Clinical trial results:
Phase II Clinical Trial of 6-Mercaptopurine(6MP)and low-dose Methotrexate In Patients With Known BRCA Defective Tumours.

Summary

EudraCT number	2009-016846-16
Trial protocol	GB
Global end of trial date	16 February 2017

Results information

Result version number	v1 (current)
This version publication date	04 March 2018
First version publication date	04 March 2018

Trial information

Trial identification

Sponsor protocol code	OCTO-16

Additional study identifiers

ISRCTN number	ISRCTN63150635
ClinicalTrials.gov id (NCT number)	NCT01432145
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Oxford
Sponsor organisation address	Clinical Trials & Research Governance, Joint Research Office, Block 60, Churchill Hospital, Old Road, Oxford, United Kingdom, OX3 7LJ
Public contact	Ms Heather House, Clinical Trials & Research Governance, University of Oxford , 01865 572245, heather.house@admin.ox.ac.uk
Scientific contact	Ms Heather House, Clinical Trials & Research Governance, University of Oxford , 01865 572245, heather.house@admin.ox.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	02 October 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 February 2017
Global end of trial reached?	Yes
Global end of trial date	16 February 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the anti-cancer activity of 6MP with low dose Methotrexate in patients with breast, ovarian, fallopian tube or primary serous peritoneal cancer and a known BRCA mutation.

Protection of trial subjects:

The trial received ethical and regulatory approval, and was run in compliance with the Medicines for Human Use (Clinical Trials) Regulations 2004, and amendments thereafter, the guidelines for Good Clinical Practice, and the applicable policies of the Sponsor, the University of Oxford. Together, these regulations implement the ethical principles of the Declaration of Helsinki (2008) and the regulatory requirements for clinical trials of an investigational medicinal product as set out in the European Union (EU) Directives 001/20/EC (Clinical Trials) and 2005/28/EC (GCP). Patients also were seen for study assessments up to 28 days post end of treatment and thereafter every 3 months for clinical assessment up to a total of 12 months.

Background therapy:

BRCA1 and BRCA2 genes are critical in homologous recombination (HR) DNA repair and have been implicated in familial breast and ovarian cancer tumorigenesis. In a screen for novel drugs that selectively kill BRCA-defective cells, Helleday and colleagues identified 6-thioguanine (6TG). They demonstrated that 6TG induces DNA double-strand breaks that are repaired by HR. The defect in HR explains the hypersensitivity of BRCA-defective cells to 6TG. Furthermore, this pre-clinical study showed that 6TG is as efficient as the PARP inhibitor, AG014699, in selectively killing BRCA-defective tumours in a xenograft model. Importantly, 6TG also kills cisplatin-resistant or PARP inhibitor resistant BRCA-defective cells.
The findings of Helledey and colleagues suggest that 6TG/6MP might be an effective treatment in BRCA deficient tumours even after developing resistance to PARP inhibitors or platinum drugs.

Evidence for comparator: -

Actual start date of recruitment	15 June 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 67
Worldwide total number of subjects	67
EEA total number of subjects	67

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)	54
From 65 to 84 years	13
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

74 patients were consented and registered from 14 UK sites between May 2011 and October 2014, and 67 of these registered patients were found to be evaluable. This is larger than the planned sample size of 65 patients, to compensate for unevaluable patients.

Pre-assignment

Screening details:

Over 130 patients with advanced ovarian or breast cancer were screened for eligibility from 14 UK sites between May 2011 and October 2014.

Period 1

Period 1 title	Baseline (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	6MP and methotrexate

Arm description:

6MP 55mg/m2 per day, and methotrexate 15mg/m2 per week

Arm type	Experimental
Investigational medicinal product name	6MP
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The dose of 6MP was 55mg/m2 body surface area, administered orally (PO) once a day (od) in the morning at least 1 hour after eating, on a continuous schedule. Tablets should have been taken at roughly the same time each day.

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

Dosage and administration details:

Methotrexate (15 mg/m2) was taken orally, once a week, in the morning.

Number of subjects in period 1	6MP and methotrexate
Started	67
Completed	67

Baseline characteristics

Reporting groups	
Reporting group title	Baseline

Reporting group description: -

Reporting group values	Baseline	Total	
Number of subjects	67	67	
Age categorical Units: Subjects			
Adults (18-64 years)	54	54	
From 65-84 years	13	13	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	55.9		
full range (min-max)	32 to 80	-	
Gender categorical Units: Subjects			
Female	67	67	
Male	0	0	
BRCA status Units: Subjects			
BRCA 1	40	40	
BRCA 2	27	27	
Prior PARP treatment Units: Subjects			
Yes	26	26	
No	41	41	
ECOG Performance Status Units: Subjects			
PS 0	27	27	
PS 1	36	36	
PS 2	4	4	
Albumin levels Units: g/dl			
arithmetic mean	39.8		
full range (min-max)	28 to 49	-	
TPMT Units: (mU/L)			
arithmetic mean	88.3		
full range (min-max)	43 to 160	-	

End points

End points reporting groups

Reporting group title	6MP and methotrexate

Reporting group description:

6MP 55mg/m2 per day, and methotrexate 15mg/m2 per week

Primary: Overall response rate

End point title	Overall response rate[1]

End point description:

Objective response defined as complete response, partial response and stable disease as measured by radiological disease response using RECIST criteria v1.1 (Appendix 3 of the protocol) with tumour size measured radiologically with computerised tomography (CT) and/or magnetic resonance imaging (MRI) (using the same at baseline and at follow-up).

End point type	Primary

End point timeframe:

8 weeks after start of treatment

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: Point estimate of proportion of patients responding to treatment at 8 weeks is 0.33 (95% CI 0.23-0.45). Tried to enter this result but EudraCT wouldn't accept it as a statistical analysis because it is not comparing two arms, but it is only a one armed trial.

End point values	6MP and methotrexate			
Subject group type	Reporting group			
Number of subjects analysed	67			
Units: Patients	22			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall survival where length of survival is defined in whole days as the time from entry into the study until death from any cause. For those who are not observed to die during the course of the trial will be censored at their last known follow-up date.

End point type	Secondary

End point timeframe:

Over two years of follow-up

End point values	6MP and methotrexate			
Subject group type	Reporting group			
Number of subjects analysed	67			
Units: Years				
median (confidence interval 95%)	10.29 (6.90 to 14.47)			

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 where length of survival is defined in whole days as the time from entry into the study until progression or death from any cause. For those who are not observed to progress or die during the course of the trial will be censored at their last known progression-free follow-up date.

End point type	Secondary

End point timeframe:

Over two years of follow-up.

End point values	6MP and methotrexate			
Subject group type	Reporting group			
Number of subjects analysed	67			
Units: Years				
median (confidence interval 95%)	1.91 (1.71 to 2.24)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From start of treatment until end of follow-up.	
Adverse event reporting additional description:	
Grade 3 and 4 Adverse events (AE)	
Assessment type	Systematic

Dictionary used	
Dictionary name	CTCAE
Dictionary version	4.0

Reporting groups	
Reporting group title	6MP and methotrexate
Reporting group description:	
6MP 55mg/m2 per day, and methotrexate 15mg/m2 per week	

Serious adverse events	6MP and methotrexate		
Total subjects affected by serious adverse events			
subjects affected / exposed	33 / 67 (49.25%)		
number of deaths (all causes)	52		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Neutrophil count decreased			
subjects affected / exposed	6 / 67 (8.96%)		
occurrences causally related to treatment / all	6 / 6		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Thromboembolic event			
subjects affected / exposed	3 / 67 (4.48%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			

Palpitations			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Ataxia			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Pancytopenia			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Fever			
subjects affected / exposed	2 / 67 (2.99%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	5 / 67 (7.46%)		
occurrences causally related to treatment / all	1 / 7		
deaths causally related to treatment / all	0 / 0		
Ascites			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Colonic obstruction			

subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatitis			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Small intestinal obstruction			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	2 / 67 (2.99%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Female genital tract fistula			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vaginal haemorrhage			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			

Obstruction	Additional description: Blocked biliary stent		
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Urinary tract obstruction			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Anorectal infection			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infection	Additional description: TEMPERATURE OF 39.9 DEGREE CELCIUS AND FEELING GENERALLY UNWELL. INFECTIVE PROCESS SUSPECTED, BUT THROAT SWAB, URINE, STOOL SAMPLES, BLOOD CULTURES ALL NEGATIVE. TREATED WITH IV ANTIBIOTICS. SOURCE OF INFECTION NOT IDENTIFIED. HAD NOT BEEN NEUTROPENI		
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung infection			
subjects affected / exposed	3 / 67 (4.48%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	2 / 67 (2.99%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Upper Respiratory Infection			
subjects affected / exposed	2 / 67 (2.99%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			

subjects affected / exposed	2 / 67 (2.99%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	6MP and methotrexate		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	46 / 67 (68.66%)		
Investigations			
Neutrophil count decreased			
subjects affected / exposed	19 / 67 (28.36%)		
occurrences (all)	24		
Platelet count decreased			
subjects affected / exposed	4 / 67 (5.97%)		
occurrences (all)	4		
White blood cell count decreased			
subjects affected / exposed	8 / 67 (11.94%)		
occurrences (all)	8		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 67 (8.96%)		
occurrences (all)	6		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	5 / 67 (7.46%)		
occurrences (all)	5		
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	4 / 67 (5.97%)		
occurrences (all)	4		
Nausea			
subjects affected / exposed	3 / 67 (4.48%)		
occurrences (all)	4		
Vomiting			

subjects affected / exposed occurrences (all)	5 / 67 (7.46%) 5		
Hepatobiliary disorders Abdominal pain subjects affected / exposed occurrences (all)	 5 / 67 (7.46%) 6		
Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all)	 3 / 67 (4.48%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 October 2011	Additional trial site and change of PI.
11 November 2011	Change of PI, plus: To add fallopian tube and primary serous peritoneal cancers to the inclusion criteria. To clarify the assessment of disease progression. To clarify the samples required. To clarify the populations for data analysis. To include all generic forms of the drugs in the protocol.
21 August 2012	Addition of two new sites.
12 October 2012	Reduction of starting dose of both IMPs Clarification of definition of objective response Clarification of AE reporting period Addition of study sites
24 February 2014	To adjust eligibility criteria; the exclusion of patients with low TPMT activity should be removed.

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 EudraCT system will not allow us to enter the results of all secondary endpoints, i.e. Assessment of feasibility as a multi-centre study.
Quality of life, a secondary endpoint, could not be analysed due to the low questionnaire completion rate.

Notes: