



## Clinical trial results:

### Single arm NCRI feasibility study of CHOP in combination with Ofatumumab in induction and maintenance for patients with newly diagnosed Richter's Syndrome

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2009-016459-23 |
| Trial protocol           | GB             |
| Global end of trial date | 19 April 2016  |

#### Results information

|                                |                                                                                                           |
|--------------------------------|-----------------------------------------------------------------------------------------------------------|
| Result version number          | v2 (current)                                                                                              |
| This version publication date  | 15 July 2017                                                                                              |
| First version publication date | 10 May 2017                                                                                               |
| Version creation reason        | <ul style="list-style-type: none"><li>• Correction of full data set</li></ul> Correction of full data set |

#### Trial information

##### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | OCTO_018 |
|-----------------------|----------|

##### Additional study identifiers

|                                    |                |
|------------------------------------|----------------|
| ISRCTN number                      | ISRCTN88860946 |
| ClinicalTrials.gov id (NCT number) | NCT01171378    |
| WHO universal trial number (UTN)   | -              |

Notes:

#### Sponsors

|                              |                                                                                                |
|------------------------------|------------------------------------------------------------------------------------------------|
| Sponsor organisation name    | University of Oxford                                                                           |
| Sponsor organisation address | Joint Research Office, Block 60, Churchill Hospital, Old Road, Oxford, United Kingdom, OX3 7LE |
| Public contact               | Heather House, University of Oxford, +44 1865 572245, ctrg@admin.ox.ac.uk                      |
| Scientific contact           | Heather House, University of Oxford, +44 1865 572245, ctrg@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 February 2015 |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 02 February 2015 |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 19 April 2016    |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective is to determine objective response to ofatumumab plus CHOP at week 13, week 20 and week 72 as measured from start of treatment according to the Revised Response Criteria for Malignant Lymphoma.

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 (1996) and the regulatory requirements for clinical trials of an investigational medicinal product as set out in the European Union (EU) Directive.

Background therapy:

As well as Ofatumumab, all patients were treated with up to a maximum of six three-weekly cycles of CHOP chemotherapy. This consisted of: cyclophosphamide 750 mg/m<sup>2</sup> intravenous (iv) bolus, doxorubicin 50 mg/m<sup>2</sup> iv bolus, vincristine 1.4 mg/m<sup>2</sup> (maximum 2 mg or 1 mg in patients over 70 years old) iv infusion in 50 ml sodium chloride 0.9% over 10 minutes, prednisolone 40 mg/m<sup>2</sup> orally od, on day one and prednisolone 40 mg/ m<sup>2</sup> orally od on days 2–5 of each cycle. CHOP chemotherapy is not regarded as an IMP as it is standard care and all patients were treated the same.

Evidence for comparator:

No comparator used - single arm study.

|                                                           |               |
|-----------------------------------------------------------|---------------|
| Actual start date of recruitment                          | 27 April 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: 43 |
| Worldwide total number of subjects   | 43                 |
| EEA total number of subjects         | 43                 |

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)                     | 19 |
| From 65 to 84 years                      | 21 |
| 85 years and over                        | 3  |

## Subject disposition

### Recruitment

Recruitment details:

43 patients were recruited across 10 active sites in UK, of which 37 were found to be evaluable (received at least 1 full cycle of treatment and had a response assessment). The first patient was recruited on 05May2011 and the last patient was recruited on 01Dec2014.

### Pre-assignment

Screening details:

Screened 48 patients. Eligible if >18, ECOG PS 0-3, known diagnosis of B-CLL and newly diagnosed, untreated and biopsy proven DLBCL Richter's transformation according to WHO classification. Not eligible if previously treated with anthracycline-containing treatment for DLBCL within six months, or have central nervous system involvement with RS/B-CLL

### Period 1

|                              |                |
|------------------------------|----------------|
| Period 1 title               | Baseline       |
| Is this the baseline period? | Yes            |
| Allocation method            | Not applicable |
| Blinding used                | Not blinded    |

### Arms

|                                        |                                       |
|----------------------------------------|---------------------------------------|
| Arm title                              | Baseline                              |
| Arm description:                       |                                       |
| Baseline period                        |                                       |
| Arm type                               | Experimental                          |
| Investigational medicinal product name | Ofatumumab                            |
| Investigational medicinal product code |                                       |
| Other name                             |                                       |
| Pharmaceutical forms                   | Concentrate for solution for infusion |
| Routes of administration               | Intravenous use                       |

Dosage and administration details:

Ofatumumab was infused intravenously on day 1 (300 mg), day 8 (1000 mg) and day 15 (1000mg) in the first cycle, followed by infusions every 3 weeks of 1000 mg on the first day of each cycle for a total of 6 cycles.

|                                                     |          |
|-----------------------------------------------------|----------|
| <b>Number of subjects in period 1<sup>[1]</sup></b> | Baseline |
| Started                                             | 37       |
| Completed                                           | 37       |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 43 patients were registered to the trial, but only 37 of these patients were evaluable: evaluable patients must have received at least 1 full cycle of treatment and had a response assessment. If any patients were identified as non-evaluable they were replaced within the recruitment period.

**Period 2**

|                              |                |
|------------------------------|----------------|
| Period 2 title               | Induction      |
| Is this the baseline period? | No             |
| Allocation method            | Not applicable |
| Blinding used                | Not blinded    |

**Arms**

|                                        |                                       |
|----------------------------------------|---------------------------------------|
| <b>Arm title</b>                       | Ofatumumab + CHOP                     |
| Arm description: -                     |                                       |
| Arm type                               | Experimental                          |
| Investigational medicinal product name | Ofatumumab                            |
| Investigational medicinal product code |                                       |
| Other name                             |                                       |
| Pharmaceutical forms                   | Concentrate for solution for infusion |
| Routes of administration               | Intravenous use                       |

Dosage and administration details:

Ofatumumab was infused intravenously on day 1 (300 mg), day 8 (1000 mg) and day 15 (1000mg) in the first cycle, followed by infusions every 3 weeks of 1000 mg on the first day of each cycle for a total of 6 cycles.

|                                       |                   |
|---------------------------------------|-------------------|
| <b>Number of subjects in period 2</b> | Ofatumumab + CHOP |
| Started                               | 37                |
| Completed                             | 37                |

**Period 3**

|                              |                |
|------------------------------|----------------|
| Period 3 title               | Maintenance    |
| Is this the baseline period? | No             |
| Allocation method            | Not applicable |
| Blinding used                | Not blinded    |

**Arms**

|                                        |                                       |
|----------------------------------------|---------------------------------------|
| <b>Arm title</b>                       | Ofatumumab + CHOP                     |
| Arm description: -                     |                                       |
| Arm type                               | Experimental                          |
| Investigational medicinal product name | Ofatumumab                            |
| Investigational medicinal product code |                                       |
| Other name                             |                                       |
| Pharmaceutical forms                   | Concentrate for solution for infusion |
| Routes of administration               | Intravenous use                       |

Dosage and administration details:

Ofatumumab was infused intravenously on day 1 (300 mg), day 8 (1000 mg) and day 15 (1000mg) in the first cycle, followed by infusions every 3 weeks of 1000 mg on the first day of each cycle for a total of 6 cycles.

| <b>Number of subjects in period 3</b> | Ofatumumab +<br>CHOP |
|---------------------------------------|----------------------|
| Started                               | 37                   |
| Completed                             | 37                   |

## Baseline characteristics

### Reporting groups

|                       |          |
|-----------------------|----------|
| Reporting group title | Baseline |
|-----------------------|----------|

Reporting group description:

All evaluable patients.

| Reporting group values                                                                         | Baseline | Total |  |
|------------------------------------------------------------------------------------------------|----------|-------|--|
| Number of subjects                                                                             | 37       | 37    |  |
| Age categorical                                                                                |          |       |  |
| Units: Subjects                                                                                |          |       |  |
| In utero                                                                                       | 0        | 0     |  |
| Preterm newborn infants (gestational age < 37 wks)                                             | 0        | 0     |  |
| Newborns (0-27 days)                                                                           | 0        | 0     |  |
| Infants and toddlers (28 days-23 months)                                                       | 0        | 0     |  |
| Children (2-11 years)                                                                          | 0        | 0     |  |
| Adolescents (12-17 years)                                                                      | 0        | 0     |  |
| Adults (18-64 years)                                                                           | 18       | 18    |  |
| From 65-84 years                                                                               | 16       | 16    |  |
| 85 years and over                                                                              | 3        | 3     |  |
| Age continuous                                                                                 |          |       |  |
| Units: years                                                                                   |          |       |  |
| arithmetic mean                                                                                | 66.3     |       |  |
| standard deviation                                                                             | ± 11     | -     |  |
| Gender categorical                                                                             |          |       |  |
| Units: Subjects                                                                                |          |       |  |
| Female                                                                                         | 11       | 11    |  |
| Male                                                                                           | 26       | 26    |  |
| ECOG Performance Status                                                                        |          |       |  |
| Eastern Cooperative Oncology Group (ECOG) Performance Status: Activity Performance Description |          |       |  |
| Units: Subjects                                                                                |          |       |  |
| Score 0                                                                                        | 17       | 17    |  |
| Score 1                                                                                        | 12       | 12    |  |
| Score 2                                                                                        | 4        | 4     |  |
| Score 3                                                                                        | 4        | 4     |  |
| Ann Arbour Staging                                                                             |          |       |  |
| Ann Arbour Staging (DBCL criteria)                                                             |          |       |  |
| Units: Subjects                                                                                |          |       |  |
| Not assessed/documentated                                                                      | 1        | 1     |  |
| Stage I                                                                                        | 6        | 6     |  |
| Stage II                                                                                       | 6        | 6     |  |
| Stage III                                                                                      | 15       | 15    |  |
| Stage IV                                                                                       | 9        | 9     |  |
| Rai Staging                                                                                    |          |       |  |
| Units: Subjects                                                                                |          |       |  |
| Stage 0                                                                                        | 11       | 11    |  |
| Stage I                                                                                        | 11       | 11    |  |

|                                                                             |    |    |  |
|-----------------------------------------------------------------------------|----|----|--|
| Stage II                                                                    | 9  | 9  |  |
| Stage III                                                                   | 3  | 3  |  |
| Stage IV                                                                    | 2  | 2  |  |
| Not assessed/documented                                                     | 1  | 1  |  |
| Binet Staging                                                               |    |    |  |
| Units: Subjects                                                             |    |    |  |
| Clinical stage A                                                            | 19 | 19 |  |
| Clinical stage B                                                            | 12 | 12 |  |
| Clinical stage C                                                            | 6  | 6  |  |
| B-symptoms history                                                          |    |    |  |
| History of constitutional symptoms (B-symptoms):                            |    |    |  |
| o Experience of night sweats (without signs of infection)                   |    |    |  |
| o Unexplained, unintentional weight loss > 10% within the previous 6 months |    |    |  |
| o Experience of extreme fatigue                                             |    |    |  |
| o Recurrent, unexplained fever of greater than 38'C or 100.5'F for 2 weeks  |    |    |  |
| Units: Subjects                                                             |    |    |  |
| Yes                                                                         | 22 | 22 |  |
| No                                                                          | 15 | 15 |  |
| Platelet Count                                                              |    |    |  |
| Units: Subjects                                                             |    |    |  |
| < 100 x 10 <sup>9</sup> /l                                                  | 10 | 10 |  |
| >100 x 10 <sup>9</sup> /l                                                   | 27 | 27 |  |
| Bulk in lymph node over 5 cm                                                |    |    |  |
| Units: Subjects                                                             |    |    |  |
| Yes                                                                         | 18 | 18 |  |
| No                                                                          | 19 | 19 |  |
| Previous treatments                                                         |    |    |  |
| Previous treatments of B-CLL                                                |    |    |  |
| Units: Subjects                                                             |    |    |  |
| None                                                                        | 17 | 17 |  |
| One                                                                         | 12 | 12 |  |
| Two or more                                                                 | 8  | 8  |  |

## End points

### End points reporting groups

|                                                                                                                                                        |                    |
|--------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|
| Reporting group title                                                                                                                                  | Baseline           |
| Reporting group description:                                                                                                                           |                    |
| Baseline period                                                                                                                                        |                    |
| Reporting group title                                                                                                                                  | Ofatumumab + CHOP  |
| Reporting group description: -                                                                                                                         |                    |
| Reporting group title                                                                                                                                  | Ofatumumab + CHOP  |
| Reporting group description: -                                                                                                                         |                    |
| Subject analysis set title                                                                                                                             | Baseline           |
| Subject analysis set type                                                                                                                              | Full analysis      |
| Subject analysis set description:                                                                                                                      |                    |
| All evaluable patients have baseline characteristics available.                                                                                        |                    |
| Subject analysis set title                                                                                                                             | Evaluable patients |
| Subject analysis set type                                                                                                                              | Intention-to-treat |
| Subject analysis set description:                                                                                                                      |                    |
| All patients recruited who received at least one full cycle of CHOP-O and had a response assessment by either clinical examination or CT scan.         |                    |
| Subject analysis set title                                                                                                                             | Responders         |
| Subject analysis set type                                                                                                                              | Intention-to-treat |
| Subject analysis set description:                                                                                                                      |                    |
| Responders are those patients with complete remission (CR), partial remission (PR) or complete remission unconfirmed (CRu) at post cycle 6 assessment. |                    |
| Subject analysis set title                                                                                                                             | Non-responders     |
| Subject analysis set type                                                                                                                              | Intention-to-treat |
| Subject analysis set description:                                                                                                                      |                    |
| Non-responders are those patients with stable disease (SD) or progressive disease (PD) at post cycle 6 assessment.                                     |                    |

### Primary: Objective response rate

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                         |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Objective response rate |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                         |
| The primary objective of the trial is to determine the objective response rate (ORR) of ofatumumab plus CHOP according to the Revised Response Criteria for Malignant Lymphoma (Cheson criteria) as measured after induction. Patients will be classified as responders/non-responders as follows: complete remission (CR), partial remission (PR) or nodular partial remission (nPR) as responders while stable disease (SD) and progressive disease (PD) as non-responders. |                         |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Primary                 |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                         |
| After cycle 6 of treatment, or if the patient withdraws from treatment earlier than cycle 6, their response recorded at withdrawal will be used. Or if an assessment is not performed at withdrawal, the latest disease response is used (i.e. post cycle 4).                                                                                                                                                                                                                 |                         |

| End point values            | Responders           | Non-responders       |  |  |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type          | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed | 17                   | 20                   |  |  |
| Units: Patients             |                      |                      |  |  |
| number (not applicable)     |                      |                      |  |  |
| Responders                  | 17                   | 0                    |  |  |

## Statistical analyses

| Statistical analysis title                                                                                                                                                                                                                                                                                                                                                                          | Objective Response Rate     |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|
| Statistical analysis description:                                                                                                                                                                                                                                                                                                                                                                   |                             |
| Patients are classified as responders/non-responders as follows: complete remission (CR), partial remission (PR) and complete remission unconfirmed (CRu) are classified as responders; while stable disease (SD) and progressive disease (PD) are classified as non-responders. The ORR is reported as the proportion of responders at post cycle 6, including two-sided 95% confidence intervals. |                             |
| Comparison groups                                                                                                                                                                                                                                                                                                                                                                                   | Non-responders v Responders |
| Number of subjects included in analysis                                                                                                                                                                                                                                                                                                                                                             | 37                          |
| Analysis specification                                                                                                                                                                                                                                                                                                                                                                              | Pre-specified               |
| Analysis type                                                                                                                                                                                                                                                                                                                                                                                       | other <sup>[1]</sup>        |
| Parameter estimate                                                                                                                                                                                                                                                                                                                                                                                  | Objective Response Rate     |
| Point estimate                                                                                                                                                                                                                                                                                                                                                                                      | 46                          |
| Confidence interval                                                                                                                                                                                                                                                                                                                                                                                 |                             |
| level                                                                                                                                                                                                                                                                                                                                                                                               | 95 %                        |
| sides                                                                                                                                                                                                                                                                                                                                                                                               | 2-sided                     |
| lower limit                                                                                                                                                                                                                                                                                                                                                                                         | 29.7                        |
| upper limit                                                                                                                                                                                                                                                                                                                                                                                         | 62.2                        |

Notes:

[1] - No formal comparison of the primary end point can be made as there is only one treatment arm.

## Secondary: Overall Survival

| End point title                                                                                                                                                                                                                 | Overall Survival |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|
| End point description:                                                                                                                                                                                                          |                  |
| End point type                                                                                                                                                                                                                  | Secondary        |
| End point timeframe:                                                                                                                                                                                                            |                  |
| Length of survival is defined in months as the time from entry into the study until death from any cause. 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 values                 | Evaluable patients   |  |  |  |
|----------------------------------|----------------------|--|--|--|
| Subject group type               | Subject analysis set |  |  |  |
| Number of subjects analysed      | 37                   |  |  |  |
| Units: Months                    |                      |  |  |  |
| median (confidence interval 95%) | 11.4 (6.4 to 25.6)   |  |  |  |

## 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:

Length of survival is defined in months as the time from entry into the study until lymphoma progression or death from any cause. Those who are not observed to progress or die during the course of the trial will be censored at their last known progress

| End point values                 | Evaluable patients   |  |  |  |
|----------------------------------|----------------------|--|--|--|
| Subject group type               | Subject analysis set |  |  |  |
| Number of subjects analysed      | 37                   |  |  |  |
| Units: Months                    |                      |  |  |  |
| median (confidence interval 95%) | 6.2 (4.9 to 14)      |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Constitutional symptoms (B-symptoms)

|                 |                                      |
|-----------------|--------------------------------------|
| End point title | Constitutional symptoms (B-symptoms) |
|-----------------|--------------------------------------|

End point description:

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

End point timeframe:

Baseline.

| End point values                                   | Evaluable patients   |  |  |  |
|----------------------------------------------------|----------------------|--|--|--|
| Subject group type                                 | Subject analysis set |  |  |  |
| Number of subjects analysed                        |                      |  |  |  |
| Units: Patients                                    |                      |  |  |  |
| Experience of night sweats                         | 15                   |  |  |  |
| No experience of night sweats                      | 22                   |  |  |  |
| Unexplained weight loss >10% within last 6 months  | 9                    |  |  |  |
| No unexplained weight loss >10% within last 6 mths | 28                   |  |  |  |
| Experience of extreme fatigue                      | 6                    |  |  |  |
| No experience of extreme fatigue                   | 31                   |  |  |  |
| Recurrent, unexplained fever >38 deg's for 2 weeks | 4                    |  |  |  |
| No recurrent, unexplained fever >38 for 2 weeks    | 33                   |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: ECOG Performance Status

|                        |                         |
|------------------------|-------------------------|
| End point title        | ECOG Performance Status |
| End point description: |                         |
| End point type         | Secondary               |
| End point timeframe:   |                         |
| Post cycle 6           |                         |

| End point values             | Evaluable patients   |  |  |  |
|------------------------------|----------------------|--|--|--|
| Subject group type           | Subject analysis set |  |  |  |
| Number of subjects analysed  | 37                   |  |  |  |
| Units: Patients              |                      |  |  |  |
| Zero                         | 10                   |  |  |  |
| One                          | 6                    |  |  |  |
| Two                          | 0                    |  |  |  |
| Three                        | 0                    |  |  |  |
| Not assessed/documentated    | 3                    |  |  |  |
| Withdrew prior to assessment | 18                   |  |  |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse Event Monitoring starts from the time the patient gives informed consent, unless specified otherwise, and until they complete the trial.

Adverse event reporting additional description:

Only AEs of CTCAE grade 3 or grade 4 are reported here.

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

### Dictionary used

|                 |           |
|-----------------|-----------|
| Dictionary name | NCI-CTCAE |
|-----------------|-----------|

|                    |     |
|--------------------|-----|
| Dictionary version | 4.0 |
|--------------------|-----|

### Reporting groups

|                       |                   |
|-----------------------|-------------------|
| Reporting group title | Safety population |
|-----------------------|-------------------|

Reporting group description:

All patients who received at least one dose of the trial treatment, including those deemed not evaluable for the primary outcome.

| Serious adverse events                                              | Safety population                                                        |  |  |
|---------------------------------------------------------------------|--------------------------------------------------------------------------|--|--|
| Total subjects affected by serious adverse events                   |                                                                          |  |  |
| subjects affected / exposed                                         | 36 / 43 (83.72%)                                                         |  |  |
| number of deaths (all causes)                                       | 28                                                                       |  |  |
| number of deaths resulting from adverse events                      | 0                                                                        |  |  |
| Investigations                                                      |                                                                          |  |  |
| Neutrophil count decreased                                          |                                                                          |  |  |
| subjects affected / exposed                                         | 2 / 43 (4.65%)                                                           |  |  |
| occurrences causally related to treatment / all                     | 3 / 4                                                                    |  |  |
| deaths causally related to treatment / all                          | 0 / 0                                                                    |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                                                                          |  |  |
| Soft tissue mass                                                    | Additional description: Soft tissue paravertebral mass (necrotic tumour) |  |  |
| subjects affected / exposed                                         | 1 / 43 (2.33%)                                                           |  |  |
| occurrences causally related to treatment / all                     | 0 / 1                                                                    |  |  |
| deaths causally related to treatment / all                          | 0 / 0                                                                    |  |  |
| Adenocarcinoma of colon                                             | Additional description: Adenocarcinoma - Sigmoid Colon                   |  |  |
| subjects affected / exposed                                         | 1 / 43 (2.33%)                                                           |  |  |
| occurrences causally related to treatment / all                     | 0 / 1                                                                    |  |  |
| deaths causally related to treatment / all                          | 0 / 0                                                                    |  |  |
| Injury, poisoning and procedural complications                      |                                                                          |  |  |

|                                                 |                                                   |  |  |
|-------------------------------------------------|---------------------------------------------------|--|--|
| Fracture                                        |                                                   |  |  |
| subjects affected / exposed                     | 1 / 43 (2.33%)                                    |  |  |
| occurrences causally related to treatment / all | 0 / 1                                             |  |  |
| deaths causally related to treatment / all      | 0 / 0                                             |  |  |
| Vascular disorders                              |                                                   |  |  |
| Thromboembolic event                            |                                                   |  |  |
| subjects affected / exposed                     | 2 / 43 (4.65%)                                    |  |  |
| occurrences causally related to treatment / all | 0 / 2                                             |  |  |
| deaths causally related to treatment / all      | 0 / 1                                             |  |  |
| Cardiac disorders                               |                                                   |  |  |
| Cardiac arrest                                  |                                                   |  |  |
| subjects affected / exposed                     | 1 / 43 (2.33%)                                    |  |  |
| occurrences causally related to treatment / all | 0 / 1                                             |  |  |
| deaths causally related to treatment / all      | 0 / 1                                             |  |  |
| Nervous system disorders                        |                                                   |  |  |
| Ischaemia                                       | Additional description: Ischaemia cerebrovascular |  |  |
| subjects affected / exposed                     | 1 / 43 (2.33%)                                    |  |  |
| occurrences causally related to treatment / all | 0 / 1                                             |  |  |
| deaths causally related to treatment / all      | 0 / 0                                             |  |  |
| Memory impairment                               |                                                   |  |  |
| subjects affected / exposed                     | 1 / 43 (2.33%)                                    |  |  |
| occurrences causally related to treatment / all | 0 / 1                                             |  |  |
| deaths causally related to treatment / all      | 0 / 0                                             |  |  |
| Blood and lymphatic system disorders            |                                                   |  |  |
| Anaemia                                         |                                                   |  |  |
| subjects affected / exposed                     | 2 / 43 (4.65%)                                    |  |  |
| occurrences causally related to treatment / all | 1 / 3                                             |  |  |
| deaths causally related to treatment / all      | 0 / 0                                             |  |  |
| Neutropenia                                     |                                                   |  |  |
| subjects affected / exposed                     | 3 / 43 (6.98%)                                    |  |  |
| occurrences causally related to treatment / all | 2 / 3                                             |  |  |
| deaths causally related to treatment / all      | 0 / 0                                             |  |  |
| Febrile neutropenia                             |                                                   |  |  |

|                                                      |                                                         |  |  |
|------------------------------------------------------|---------------------------------------------------------|--|--|
| subjects affected / exposed                          | 7 / 43 (16.28%)                                         |  |  |
| occurrences causally related to treatment / all      | 8 / 9                                                   |  |  |
| deaths causally related to treatment / all           | 0 / 0                                                   |  |  |
| General disorders and administration site conditions |                                                         |  |  |
| Unwell                                               | Additional description: Patient looked generally unwell |  |  |
| subjects affected / exposed                          | 1 / 43 (2.33%)                                          |  |  |
| occurrences causally related to treatment / all      | 1 / 1                                                   |  |  |
| deaths causally related to treatment / all           | 0 / 0                                                   |  |  |
| Pyrexia                                              |                                                         |  |  |
| subjects affected / exposed                          | 1 / 43 (2.33%)                                          |  |  |
| occurrences causally related to treatment / all      | 0 / 1                                                   |  |  |
| deaths causally related to treatment / all           | 0 / 0                                                   |  |  |
| Fatigue                                              |                                                         |  |  |
| subjects affected / exposed                          | 1 / 43 (2.33%)                                          |  |  |
| occurrences causally related to treatment / all      | 0 / 1                                                   |  |  |
| deaths causally related to treatment / all           | 0 / 0                                                   |  |  |
| Fever                                                |                                                         |  |  |
| subjects affected / exposed                          | 4 / 43 (9.30%)                                          |  |  |
| occurrences causally related to treatment / all      | 4 / 7                                                   |  |  |
| deaths causally related to treatment / all           | 0 / 0                                                   |  |  |
| Disease progression                                  |                                                         |  |  |
| subjects affected / exposed                          | 7 / 43 (16.28%)                                         |  |  |
| occurrences causally related to treatment / all      | 0 / 7                                                   |  |  |
| deaths causally related to treatment / all           | 0 / 7                                                   |  |  |
| Infusion related reaction                            |                                                         |  |  |
| subjects affected / exposed                          | 1 / 43 (2.33%)                                          |  |  |
| occurrences causally related to treatment / all      | 1 / 1                                                   |  |  |
| deaths causally related to treatment / all           | 0 / 0                                                   |  |  |
| Infusion site extravasation                          |                                                         |  |  |
| subjects affected / exposed                          | 1 / 43 (2.33%)                                          |  |  |
| occurrences causally related to treatment / all      | 1 / 1                                                   |  |  |
| deaths causally related to treatment / all           | 0 / 0                                                   |  |  |
| Gastrointestinal disorders                           |                                                         |  |  |

|                                                                   |                |                                                                       |  |
|-------------------------------------------------------------------|----------------|-----------------------------------------------------------------------|--|
| Lower gastrointestinal haemorrhage<br>subjects affected / exposed | 1 / 43 (2.33%) |                                                                       |  |
| occurrences causally related to<br>treatment / all                | 0 / 1          |                                                                       |  |
| deaths causally related to<br>treatment / all                     | 0 / 0          |                                                                       |  |
| Gastrointestinal disorder<br>subjects affected / exposed          | 1 / 43 (2.33%) | Additional description: Patient unwell overnight, D&V, stomach pains. |  |
| occurrences causally related to<br>treatment / all                | 0 / 1          |                                                                       |  |
| deaths causally related to<br>treatment / all                     | 0 / 0          |                                                                       |  |
| Abdominal pain<br>subjects affected / exposed                     | 1 / 43 (2.33%) |                                                                       |  |
| occurrences causally related to<br>treatment / all                | 0 / 1          |                                                                       |  |
| deaths causally related to<br>treatment / all                     | 0 / 0          |                                                                       |  |
| Colonic perforation<br>subjects affected / exposed                | 1 / 43 (2.33%) |                                                                       |  |
| occurrences causally related to<br>treatment / all                | 1 / 1          |                                                                       |  |
| deaths causally related to<br>treatment / all                     | 0 / 0          |                                                                       |  |
| Respiratory, thoracic and mediastinal<br>disorders                |                |                                                                       |  |
| Aspiration<br>subjects affected / exposed                         | 2 / 43 (4.65%) |                                                                       |  |
| occurrences causally related to<br>treatment / all                | 0 / 2          |                                                                       |  |
| deaths causally related to<br>treatment / all                     | 0 / 0          |                                                                       |  |
| Pleural effusion<br>subjects affected / exposed                   | 1 / 43 (2.33%) |                                                                       |  |
| occurrences causally related to<br>treatment / all                | 0 / 1          |                                                                       |  |
| deaths causally related to<br>treatment / all                     | 0 / 0          |                                                                       |  |
| Pulmonary fibrosis<br>subjects affected / exposed                 | 1 / 43 (2.33%) |                                                                       |  |
| occurrences causally related to<br>treatment / all                | 1 / 1          |                                                                       |  |
| deaths causally related to<br>treatment / all                     | 0 / 0          |                                                                       |  |
| Infections and infestations                                       |                |                                                                       |  |
| Endocarditis<br>subjects affected / exposed                       | 1 / 43 (2.33%) | Additional description: Endocarditis infective                        |  |
| occurrences causally related to<br>treatment / all                | 1 / 1          |                                                                       |  |
| deaths causally related to<br>treatment / all                     | 0 / 0          |                                                                       |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| Infection                                       |                 |  |  |
| subjects affected / exposed                     | 2 / 43 (4.65%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Lower respiratory tract infection               |                 |  |  |
| subjects affected / exposed                     | 3 / 43 (6.98%)  |  |  |
| occurrences causally related to treatment / all | 1 / 3           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Lung infection                                  |                 |  |  |
| subjects affected / exposed                     | 2 / 43 (4.65%)  |  |  |
| occurrences causally related to treatment / all | 2 / 3           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Neutropenic sepsis                              |                 |  |  |
| subjects affected / exposed                     | 2 / 43 (4.65%)  |  |  |
| occurrences causally related to treatment / all | 2 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Parainfluenzae virus infection                  |                 |  |  |
| subjects affected / exposed                     | 1 / 43 (2.33%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Sepsis                                          |                 |  |  |
| subjects affected / exposed                     | 5 / 43 (11.63%) |  |  |
| occurrences causally related to treatment / all | 8 / 8           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Skin infection                                  |                 |  |  |
| subjects affected / exposed                     | 1 / 43 (2.33%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Metabolism and nutrition disorders              |                 |  |  |
| Tumour lysis syndrome                           |                 |  |  |
| subjects affected / exposed                     | 1 / 43 (2.33%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |

Frequency threshold for reporting non-serious adverse events: 0 %

| Non-serious adverse events                                          | Safety population                                                                                                    |  |  |
|---------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|--|--|
| Total subjects affected by non-serious adverse events               |                                                                                                                      |  |  |
| subjects affected / exposed                                         | 43 / 43 (100.00%)                                                                                                    |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                                                                                                                      |  |  |
| Adenocarcinoma of colon                                             | Additional description: Adenocarcinoma of sigmoid colon unrelated to the trial treatment.                            |  |  |
| subjects affected / exposed                                         | 1 / 43 (2.33%)                                                                                                       |  |  |
| occurrences (all)                                                   | 1                                                                                                                    |  |  |
| Soft tissue mass                                                    | Additional description: Soft tissue paravertebral mass (necrotic tumor)                                              |  |  |
| subjects affected / exposed                                         | 1 / 43 (2.33%)                                                                                                       |  |  |
| occurrences (all)                                                   | 1                                                                                                                    |  |  |
| Vascular disorders                                                  |                                                                                                                      |  |  |
| Thromboembolic event                                                |                                                                                                                      |  |  |
| subjects affected / exposed                                         | 2 / 43 (4.65%)                                                                                                       |  |  |
| occurrences (all)                                                   | 2                                                                                                                    |  |  |
| General disorders and administration site conditions                |                                                                                                                      |  |  |
| Fatigue                                                             |                                                                                                                      |  |  |
| subjects affected / exposed                                         | 1 / 43 (2.33%)                                                                                                       |  |  |
| occurrences (all)                                                   | 1                                                                                                                    |  |  |
| Fever                                                               |                                                                                                                      |  |  |
| subjects affected / exposed                                         | 2 / 43 (4.65%)                                                                                                       |  |  |
| occurrences (all)                                                   | 4                                                                                                                    |  |  |
| Infusion related reaction                                           |                                                                                                                      |  |  |
| subjects affected / exposed                                         | 2 / 43 (4.65%)                                                                                                       |  |  |
| occurrences (all)                                                   | 2                                                                                                                    |  |  |
| Malaise                                                             |                                                                                                                      |  |  |
| subjects affected / exposed                                         | 1 / 43 (2.33%)                                                                                                       |  |  |
| occurrences (all)                                                   | 1                                                                                                                    |  |  |
| Other                                                               | Additional description: Fever and diarrhoea - treated as neutropenic sepsis with antibiotics however was not septic. |  |  |
| subjects affected / exposed                                         | 1 / 43 (2.33%)                                                                                                       |  |  |
| occurrences (all)                                                   | 1                                                                                                                    |  |  |
| Respiratory, thoracic and mediastinal disorders                     |                                                                                                                      |  |  |

|                                                                                                                                                                                                                                                                       |                                                                             |  |  |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|--|--|
| Bronchiectasis<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                    | 1 / 43 (2.33%)<br>1                                                         |  |  |
| Aspiration<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                        | 1 / 43 (2.33%)<br>1                                                         |  |  |
| Pleural effusion<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                  | 1 / 43 (2.33%)<br>1                                                         |  |  |
| Psychiatric disorders<br>Suicidal ideation<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                        | 1 / 43 (2.33%)<br>1                                                         |  |  |
| Investigations<br>Neutrophil count decreased<br>subjects affected / exposed<br>occurrences (all)<br><br>Platelet count decreased<br>subjects affected / exposed<br>occurrences (all)                                                                                  | 8 / 43 (18.60%)<br>10<br><br>2 / 43 (4.65%)<br>2                            |  |  |
| Injury, poisoning and procedural complications<br>Fracture<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                        | 1 / 43 (2.33%)<br>1                                                         |  |  |
| Blood and lymphatic system disorders<br>Febrile neutropenia<br>subjects affected / exposed<br>occurrences (all)<br><br>Non-Febrile Neutropenia<br>subjects affected / exposed<br>occurrences (all)<br><br>Anaemia<br>subjects affected / exposed<br>occurrences (all) | 9 / 43 (20.93%)<br>14<br><br>1 / 43 (2.33%)<br>1<br><br>4 / 43 (9.30%)<br>5 |  |  |
| Gastrointestinal disorders                                                                                                                                                                                                                                            |                                                                             |  |  |

|                                                                                                          |                     |  |  |
|----------------------------------------------------------------------------------------------------------|---------------------|--|--|
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)                                       | 1 / 43 (2.33%)<br>1 |  |  |
| Anal pain<br>subjects affected / exposed<br>occurrences (all)                                            | 1 / 43 (2.33%)<br>1 |  |  |
| Colonic perforation<br>subjects affected / exposed<br>occurrences (all)                                  | 1 / 43 (2.33%)<br>1 |  |  |
| Lower gastrointestinal haemorrhage<br>subjects affected / exposed<br>occurrences (all)                   | 1 / 43 (2.33%)<br>1 |  |  |
| Gastrointestinal disorder<br>subjects affected / exposed<br>occurrences (all)                            | 1 / 43 (2.33%)<br>1 |  |  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)                                             | 1 / 43 (2.33%)<br>1 |  |  |
| Skin and subcutaneous tissue disorders<br>Rash<br>subjects affected / exposed<br>occurrences (all)       | 1 / 43 (2.33%)<br>1 |  |  |
| Hyperhidrosis<br>subjects affected / exposed<br>occurrences (all)                                        | 1 / 43 (2.33%)<br>1 |  |  |
| Rash maculo-papular<br>subjects affected / exposed<br>occurrences (all)                                  | 1 / 43 (2.33%)<br>1 |  |  |
| Urticaria<br>subjects affected / exposed<br>occurrences (all)                                            | 1 / 43 (2.33%)<br>1 |  |  |
| Renal and urinary disorders<br>Cystitis noninfective<br>subjects affected / exposed<br>occurrences (all) | 1 / 43 (2.33%)<br>1 |  |  |
| Musculoskeletal and connective tissue disorders                                                          |                     |  |  |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                             |  |  |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|--|
| Pain in extremity<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 1 / 43 (2.33%)<br>1                                                                                                                                                                                                                         |  |  |
| Infections and infestations<br>Infection<br>subjects affected / exposed<br>occurrences (all)<br><br>Lower respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)<br><br>Parainfluenzae virus infection<br>subjects affected / exposed<br>occurrences (all)<br><br>Anorectal infection<br>subjects affected / exposed<br>occurrences (all)<br><br>Endocarditis<br>subjects affected / exposed<br>occurrences (all)<br><br>Lung infection<br>subjects affected / exposed<br>occurrences (all)<br><br>Sepsis<br>subjects affected / exposed<br>occurrences (all)<br><br>Skin infection<br>subjects affected / exposed<br>occurrences (all)<br><br>Tooth infection<br>subjects affected / exposed<br>occurrences (all) | 3 / 43 (6.98%)<br>3<br><br>3 / 43 (6.98%)<br>3<br><br>1 / 43 (2.33%)<br>1<br><br>1 / 43 (2.33%)<br>1<br><br>1 / 43 (2.33%)<br>1<br><br>4 / 43 (9.30%)<br>4<br><br>4 / 43 (9.30%)<br>7<br><br>1 / 43 (2.33%)<br>1<br><br>1 / 43 (2.33%)<br>1 |  |  |
| Metabolism and nutrition disorders<br>Hyponatraemia<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 1 / 43 (2.33%)<br>1                                                                                                                                                                                                                         |  |  |



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment                                                                                                                                                                            |
|-------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 07 February 2011  | Substantial Amendment 001: Addition of new sites – Kings College Hospital and UCLH                                                                                                   |
| 30 March 2011     | Substantial Amendment 002: Addition of new site – Nottingham, Removal of existing site – Queen Elizabeth Hospital                                                                    |
| 13 June 2011      | Substantial Amendment 003: PIS update                                                                                                                                                |
| 17 June 2011      | Substantial Amendment 004: Addition of a new site – Queen Elizabeth Hospital, Birmingham                                                                                             |
| 26 October 2011   | Substantial Amendment 005: Addition of questionnaire booklets                                                                                                                        |
| 24 April 2012     | Substantial Amendment 006: Addition of a new site – Royal Marsden Hospital London                                                                                                    |
| 09 July 2012      | Substantial Amendment 007: Change of drug distribution centre – from Aptuit to Catalent                                                                                              |
| 30 April 2013     | Substantial Amendment 008: PIS update                                                                                                                                                |
| 02 September 2013 | Substantial Amendment 009: Protocol update: change to exclusion criteria, timing of assessments and SAE criteria.                                                                    |
| 22 January 2014   | Substantial Amendment 010: Change of PI at Royal Bournemouth Hospital                                                                                                                |
| 16 July 2014      | Substantial Amendment 011: PIS update                                                                                                                                                |
| 31 October 2014   | Substantial Amendment 012: Protocol update: addition of list of adverse events, clarification of 'objective response', changes to contact information<br>GP Letter update, IB update |

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 data is not compared in a prospective randomized clinical trial. The small number of patients is one limitation, and unfortunately, only limited data of sufficient quality were available for a number of endpoints, meaning no formal analyses.

Notes:

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## Online references

<http://www.ncbi.nlm.nih.gov/pubmed/27378086>