

**Clinical trial results:****A Randomised Stratified Multicentre Phase II Clinical Trial of Single-Agent ADI-PEG 20 (Pegylated Arginine Deiminase) in Patients with Malignant Pleural Mesothelioma.****Summary**

| | |
|--------------------------|----------------|
| EudraCT number | 2006-004592-35 |
| Trial protocol | GB |
| Global end of trial date | 30 April 2015 |

Results information

| | |
|-----------------------------------|--|
| Result version number | v2 (current) |
| This version publication date | 19 December 2021 |
| First version publication date | 16 September 2017 |
| Version creation reason | <ul style="list-style-type: none">• Correction of full data set A p value anomaly has been identified that needs correcting |
| Summary attachment (see zip file) | ADAM Publication_Sep2016 (Arginine Deprivation With Pegylated Arginine Deiminase in Patients With Argininosuccinate Synthetase 1-Deficient Malignant Pleural Mesothelioma A Randomized Clinical Trial.pdf) |

Trial information**Trial identification**

| | |
|-----------------------|------|
| Sponsor protocol code | 6836 |
|-----------------------|------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01279967 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Barts Health NHS Trust |
| Sponsor organisation address | 5 Walden Street, London, United Kingdom, E1 2EF |
| Public contact | CECM Trials Team, Queen Mary University London, 0044 02078828197, bci-cecmmonitoring@qmul.ac.uk |
| Scientific contact | CECM Trials Team, Queen Mary University London, 0044 02078828197, bci-cecmmonitoring@qmul.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 | 01 September 2016 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 30 April 2015 |
| Global end of trial reached? | Yes |
| Global end of trial date | 30 April 2015 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To assess the time to disease progression between the control group receiving best supportive care and the group receiving ADI-PEG 20 and best supportive care.

Protection of trial subjects:

The Trial Management Group consisted of an independent chairperson, the Chief Investigator, trial co-ordination team, collaborators, and the trial statistician and provided review of cumulative reports of all Serious Adverse Events (SAEs) on a minimum 6 monthly basis to identify patterns or trends of events or identify safety issues, which would not be apparent on an individual basis.

Background therapy: -

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 14 January 2011 |
| 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: 68 |
| Worldwide total number of subjects | 68 |
| EEA total number of subjects | 68 |

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) | 29 |

| | |
|---------------------|----|
| From 65 to 84 years | 39 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

From March 2, 2011 to March 21, 2013 201 patients were screened to take part in ADAM.

Pre-assignment

Screening details:

From March 2, 2011 to March 21, 2013 201 patients were screened to take part in ADAM. Of these 97 were found to be ASS1 negative and 70 were randomised into the trial. 2 patients were subsequently found to be ineligible so that the total number of patients randomised into the trial is 68.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Blinding implementation details:

Not applicable

Arms

| | |
|------------------------------|-----------------|
| Are arms mutually exclusive? | Yes |
| Arm title | ADI-PEG20 + BSC |

Arm description:

Patients randomised into this arm received a weekly intramuscular injection of ADI-PEG20 (36.8mg/m²) for up to 6 months (cycles) plus best supportive care (BSC). Patients continued to receive study treatment, with regular blood sampling, until disease progression, withdrawal of consent, or unacceptable toxic effects. ADI-PEG20-treated patients with disease control were allowed to exceed 6 cycles. Chemotherapy-naïve patients were offered chemotherapy on progression.

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | Pegylated arginine deiminase (ADI-PEG 20) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Weekly intramuscular injection of ADI-PEG20 dose of 36.8mg/m² (equivalent to 320IU/m²) for up to 6 months.

| | |
|------------------|-----------|
| Arm title | BSC alone |
|------------------|-----------|

Arm description:

Best supportive care

| | |
|---|---------|
| Arm type | Control |
| No investigational medicinal product assigned in this arm | |

| Number of subjects in period 1 | ADI-PEG20 + BSC | BSC alone |
|--------------------------------|-----------------|-----------|
| Started | 44 | 24 |
| Completed | 44 | 24 |

