



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 Helleday 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/m ² per day, and methotrexate 15mg/m ² 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: