



Clinical trial results:

BREVITY: A phase II study of brentuximab vedotin using a response adapted design in patients with Hodgkin lymphoma unsuitable for chemotherapy due to age, frailty or co-morbidity

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2012-000214-11 |
| Trial protocol | GB |
| Global end of trial date | 18 July 2018 |

Results information

| | |
|--------------------------------|----------------|
| Result version number | v1 (current) |
| This version publication date | 02 August 2019 |
| First version publication date | 02 August 2019 |

Trial information

Trial identification

| | |
|-----------------------|-----------|
| Sponsor protocol code | RG_11-225 |
|-----------------------|-----------|

Additional study identifiers

| | |
|------------------------------------|---|
| ISRCTN number | ISRCTN77650947 |
| ClinicalTrials.gov id (NCT number) | NCT02567851 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | Sponsors SAF number: ERN_11-0718, Sponsors RG Number: RG_11-225 |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | University of Birmingham |
| Sponsor organisation address | Edgbaston, Birmingham, Birmingham, United Kingdom, B15 2TT |
| Public contact | BREVITY trial coordinator, University of Birmingham, +44 1213717863, brevity@trials.bham.ac.uk |
| Scientific contact | BREVITY trial coordinator, University of Birmingham, +44 1213717863, brevity@trials.bham.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 | 04 September 2018 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 18 July 2018 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To determine how many patients treated with 4 cycles of brentuximab vedotin, who are unsuitable for conventional chemotherapy, have a complete response to the treatment (as measured by PET scan Deauville score 1,2 or 3).

Protection of trial subjects:

Patients were carefully monitored during and for 1-hour after the first infusion for infusion-related reactions. If an infusion-related reaction occurred, the infusion was interrupted and appropriate medical management instituted. All general supportive care measures, including red cell transfusion to alleviate disease related symptoms and treatment toxicities were allowed at the investigators discretion.

Background therapy: -

Evidence for comparator:

Brentuximab vedotin (BV) is a new CD30 targeted antibody, composed of the anti-CD30 monoclonal antibody cAC10 and a potent antimicrotubule drug, monomethyl auristatin E (MMAE). It binds to CD30, which has very low expression in normal cells but is consistently expressed in Hodgkin Reed-Sternberg cells. Phase 1 and 2 data in the relapsed/refractory Hodgkin Lymphoma population suggest that BV has a high level of efficacy and a very manageable toxicity profile with no known cardiac or pulmonary toxicity when given as a single agent.

| | |
|---|------------------|
| Actual start date of recruitment | 14 February 2014 |
| 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: 38 |
| Worldwide total number of subjects | 38 |
| EEA total number of subjects | 38 |

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) | 3 |
| From 65 to 84 years | 29 |
| 85 years and over | 6 |

Subject disposition

Recruitment

Recruitment details:

Patients were invited to attend from 13 UK Haematology-oncology centres, as selected for the LLR Trials Acceleration Programme (TAP) and additional UK Haemato-Oncology centres. Recruitment ran between 14-FEB-2014 and 20-OCT-2017.

Pre-assignment

Screening details:

Screening commenced following consent and prior to patient registration in order to confirm eligibility. All patients had a full medical and drug history, PET scan and physical examination, with particular attention paid to cardiovascular risk factors and assessments to exclude symptoms or signs of Progressive Multifocal Leukoencephalopathy.

Pre-assignment period milestones

| | |
|------------------------------|-------------------|
| Number of subjects started | 47 ^[1] |
| Number of subjects completed | 38 |

Pre-assignment subject non-completion reasons

| | |
|----------------------------|---|
| Reason: Number of subjects | ineligible: 5 |
| Reason: Number of subjects | Died: 1 |
| Reason: Number of subjects | Consent withdrawn by subject: 1 |
| Reason: Number of subjects | PET accreditation issue, couldn't finish screening: 1 |
| Reason: Number of subjects | Patient too unwell: 1 |

Notes:

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

Justification: Patients were screened prior to enrolment into the study. This occurred prior to registration therefore the number in the pre-enrolment period is greater than the number registered into the trial.

Period 1

| | |
|------------------------------|----------------|
| Period 1 title | Registration |
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|--|------------------------|
| Arm title | Brentuximab vedotin |
| Arm description: - | |
| Arm type | Experimental |
| Investigational medicinal product name | Brentuximab vedotin |
| Investigational medicinal product code | SGN-35 |
| Other name | Adcetris |
| Pharmaceutical forms | Powder for concentrate |
| Routes of administration | Intravenous use |

Dosage and administration details:

Brentuximab vedotin was administered at an initial dose of 1.8 mg/kg every 3 weeks as a 30-minute outpatient i.v. infusion. After the initial 4 cycles of BV, subsequent treatment was response-adapted. Dose reduction to 1.2mg/kg every 3 weeks was permitted in response to levels of toxicity.

| | |
|---------------------------------------|---------------------|
| Number of subjects in period 1 | Brentuximab vedotin |
| Started | 38 |
| Completed | 38 |

Period 2

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

Arms

| | |
|--|------------------------|
| Arm title | Brentuximab vedotin |
| Arm description: | |
| Treatment with 4 cycles of BV | |
| Arm type | Experimental |
| Investigational medicinal product name | Brentuximab vedotin |
| Investigational medicinal product code | SGN-35 |
| Other name | Adcetris |
| Pharmaceutical forms | Powder for concentrate |
| Routes of administration | Intravenous use |

Dosage and administration details:

Brentuximab vedotin was administered at an initial dose of 1.8 mg/kg every 3 weeks as a 30-minute outpatient i.v. infusion. After the initial 4 cycles of BV, subsequent treatment was response-adapted. Dose reduction to 1.2mg/kg every 3 weeks was permitted in response to levels of toxicity.

| | |
|---------------------------------------|---------------------|
| Number of subjects in period 2 | Brentuximab vedotin |
| Started | 38 |
| Completed | 31 |
| Not completed | 7 |
| Failed to start treatment | 1 |
| ineligible | 6 |

Period 3

| | |
|------------------------------|--------------------|
| Period 3 title | Efficacy |
| Is this the baseline period? | Yes ^[2] |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|------------------|---------------------|
| Arm title | Brentuximab vedotin |
|------------------|---------------------|

Arm description:

Treatment with 4 cycles of BV

| | |
|--|------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Brentuximab vedotin |
| Investigational medicinal product code | SGN-35 |
| Other name | Adcetris |
| Pharmaceutical forms | Powder for concentrate |
| Routes of administration | Intravenous use |

Dosage and administration details:

Brentuximab vedotin was administered at an initial dose of 1.8 mg/kg every 3 weeks as a 30-minute outpatient i.v. infusion. After the initial 4 cycles of BV, subsequent treatment was response-adapted. Dose reduction to 1.2mg/kg every 3 weeks was permitted in response to levels of toxicity.

Notes:

[2] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: This is a single arm phase II trial in which 7 patients were replaced. Period one includes all patients registered to the trial, period three includes only those who were evaluable for efficacy. It is the baseline characteristics of those patients who were evaluated for efficacy which are of clinical importance.

| | |
|---|---------------------|
| Number of subjects in period 3^[3] | Brentuximab vedotin |
| Started | 31 |
| Completed | 31 |

Notes:

[3] - 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: This is a single arm phase II trial in which 7 patients were replaced. Period one includes all patients registered to the trial, period three includes only those who were evaluable for efficacy. It is the baseline characteristics of those patients who were evaluated for efficacy which are of clinical importance.

Baseline characteristics

Reporting groups

| | |
|-----------------------|----------|
| Reporting group title | Efficacy |
|-----------------------|----------|

Reporting group description: -

| Reporting group values | Efficacy | Total | |
|--|----------|-------|--|
| Number of subjects | 31 | 31 | |
| 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) | 2 | 2 | |
| From 65-84 years | 25 | 25 | |
| 85 years and over | 4 | 4 | |
| Age continuous | | | |
| Units: years | | | |
| median | 77 | | |
| inter-quartile range (Q1-Q3) | 69 to 82 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 11 | 11 | |
| Male | 20 | 20 | |
| ECOG Performance Status | | | |
| Units: Subjects | | | |
| Zero | 1 | 1 | |
| One | 16 | 16 | |
| Two | 9 | 9 | |
| Three | 5 | 5 | |
| Disease stage | | | |
| Units: Subjects | | | |
| II | 6 | 6 | |
| III | 9 | 9 | |
| IV | 16 | 16 | |
| B Symptoms | | | |
| Units: Subjects | | | |
| No | 8 | 8 | |
| Yes | 23 | 23 | |
| Extra Nodal Disease | | | |
| Units: Subjects | | | |
| No | 13 | 13 | |
| Yes | 18 | 18 | |
| Bulky Disease | | | |

| | | | |
|--|--------------|----|--|
| Units: Subjects | | | |
| No | 28 | 28 | |
| Yes | 3 | 3 | |
| Nodal Involvement | | | |
| Units: Subjects | | | |
| No | 4 | 4 | |
| Yes | 26 | 26 | |
| Not known | 1 | 1 | |
| Histotype | | | |
| Units: Subjects | | | |
| Nodular Sclerosing | 16 | 16 | |
| Mixed Cellularity | 8 | 8 | |
| Not Known | 7 | 7 | |
| Reason Standard Chemotherapy is Unsuitable | | | |
| Units: Subjects | | | |
| Left ventricular ejection fraction (LVEF) | 4 | 4 | |
| Left ventricular ejection and ECOG | 7 | 7 | |
| LVEF, Impaired respiratory and ECOG | 1 | 1 | |
| Impaired respiratory and ECOG | 4 | 4 | |
| ECOG | 9 | 9 | |
| LVEF and Impaired respiratory | 1 | 1 | |
| Impaired respiratory | 1 | 1 | |
| Impaired cardiac, LVEF and ECOG | 1 | 1 | |
| Impaired cardiac plus respiratory and ECOG | 1 | 1 | |
| Impaired cardiac and ECOG | 2 | 2 | |
| CIRS-G: Total number of categorised endorsed | | | |
| Units: Subjects | | | |
| median | 3.00 | | |
| inter-quartile range (Q1-Q3) | 2.00 to 5.00 | - | |
| CIRS-G: Total Score | | | |
| Units: Subjects | | | |
| median | 6.00 | | |
| inter-quartile range (Q1-Q3) | 4.00 to 7.00 | - | |
| CIRS-G: Severity Index | | | |
| Units: Subjects | | | |
| median | 2.00 | | |
| inter-quartile range (Q1-Q3) | 2.00 to 2.00 | - | |
| CIRS-G: Number categorised at level 3 | | | |
| Units: Subjects | | | |
| median | 0.00 | | |
| inter-quartile range (Q1-Q3) | 0.00 to 0.00 | - | |
| CIRS-G: Number categorised at level 4 | | | |
| Units: Subjects | | | |
| median | 0.00 | | |
| inter-quartile range (Q1-Q3) | 0.00 to 0.00 | - | |

End points

End points reporting groups

| | |
|--------------------------------|---------------------|
| Reporting group title | Brentuximab vedotin |
| Reporting group description: - | |
| Reporting group title | Brentuximab vedotin |
| Reporting group description: | |
| Treatment with 4 cycles of BV | |
| Reporting group title | Brentuximab vedotin |
| Reporting group description: | |
| Treatment with 4 cycles of BV | |

Primary: Complete (metabolic) response rate after 4 cycles of Brentuximab vedotin defined as Deauville Score of 1, 2 or 3 at PET 4.

| | |
|------------------------|--|
| End point title | Complete (metabolic) response rate after 4 cycles of Brentuximab vedotin defined as Deauville Score of 1, 2 or 3 at PET 4. ^[1] |
| End point description: | No statistical analysis were preformed. During the design of this trial a response rate of 40% was deemed unacceptable for further investigation and a response rate of 60% was deemed worthy of further investigation. These figures were used in the Simon's two-stage minimax design which determined that in order for the BV to be worthy of further investigation as a single agent treatment the trial needed to show a minimum of 15 complete metabolic responses. |
| End point type | Primary |
| End point timeframe: | Assessed by PET-CT scan after 4 cycles of Brentuximab Vedotin. Scans were conducted within the day 15-19 window of cycle 4. |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis were conducted in relation to this primary outcome as this is a single arm trial so the interpretation of the primary outcome was made in relation to desirable characteristics defined in the sample size calculation.

| | | | | |
|---|---------------------|--|--|--|
| End point values | Brentuximab vedotin | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 31 | | | |
| Units: Number of patients achieving CMR | 8 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Dose intensity

| | |
|------------------------|----------------|
| End point title | Dose intensity |
| End point description: | |
| End point type | Secondary |

End point timeframe:

Dose intensity reported as the median dose intensity over the treatment period for all patients across all cycles.

| | | | | |
|---------------------------------------|---------------------|--|--|--|
| End point values | Brentuximab vedotin | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 31 | | | |
| Units: Dose Intensity | | | | |
| median (inter-quartile range (Q1-Q3)) | 100 (70 to 100) | | | |

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:

PFS estimates calculated using Kaplan-Meier method presented as median, 12 and 24 month survival.

| | | | | |
|----------------------------------|---------------------|--|--|--|
| End point values | Brentuximab vedotin | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 31 | | | |
| Units: PFS | | | | |
| median (confidence interval 95%) | | | | |
| Median PFS time (months) | 7.3 (5.2 to 9.0) | | | |
| 12 months PFS (%) | 13.7 (4.3 to 28.4) | | | |
| 24 months PFS (%) | 6.9 (1.2 to 19.6) | | | |

| | |
|-----------------------------------|---------|
| Attachments (see zip file) | PFS.pdf |
|-----------------------------------|---------|

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

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

End point description:

The upper estimate of the 95% confidence interval for median overall survival has not yet been reached. Maximum range has been entered.

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

End point timeframe:

Overall survival is defined as the time from cycle 1 day 1 to the date of death from any cause.

| End point values | Brentuximab vedotin | | | |
|----------------------------------|---------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 31 | | | |
| Units: OS | | | | |
| number (confidence interval 95%) | | | | |
| Median OS time months | 19.5 (12.6 to 51.0) | | | |
| 12 month OS (%) | 73.4 (53.7 to 85.7) | | | |
| 24 months OS (%) | 42.0 (24.1 to 58.8) | | | |

| | |
|----------------------------|--------|
| Attachments (see zip file) | OS.pdf |
|----------------------------|--------|

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR) at PET 4

| | |
|-----------------|--|
| End point title | Objective Response Rate (ORR) at PET 4 |
|-----------------|--|

End point description:

ORR is defined as achieving either complete or partial metabolic response and is calculated using Wilsons estimates due to its increased accuracy with small sample sizes.

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

End point timeframe:

ORR after 4 cycles of treatment with Brentuximab vedotin according to the Revised Response Criteria for malignant lymphoma.

| End point values | Brentuximab vedotin | | | |
|----------------------------------|---------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 31 | | | |
| Units: CMR or PMR % | | | | |
| number (confidence interval 95%) | 83.9 (67.4 to 92.9) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Tolerability

| | |
|-----------------|--------------|
| End point title | Tolerability |
|-----------------|--------------|

End point description:

Tolerability was defined in terms of the absence of toxicities related to Brentuximab Vedotin quantified by the CTCAE v4 criteria. All 35 treated patients experienced at least one related event during the trial. In total 246 related toxicities were reported, 55% were grade 1, 29% grade 2, 15% grade 3 and 0.5% was grade 4.

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

End point timeframe:

Patients were assessed for toxicities related to Brentuximab Vedotin throughout the treatment period.

| | | | | |
|--|---------------------|--|--|--|
| End point values | Brentuximab vedotin | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 31 | | | |
| Units: Patients without related toxicities | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR) at 16 cycles

| | |
|-----------------|--|
| End point title | Objective Response Rate (ORR) at 16 cycles |
|-----------------|--|

End point description:

ORR is defined as achieving either complete or partial metabolic response.

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

End point timeframe:

ORR after 16 cycles of treatment with Brentuximab vedotin according to the Revised Response Criteria for malignant lymphoma.

| | | | | |
|----------------------------------|---------------------|--|--|--|
| End point values | Brentuximab vedotin | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 31 | | | |
| Units: CMR or PMR % | | | | |
| number (confidence interval 95%) | 9.7 (3.3 to 24.9) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulative illness rating scale for geriatrics (CIRS-G)

| | |
|-----------------|---|
| End point title | Cumulative illness rating scale for geriatrics (CIRS-G) |
|-----------------|---|

End point description:

CIRS-G Index score of 1 = Current mild problems or past significant problems.

CIRS-G Index score of 2 = Moderate disability of morbidity - requires first line therapy

CIRS-G Index score of 3 = Severe - constant significant disability - 'uncontrollable' chronic pain.

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

End point timeframe:

Assessed as part of baseline measures prior to commencement of trial treatment.

| | | | | |
|-----------------------------|---------------------|--|--|--|
| End point values | Brentuximab vedotin | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 31 | | | |
| Units: Number of patients | | | | |
| Index score 1 | 7 | | | |
| Index score 2 | 22 | | | |
| Index score 3 | 2 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Co-morbidities satisfying eligibility criteria

| | |
|-----------------|--|
| End point title | Co-morbidities satisfying eligibility criteria |
|-----------------|--|

End point description:

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

End point timeframe:

Emergence of any new co-morbidity throughout the course of the trial which would satisfy the eligibility criteria

| | | | | |
|-----------------------------|---------------------|--|--|--|
| End point values | Brentuximab vedotin | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 31 | | | |
| Units: Number Patients | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Deauville score after cycle 2 based on blinded PET2 scan

| | |
|-----------------|--|
| End point title | Deauville score after cycle 2 based on blinded PET2 scan |
|-----------------|--|

End point description:

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

End point timeframe:

Blinded PET scans were taken following 2 cycles of BV.

| | | | | |
|-----------------------------|---------------------|--|--|--|
| End point values | Brentuximab vedotin | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 31 | | | |
| Units: Number patients | | | | |
| Deauville 1 | 0 | | | |
| Deauville 2 | 3 | | | |
| Deauville 3 | 5 | | | |
| Deauville 4 | 15 | | | |
| Deauville 5 | 2 | | | |
| Not done | 6 | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events were reported from the date of commencement of protocol defined treatment until 30 days after the administration of treatment.

Adverse event reporting additional description:

Adverse Events (AEs) were reported on an AE form and returned to the Trials Office. AE's were reviewed using the Common Terminology Criteria for Adverse Events (CTCAE), version 4. SAE forms were faxed to the Trials Office; seriousness and causality were determined independently by a Clinical Coordinator.

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

Dictionary used

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

| | |
|--------------------|---|
| Dictionary version | 4 |
|--------------------|---|

Reporting groups

| | |
|-----------------------|------------------|
| Reporting group title | Treated patients |
|-----------------------|------------------|

Reporting group description:

All 35 patients who received Bretuximab Vedotin.

| Serious adverse events | Treated patients | | |
|---|------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 21 / 35 (60.00%) | | |
| number of deaths (all causes) | 21 | | |
| number of deaths resulting from adverse events | 1 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) other | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Surgical and medical procedures | | | |
| Surgical and medical procedures other | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Chills | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Fatigue | | | |
| subjects affected / exposed | 2 / 35 (5.71%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Fever | | | |
| subjects affected / exposed | 4 / 35 (11.43%) | | |
| occurrences causally related to treatment / all | 4 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Malaise | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Immune system disorders | | | |
| Anaphylaxis | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Immune system disorder other | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pneumonitis | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Heart failure | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Facial muscle weakness | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders other | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Eye disorders | | | |
| Blurred vision | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diarrhea | | | |
| subjects affected / exposed | 2 / 35 (5.71%) | | |
| occurrences causally related to treatment / all | 3 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| Palmar-plantar erythrodysesthesia syndrome | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Erythroderma | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rash maculo-papular | | | |
| subjects affected / exposed | 2 / 35 (5.71%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Lung infection | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sepsis | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 1 / 1 | | |

| | | | |
|---|----------------|--|--|
| Urinary tract infection | | | |
| subjects affected / exposed | 2 / 35 (5.71%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations other | | | |
| subjects affected / exposed | 3 / 35 (8.57%) | | |
| occurrences causally related to treatment / all | 1 / 3 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Metabolism and nutrition disorders | | | |
| Anorexia | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyperkalemia | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypomagnesemia | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 1 %

| Non-serious adverse events | Treated patients | | |
|---|-------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 35 / 35 (100.00%) | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) - other | | | |
| subjects affected / exposed | 4 / 35 (11.43%) | | |
| occurrences (all) | 5 | | |
| Vascular disorders | | | |

| | | | |
|--|------------------------|--|--|
| Hypertension subjects affected / exposed occurrences (all) | 2 / 35 (5.71%) 4 | | |
| Hypotension subjects affected / exposed occurrences (all) | 3 / 35 (8.57%) 3 | | |
| Surgical and medical procedures Surgical and medical procedures - other subjects affected / exposed occurrences (all) | 1 / 35 (2.86%) 1 | | |
| General disorders and administration site conditions Gait disturbance subjects affected / exposed occurrences (all) | 1 / 35 (2.86%) 2 | | |
| Chills subjects affected / exposed occurrences (all) | 2 / 35 (5.71%) 3 | | |
| Edema limbs subjects affected / exposed occurrences (all) | 2 / 35 (5.71%) 2 | | |
| Hypothermia subjects affected / exposed occurrences (all) | 1 / 35 (2.86%) 1 | | |
| Fatigue subjects affected / exposed occurrences (all) | 18 / 35 (51.43%) 35 | | |
| Fever subjects affected / exposed occurrences (all) | 11 / 35 (31.43%) 12 | | |
| Flu like symptoms subjects affected / exposed occurrences (all) | 2 / 35 (5.71%) 3 | | |
| Infusion related reaction subjects affected / exposed occurrences (all) | 2 / 35 (5.71%) 2 | | |
| Malaise | | | |

| | | | |
|---|------------------------|--|--|
| subjects affected / exposed occurrences (all) | 2 / 35 (5.71%) 2 | | |
| Pain subjects affected / exposed occurrences (all) | 11 / 35 (31.43%) 18 | | |
| General disorders and administration site conditions - other subjects affected / exposed occurrences (all) | 9 / 35 (25.71%) 16 | | |
| Immune system disorders Anaphylaxis subjects affected / exposed occurrences (all) | 1 / 35 (2.86%) 1 | | |
| Reproductive system and breast disorders Uterine pain subjects affected / exposed occurrences (all) | 1 / 35 (2.86%) 1 | | |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 6 / 35 (17.14%) 6 | | |
| Dyspnea subjects affected / exposed occurrences (all) | 4 / 35 (11.43%) 6 | | |
| Sore throat subjects affected / exposed occurrences (all) | 1 / 35 (2.86%) 1 | | |
| Wheezing subjects affected / exposed occurrences (all) | 1 / 35 (2.86%) 1 | | |
| Bronchospasm subjects affected / exposed occurrences (all) | 1 / 35 (2.86%) 1 | | |
| Sleep apnea subjects affected / exposed occurrences (all) | 1 / 35 (2.86%) 1 | | |

| | | | |
|---|---|--|--|
| Respiratory, thoracic and mediastinal disorders - other subjects affected / exposed occurrences (all) | 3 / 35 (8.57%) 4 | | |
| Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) Anxiety subjects affected / exposed occurrences (all) Confusion subjects affected / exposed occurrences (all) Psychiatric disorders - other subjects affected / exposed occurrences (all) | 2 / 35 (5.71%) 2 1 / 35 (2.86%) 1 1 / 35 (2.86%) 1 1 / 35 (2.86%) 1 | | |
| Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all) Alkaline phosphatase increased subjects affected / exposed occurrences (all) Aspartate aminotransferase increased subjects affected / exposed occurrences (all) Creatinine increased subjects affected / exposed occurrences (all) GGT increased subjects affected / exposed occurrences (all) Lymphocyte count decreased subjects affected / exposed occurrences (all) Lymphocyte count increased | 2 / 35 (5.71%) 5 4 / 35 (11.43%) 5 1 / 35 (2.86%) 2 2 / 35 (5.71%) 2 5 / 35 (14.29%) 17 5 / 35 (14.29%) 12 | | |

| | | | |
|--|-----------------|--|--|
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences (all) | 1 | | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 6 / 35 (17.14%) | | |
| occurrences (all) | 9 | | |
| Platelet count decreased | | | |
| subjects affected / exposed | 3 / 35 (8.57%) | | |
| occurrences (all) | 8 | | |
| Weight loss | | | |
| subjects affected / exposed | 5 / 35 (14.29%) | | |
| occurrences (all) | 7 | | |
| White blood cell decreased | | | |
| subjects affected / exposed | 3 / 35 (8.57%) | | |
| occurrences (all) | 8 | | |
| Investigations - other | | | |
| subjects affected / exposed | 8 / 35 (22.86%) | | |
| occurrences (all) | 117 | | |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 4 / 35 (11.43%) | | |
| occurrences (all) | 7 | | |
| Fracture | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences (all) | 1 | | |
| Injury, poisoning and procedural complications - other | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences (all) | 1 | | |
| Cardiac disorders | | | |
| Heart failure | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences (all) | 1 | | |
| Palpitations | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences (all) | 2 | | |
| Cardiac disorders - other | | | |

| | | | |
|-------------------------------|------------------|--|--|
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences (all) | 2 | | |
| Nervous system disorders | | | |
| Presyncope | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences (all) | 1 | | |
| Vasovagal reaction | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences (all) | 1 | | |
| Dysesthesia | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences (all) | 2 | | |
| Facial muscle weakness | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences (all) | 1 | | |
| Headache | | | |
| subjects affected / exposed | 4 / 35 (11.43%) | | |
| occurrences (all) | 5 | | |
| Memory impairment | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences (all) | 1 | | |
| Paresthesia | | | |
| subjects affected / exposed | 2 / 35 (5.71%) | | |
| occurrences (all) | 2 | | |
| Peripheral motor neuropathy | | | |
| subjects affected / exposed | 6 / 35 (17.14%) | | |
| occurrences (all) | 7 | | |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 19 / 35 (54.29%) | | |
| occurrences (all) | 51 | | |
| Dizziness | | | |
| subjects affected / exposed | 5 / 35 (14.29%) | | |
| occurrences (all) | 5 | | |
| Lethargy | | | |
| subjects affected / exposed | 4 / 35 (11.43%) | | |
| occurrences (all) | 5 | | |

| | | | |
|--|-----------------------|--|--|
| Nervous system disorders - other subjects affected / exposed occurrences (all) | 3 / 35 (8.57%) 3 | | |
| Blood and lymphatic system disorders Anemia subjects affected / exposed occurrences (all) | 8 / 35 (22.86%) 29 | | |
| Leukocytosis subjects affected / exposed occurrences (all) | 5 / 35 (14.29%) 7 | | |
| Lymph node pain subjects affected / exposed occurrences (all) | 1 / 35 (2.86%) 1 | | |
| Febrile neutropenia subjects affected / exposed occurrences (all) | 2 / 35 (5.71%) 2 | | |
| Ear and labyrinth disorders External ear inflammation subjects affected / exposed occurrences (all) | 1 / 35 (2.86%) 1 | | |
| Vertigo subjects affected / exposed occurrences (all) | 1 / 35 (2.86%) 3 | | |
| Eye disorders Blurred vision subjects affected / exposed occurrences (all) | 1 / 35 (2.86%) 1 | | |
| Conjunctivitis subjects affected / exposed occurrences (all) | 1 / 35 (2.86%) 1 | | |
| Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) | 3 / 35 (8.57%) 6 | | |
| Constipation subjects affected / exposed occurrences (all) | 6 / 35 (17.14%) 7 | | |

| | | | |
|--|------------------|--|--|
| Diarrhea | | | |
| subjects affected / exposed | 11 / 35 (31.43%) | | |
| occurrences (all) | 27 | | |
| Dry mouth | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences (all) | 1 | | |
| Dyspepsia | | | |
| subjects affected / exposed | 3 / 35 (8.57%) | | |
| occurrences (all) | 3 | | |
| Gastric ulcer | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences (all) | 1 | | |
| Gastroesophageal reflux disease | | | |
| subjects affected / exposed | 3 / 35 (8.57%) | | |
| occurrences (all) | 4 | | |
| Hemorrhoids | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences (all) | 1 | | |
| Mucositis oral | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences (all) | 4 | | |
| Nausea | | | |
| subjects affected / exposed | 3 / 35 (8.57%) | | |
| occurrences (all) | 3 | | |
| Toothache | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences (all) | 1 | | |
| Vomiting | | | |
| subjects affected / exposed | 4 / 35 (11.43%) | | |
| occurrences (all) | 5 | | |
| Gastrointestinal disorders - other | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences (all) | 3 | | |
| Skin and subcutaneous tissue disorders | | | |
| Palmar-plantar erythrodysesthesia syndrome | | | |

| | | | |
|--|------------------|--|--|
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences (all) | 1 | | |
| Alopecia | | | |
| subjects affected / exposed | 3 / 35 (8.57%) | | |
| occurrences (all) | 4 | | |
| Dry skin | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences (all) | 1 | | |
| Erythema multiforme | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences (all) | 1 | | |
| Erythroderma | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences (all) | 2 | | |
| Pruritus | | | |
| subjects affected / exposed | 5 / 35 (14.29%) | | |
| occurrences (all) | 5 | | |
| Rash maculo-papular | | | |
| subjects affected / exposed | 11 / 35 (31.43%) | | |
| occurrences (all) | 18 | | |
| Skin induration | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences (all) | 1 | | |
| Hirsutism | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences (all) | 1 | | |
| Skin ulceration | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences (all) | 2 | | |
| Skin and subcutaneous tissue disorders - other | | | |
| subjects affected / exposed | 4 / 35 (11.43%) | | |
| occurrences (all) | 5 | | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 5 / 35 (14.29%) | | |
| occurrences (all) | 5 | | |
| Chronic kidney disease | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences (all) | 1 | | |
| Urinary retention | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences (all) | 1 | | |
| Endocrine disorders | | | |
| Endocrine disorders - other | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences (all) | 1 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Muscle weakness lower limb | | | |
| subjects affected / exposed | 2 / 35 (5.71%) | | |
| occurrences (all) | 2 | | |
| Back pain | | | |
| subjects affected / exposed | 5 / 35 (14.29%) | | |
| occurrences (all) | 8 | | |
| Myalgia | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences (all) | 1 | | |
| Neck pain | | | |
| subjects affected / exposed | 2 / 35 (5.71%) | | |
| occurrences (all) | 2 | | |
| Musculoskeletal and connective tissue disorders - other | | | |
| subjects affected / exposed | 2 / 35 (5.71%) | | |
| occurrences (all) | 4 | | |
| Infections and infestations | | | |
| Lung infection | | | |
| subjects affected / exposed | 2 / 35 (5.71%) | | |
| occurrences (all) | 3 | | |
| Upper respiratory infection | | | |
| subjects affected / exposed | 3 / 35 (8.57%) | | |
| occurrences (all) | 5 | | |
| Nail infection | | | |

| | | | |
|-------------------------------------|------------------|--|--|
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences (all) | 1 | | |
| Sepsis | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences (all) | 1 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 3 / 35 (8.57%) | | |
| occurrences (all) | 5 | | |
| Wound infection | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences (all) | 1 | | |
| Infections and infestations - other | | | |
| subjects affected / exposed | 6 / 35 (17.14%) | | |
| occurrences (all) | 12 | | |
| Metabolism and nutrition disorders | | | |
| Hypercalcemia | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences (all) | 4 | | |
| Anorexia | | | |
| subjects affected / exposed | 13 / 35 (37.14%) | | |
| occurrences (all) | 15 | | |
| Dehydration | | | |
| subjects affected / exposed | 3 / 35 (8.57%) | | |
| occurrences (all) | 3 | | |
| Hyperglycemia | | | |
| subjects affected / exposed | 8 / 35 (22.86%) | | |
| occurrences (all) | 12 | | |
| Hyperkalemia | | | |
| subjects affected / exposed | 3 / 35 (8.57%) | | |
| occurrences (all) | 3 | | |
| Hyperuricemia | | | |
| subjects affected / exposed | 3 / 35 (8.57%) | | |
| occurrences (all) | 3 | | |
| Hypoalbuminemia | | | |
| subjects affected / exposed | 7 / 35 (20.00%) | | |
| occurrences (all) | 12 | | |

| | | | |
|--|-----------------|--|--|
| Hypocalcemia | | | |
| subjects affected / exposed | 2 / 35 (5.71%) | | |
| occurrences (all) | 6 | | |
| Hypoglycemia | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences (all) | 1 | | |
| Hypokalemia | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences (all) | 1 | | |
| Hypomagnesemia | | | |
| subjects affected / exposed | 4 / 35 (11.43%) | | |
| occurrences (all) | 5 | | |
| Hyponatremia | | | |
| subjects affected / exposed | 5 / 35 (14.29%) | | |
| occurrences (all) | 11 | | |
| Hypophosphatemia | | | |
| subjects affected / exposed | 3 / 35 (8.57%) | | |
| occurrences (all) | 5 | | |
| Metabolism and nutrition disorders - other | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences (all) | 3 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 29 October 2013 | Clarifications of the eligibility assessments; the addition of radionuclide GFR assessment to the ARSAC information and the correction of spelling and typographical errors. |
| 21 March 2014 | This amendment contained: <ul style="list-style-type: none">• Change to dose rounding• Addition of serum amylase and lipase measurements• Addition of acute pancreatitis information• Increased duration of contraception usage required for patients and their partners |
| 28 April 2014 | This amendment covered the addition of 2 study sites and a change of PI at a current site. |
| 28 August 2014 | The RSI for the BREVITY trial was updated to reflect new information provided in the SPC. This was reported in the DSUR submitted on 01-August-14. The new information provided added pancreatitis, pulmonary toxicity, sepsis, septic shock and ALT/AST increase as new expected side effects and an extension to the period in which contraception should be used to 6 months after treatment. The Patient Information Sheet/Informed Consent Form was updated accordingly. |
| 04 November 2014 | Amendment was made to allow patients to continue on trial treatment if they had a partial response, and the addition of an extra PET scan for these patients. In addition several small changes were made to update the trial to the new lymphoma response criteria and to reduce the AE reporting. |
| 23 July 2015 | The BREVITY trial submitted this amendment in order to clarify the IMP processing for the trial following new information received and discussion with the MHRA pharmacist. No other changes were made to the trial. |
| 19 January 2016 | Amendment concerned the change of PI at an existing BREVITY site. |
| 30 November 2016 | Amendment resolved an inconsistency in end of trial definition on the NHS REC form and MHRA medicines (EudraCT application form). These have been amended bringing them in line with current practices. |
| 09 April 2018 | An update to the follow-up period; reducing the follow-up period from 5 to 2 years. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported