bolus loading dose in 250ml 0.9% sodium chloride followed by 12-hour infusion in 1000ml 0.9% sodium chloride on Day 1 of 21day cycle for 4 cycles. Doses are titrated against renal function. If serum creatinine rises by >15% the creatinine clearance should be recalculated.

Investigational medicinal product name	Oxaliplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Oxaliplatin 85mg/m<sup>2</sup> in 500 ml 0.9% sodium chloride over 2 hours on Day 4 of 21day cycle for 4 cycles.

<b>Number of subjects in period 1</b>	Recruitment
Started	44
Completed	44

## Baseline characteristics

### Reporting groups

Reporting group title	Recruitment
Reporting group description: -	

Reporting group values	Recruitment	Total	
Number of subjects	44	44	
Age categorical			
Units: Subjects			
Adults (18-64 years)	44	44	
Gender categorical			
Units: Subjects			
Female	3	3	
Male	41	41	
IGCCCG2			
Units: Subjects			
-1 - Very Low Risk	2	2	
0 - Low Risk	10	10	
1 - Intermediate Risk	16	16	
2 - High Risk	6	6	
3 - Very High Risk	9	9	
n/a	1	1	
Not recorded	0	0	
ECOG Performance Status			
Units: Subjects			
0 - Fully Active	27	27	
1 - Ambulatory, capable of light work	8	8	
2 - Up and about >50% of time	2	2	
3 - Up and about <50% of time	3	3	
4 - Totally confined to bed or chair	4	4	
Not Recorded	0	0	

### Subject analysis sets

Subject analysis set title	Evaluable Population
Subject analysis set type	Per protocol

Subject analysis set description:

This population includes all patients enrolled into the trial who completed at least 2 cycles of study medication, regardless of whether they were later found to be ineligible or a protocol violator. All efficacy analysis will also be performed on the evaluable population.

Reporting group values	Evaluable Population		
Number of subjects	39		
Age categorical			
Units: Subjects			
Adults (18-64 years)	39		

Gender categorical			
Units: Subjects			
Female	2		
Male	37		
IGCCCG2			
Units: Subjects			
-1 - Very Low Risk	1		
0 - Low Risk	9		
1 - Intermediate Risk	16		
2 - High Risk	5		
3 - Very High Risk	7		
n/a	1		
Not recorded	0		
ECOG Performance Status			
Units: Subjects			
0 - Fully Active	24		
1 - Ambulatory, capable of light work	8		
2 - Up and about >50% of time	2		
3 - Up and about <50% of time	3		
4 - Totally confined to bed or chair	2		
Not Recorded	0		

## End points

### End points reporting groups

Reporting group title	Recruitment
Reporting group description: This is a single arm phase II clinical study in patients with relapsed GCT. Patients received combination therapy for four cycles of 21 days each with weekly paclitaxel on days 8 and 15.	
Subject analysis set title	Evaluable Population
Subject analysis set type	Per protocol
Subject analysis set description: This population includes all patients enrolled into the trial who completed at least 2 cycles of study medication, regardless of whether they were later found to be ineligible or a protocol violator. All efficacy analysis will also be performed on the evaluable population.	

### Primary: Objective Response Rate

End point title	Objective Response Rate
End point description: Objective response (OR) is defined as the number of patients with either (1) a CR or PRm- using the end of treatment overall response data, or (2) marker negative at screening who are operable with a post-surgery outcome of CR or PR, or (3) marker negative at screening who are not operable but survive and remain radiologically progression-free for one year from the date of enrolment. ORR is defined as the number of patients with an OR divided by the number of patients analysed.	
End point type	Primary
End point timeframe: Baseline to maximum of 1-year post treatment	

End point values	Recruitment	Evaluable Population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	44	39		
Units: percent				
number (confidence interval 95%)	58.97 (42.09 to 74.43)	52.27 (36.69 to 67.54)		

### Statistical analyses

Statistical analysis title	Objective Response Rate
Comparison groups	Recruitment v Evaluable Population
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	other <sup>[1]</sup>
Parameter estimate	Objective response rate
Point estimate	0.5897
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4209
upper limit	0.7446



Notes:

[1] - ORR is defined as the number of patients with an OR divided by the number of patients analysed.

### Secondary: Progression Free Survival

End point title	Progression Free Survival
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End point description:

End point type	Secondary
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End point timeframe:

Baseline to end of treatment PET scan

End point values	Evaluable Population			
Subject group type	Subject analysis set			
Number of subjects analysed	26			
Units: month				
median (confidence interval 95%)	9.725 (2.99 to 22.01)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Overall Survival Rate at 2 years

End point title	Overall Survival Rate at 2 years
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End point description:

End point type	Secondary
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End point timeframe:

Baseline to 2 years

End point values	Evaluable Population			
Subject group type	Subject analysis set			
Number of subjects analysed	39			
Units: percent				
number (not applicable)	65.49			

### Statistical analyses

No statistical analyses for this end point



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From informed consent to 28 days after the last treatment dose

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	Combination Therapy in GCT Patients
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Reporting group description:

This is a single arm phase II clinical study in patients with relapsed GCT. Patients will receive combination therapy for four cycles of 21 days each with weekly paclitaxel on days 8 and 15.

Serious adverse events	Combination Therapy in GCT Patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 44 (22.73%)		
number of deaths (all causes)	16		
number of deaths resulting from adverse events	2		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Obstruction gastric			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 44 (4.55%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 1		
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	4 / 44 (9.09%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Sepsis			
subjects affected / exposed	2 / 44 (4.55%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 1		

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

<b>Non-serious adverse events</b>	Combination Therapy in GCT Patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	37 / 44 (84.09%)		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	23 / 44 (52.27%)		
occurrences (all)	23		
Thrombocytopenia			
subjects affected / exposed	14 / 44 (31.82%)		
occurrences (all)	17		
Anaemia			
subjects affected / exposed	12 / 44 (27.27%)		
occurrences (all)	12		
General disorders and administration site conditions			
Febrile neutropenia			
subjects affected / exposed	15 / 44 (34.09%)		
occurrences (all)	15		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	10 / 44 (22.73%)		
occurrences (all)	10		
Asthenia			

subjects affected / exposed occurrences (all)	7 / 44 (15.91%) 7		
Nausea subjects affected / exposed occurrences (all)	4 / 44 (9.09%) 4		
Respiratory, thoracic and mediastinal disorders Stomatitis subjects affected / exposed occurrences (all)	9 / 44 (20.45%) 9		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 November 2011	PIS Updated as per REC comments in initial submission rejection letter dated 07Mar2012
30 April 2012	Documents updated to reflect the change in sponsor to Barts Health NHS Trust following a merger of trusts.
27 August 2013	Updated list of concomitant medications
13 September 2013	<ul style="list-style-type: none"><li>- Changes to the inclusion/exclusion criteria</li><li>- Pegfilgrastim reclassified as a supportive agent</li><li>- Clarification on the administration of omitted paclitaxel dose in the first 3 patients</li></ul>
02 January 2014	<ul style="list-style-type: none"><li>- Change in dosing schedule for Oxaliplatin</li><li>- PIS &amp; Consent Form amended to clarify use of anonymised study data in future ethically approved projects</li></ul>
27 October 2015	<ul style="list-style-type: none"><li>- Oxaliplatin to be administered on day 4 instead of day 3</li><li>- Trial specific ICF created for collected of samples for future research</li></ul>
16 May 2016	Expansion of the inclusion criteria to include patients with very low risk
22 February 2021	<ul style="list-style-type: none"><li>- To update the end of study definition (reduce from 2 years to 12months following completion of treatment).</li><li>- Addition of remote monitoring to the protocol.</li><li>- Minor updates to rectify errors in the statistical analysis sections as well as formatting errors.</li></ul>

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported