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 antimictrotubule 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 Leukoencephalpathy.

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

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

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

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

Diarrhea subjects affected / exposed occurrences (all)	11 / 35 (31.43%) 27		
Dry mouth subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1		
Dyspepsia subjects affected / exposed occurrences (all)	3 / 35 (8.57%) 3		
Gastric ulcer subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1		
Gastroesophageal reflux disease subjects affected / exposed occurrences (all)	3 / 35 (8.57%) 4		
Hemorrhoids subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1		
Mucositis oral subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 4		
Nausea subjects affected / exposed occurrences (all)	3 / 35 (8.57%) 3		
Toothache subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1		
Vomiting subjects affected / exposed occurrences (all)	4 / 35 (11.43%) 5		
Gastrointestinal disorders - other subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 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 occurrences (all)	2 / 35 (5.71%) 6		
Hypoglycemia subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1		
Hypokalemia subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1		
Hypomagnesemia subjects affected / exposed occurrences (all)	4 / 35 (11.43%) 5		
Hyponatremia subjects affected / exposed occurrences (all)	5 / 35 (14.29%) 11		
Hypophosphatemia subjects affected / exposed occurrences (all)	3 / 35 (8.57%) 5		
Metabolism and nutrition disorders - other subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 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: • 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