Baseline characteristics

Reporting groups

| | |
|--|-----------------|
| Reporting group title | ADI-PEG20 + BSC |
| Reporting group description: Patients randomised into this arm received a weekly intramuscular injection of ADI-PEG20 (36.8mg/m ²) for up to 6 months (cycles) plus best supportive care (BSC). Patients continued to receive study treatment, with regular blood sampling, until disease progression, withdrawal of consent, or unacceptable toxic effects. ADI-PEG20-treated patients with disease control were allowed to exceed 6 cycles. Chemotherapy-naïve patients were offered chemotherapy on progression. | |
| Reporting group title | BSC alone |
| Reporting group description: Best supportive care | |

| Reporting group values | ADI-PEG20 + BSC | BSC alone | Total |
|------------------------|-----------------|-----------|-------|
| Number of subjects | 44 | 24 | 68 |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 17 | 13 | 30 |
| From 65-84 years | 27 | 11 | 38 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 8 | 5 | 13 |
| Male | 36 | 19 | 55 |
| ECOG | | | |
| Units: Subjects | | | |
| PS 0 | 9 | 7 | 16 |
| PS 1 | 35 | 17 | 52 |
| Smoking history | | | |
| Units: Subjects | | | |
| Never smoker | 18 | 7 | 25 |
| Current smoker | 1 | 1 | 2 |
| Ex-smoker | 25 | 16 | 41 |
| Histological sub-type | | | |
| Units: Subjects | | | |
| Sarcomatoid | 1 | 1 | 2 |
| Non-sarcomatoid | 43 | 23 | 66 |
| Prior Chemotherapy | | | |
| Units: Subjects | | | |
| None | 17 | 11 | 28 |
| Platinum based | 27 | 13 | 40 |

Subject analysis sets

| | |
|--|--------------------|
| Subject analysis set title | All analyses |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: All eligible patients that had been randomised (excludes 2 patients who were randomised but not eligible, as ascertained after randomisation) | |

| | | | |
|--|--------------|--|--|
| Reporting group values | All analyses | | |
| Number of subjects | 68 | | |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 30 | | |
| From 65-84 years | 38 | | |
| Gender categorical Units: Subjects | | | |
| Female | | | |
| Male | | | |
| ECOG Units: Subjects | | | |
| PS 0 | | | |
| PS 1 | | | |
| Smoking history Units: Subjects | | | |
| Never smoker | | | |
| Current smoker | | | |
| Ex-smoker | | | |
| Histological sub-type Units: Subjects | | | |
| Sarcomatoid | | | |
| Non-sarcomatoid | | | |
| Prior Chemotherapy Units: Subjects | | | |
| None | | | |
| Platinum based | | | |

End points

End points reporting groups

| | |
|--|--------------------|
| Reporting group title | ADI-PEG20 + BSC |
| Reporting group description: Patients randomised into this arm received a weekly intramuscular injection of ADI-PEG20 (36.8mg/m ²) for up to 6 months (cycles) plus best supportive care (BSC). Patients continued to receive study treatment, with regular blood sampling, until disease progression, withdrawal of consent, or unacceptable toxic effects. ADI-PEG20-treated patients with disease control were allowed to exceed 6 cycles. Chemotherapy-naïve patients were offered chemotherapy on progression. | |
| Reporting group title | BSC alone |
| Reporting group description: Best supportive care | |
| Subject analysis set title | All analyses |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: All eligible patients that had been randomised (excludes 2 patients who were randomised but not eligible, as ascertained after randomisation) | |

Primary: Progression free survival

| | |
|--|---------------------------|
| End point title | Progression free survival |
| End point description: | |
| End point type | Primary |
| End point timeframe: Until end of follow up | |

| End point values | ADI-PEG20 + BSC | BSC alone | | |
|---------------------------------------|------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 44 | 24 | | |
| Units: Months | | | | |
| median (inter-quartile range (Q1-Q3)) | 3.2 (1.8 to 5.5) | 2 (1.8 to 3.6) | | |

Statistical analyses

| | |
|---|-----------------------------|
| Statistical analysis title | ADI-PEG20 analyses |
| Comparison groups | ADI-PEG20 + BSC v BSC alone |
| Number of subjects included in analysis | 68 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.03 ^[1] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.56 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.33 |
| upper limit | 0.96 |

Notes:

[1] - randomised phase II trial

In v1.0 of the EudraCT report the p-value was recorded as <0.15 in error. Corrected in version 2.0 in line with the study publication

Secondary: Overall Survival

| | |
|-----------------|------------------|
| End point title | Overall Survival |
|-----------------|------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Until end of follow up

| End point values | ADI-PEG20 + BSC | BSC alone | | |
|---------------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 44 | 24 | | |
| Units: Months | | | | |
| median (inter-quartile range (Q1-Q3)) | 11.5 (4.2 to 22.9) | 11.1 (6.9 to 14.2) | | |

Statistical analyses

| | |
|---|-----------------------------|
| Statistical analysis title | Overall survival |
| Comparison groups | ADI-PEG20 + BSC v BSC alone |
| Number of subjects included in analysis | 68 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[2] |
| P-value | = 0.15 ^[3] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.68 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.39 |
| upper limit | 1.16 |

Notes:

[2] - The Kaplan-Meier curves did not show proportional hazards. Therefore restricted mean survival times also provided:

RMST ADI-PEG20: 15.7 months

BSC: 12.1 months

Difference in RMST 3.6 (95% CI -1.0 to 8.1), p=0.06 (one-sided), p=0.13 (two-sided)

*In v1.0 of the EudraCT report the p-value was recorded as <0.15 in error. A RMST p value of 0.6 was also recorded in error. Corrected in version 2.0 in line with the study publication**

Secondary: Objective Response Rate

| | |
|-----------------|-------------------------|
| End point title | Objective Response Rate |
|-----------------|-------------------------|

End point description:

Proportion of evaluable subjects who achieve a confirmed SD, CR or PR per modified RECIST guidelines for plain CT and by EORTC guidelines for PET-CT. The number and percentage of subjects falling into each response category will be descriptively tabulated. At 4 months, the best response observed by patients was stable disease (SD), there were no CR or PR.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Those with evaluable disease at 4 months

| End point values | ADI-PEG20 + BSC | BSC alone | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 23 | 9 | | |
| Units: Percentage | 12 | 2 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Adverse events

| | |
|-----------------|----------------|
| End point title | Adverse events |
|-----------------|----------------|

End point description:

Assessed from adverse event and SUSAR reporting. Based on the highest grade of toxicity (grade 1 to 4) for each patient and each event type.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Until end of follow up

| End point values | ADI-PEG20 + BSC | BSC alone | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 44 | 24 | | |
| Units: Number of patients | 40 | 14 | | |

| | |
|-----------------------------------|--|
| Attachments (see zip file) | ADAM trial - Eudract toxicity table.docx |
|-----------------------------------|--|

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From consent date to 30 days post last dose of IMP.

Adverse event reporting additional description:

SAEs are as defined in the regulations.

Non-serious adverse events are all grades 1 to 2. The uploaded table shows grade 1-2 and grade 3-4 separately.

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

Dictionary used

| | |
|--------------------|-------|
| Dictionary name | CTCAE |
| Dictionary version | 4 |

Reporting groups

| | |
|-----------------------|-----------|
| Reporting group title | BSC alone |
|-----------------------|-----------|

Reporting group description:

Best supportive care

| | |
|-----------------------|-----------------|
| Reporting group title | ADI-PEG20 + BSC |
|-----------------------|-----------------|

Reporting group description:

Patients randomised into this arm received a weekly intramuscular injection of ADI-PEG20 (36.8mg/m²) for up to 6 months (cycles) plus best supportive care (BSC). Patients continued to receive study treatment, with regular blood sampling, until disease progression, withdrawal of consent, or unacceptable toxic effects. ADI-PEG20-treated patients with disease control were allowed to exceed 6 cycles. Chemotherapy-naïve patients were offered chemotherapy on progression.

| Serious adverse events | BSC alone | ADI-PEG20 + BSC | |
|--|----------------|-----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 24 (8.33%) | 9 / 44 (20.45%) | |
| number of deaths (all causes) | 20 | 35 | |
| number of deaths resulting from adverse events | | | |
| Investigations | | | |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 1 / 44 (2.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Neuropathy | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 1 / 44 (2.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Chest pain | | | |

| | | | |
|---|---|----------------|--|
| subjects affected / exposed | 1 / 24 (4.17%) | 0 / 44 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Drowsiness | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | 0 / 44 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Unwell | Additional description: pale, clammy, BP low 70/35, chest pressure and rash | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 1 / 44 (2.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain | Additional description: abdominal pain due to pericardial effusion | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 1 / 44 (2.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fever | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 1 / 44 (2.27%) | |
| 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 | | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 1 / 44 (2.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| Allergic reaction | Additional description: Allopurinol allergy with renal impairment | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 2 / 44 (4.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anaphylactoid reaction | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 1 / 44 (2.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |

| | | | |
|---|----------------|----------------|--|
| Difficulty swallowing | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | 0 / 44 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 1 / 44 (2.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Adult respiratory distress syndrome | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 1 / 44 (2.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Myositis | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 1 / 44 (2.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Rash | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 1 / 44 (2.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Purpuric rash legs | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 1 / 44 (2.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | BSC alone | ADI-PEG20 + BSC | |
|---|------------------|------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 21 / 24 (87.50%) | 43 / 44 (97.73%) | |

| | | | |
|--|-----------------|------------------|--|
| Investigations | | | |
| Abnormal haematologic test result | | | |
| subjects affected / exposed | 2 / 24 (8.33%) | 12 / 44 (27.27%) | |
| occurrences (all) | 2 | 47 | |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 4 / 44 (9.09%) | |
| occurrences (all) | 0 | 4 | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 2 / 44 (4.55%) | |
| occurrences (all) | 0 | 4 | |
| Nervous system disorders | | | |
| Dizzy spell | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 6 / 44 (13.64%) | |
| occurrences (all) | 0 | 6 | |
| General disorders and administration site conditions | | | |
| Injection site reaction | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 16 / 44 (36.36%) | |
| occurrences (all) | 0 | 21 | |
| Chest pain and/or trouble breathing | | | |
| subjects affected / exposed | 8 / 24 (33.33%) | 24 / 44 (54.55%) | |
| occurrences (all) | 8 | 45 | |
| Fatigue | | | |
| subjects affected / exposed | 6 / 24 (25.00%) | 19 / 44 (43.18%) | |
| occurrences (all) | 6 | 36 | |
| Fever | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | 1 / 44 (2.27%) | |
| occurrences (all) | 1 | 1 | |
| Pain | | | |
| subjects affected / exposed | 4 / 24 (16.67%) | 22 / 44 (50.00%) | |
| occurrences (all) | 5 | 33 | |
| Swelling in limbs | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 3 / 44 (6.82%) | |
| occurrences (all) | 0 | 5 | |
| Immune system disorders | | | |
| Allergic reaction and/or anaphylaxis | | | |

| | | | |
|--|---|--|--|
| subjects affected / exposed occurrences (all) | 0 / 24 (0.00%) 0 | 1 / 44 (2.27%) 2 | |
| Gastrointestinal disorders GI events subjects affected / exposed occurrences (all) | 6 / 24 (25.00%) 14 | 23 / 44 (52.27%) 73 | |
| Infections and infestations Infection subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all) | 3 / 24 (12.50%) 3 1 / 24 (4.17%) 1 | 12 / 44 (27.27%) 19 17 / 44 (38.64%) 24 | |
| Metabolism and nutrition disorders Abnormal biochemical test result subjects affected / exposed occurrences (all) | 1 / 24 (4.17%) 2 | 6 / 44 (13.64%) 42 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|---|
| 25 October 2010 | <ul style="list-style-type: none">- Changes to primary endpoint (TTP to PFS)- Increased sample size- IMP dose adjustment in line with recent published data |
| 10 November 2010 | IMPD updates |
| 18 February 2011 | Inclusion of patients with prior platinum therapy |
| 19 September 2011 | Changes to screening timeframe |
| 29 March 2012 | Updates to IMP thawing process, clarification of registration, screening, withdrawal and follow-up processes |
| 18 May 2012 | Change to Sponsor name |
| 19 October 2012 | <ul style="list-style-type: none">- Change of requirement to check serum uric acid levels on every day of dosing to Day 1 of each cycle- Inclusion of study schedule for patients who wish to extend treatment beyond 6 months- New Investigator Brochure |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/27584578>