Clinical trial results:
Phase II Single Agent Lenalidomide (Revlimid) in Relapsed / Refratory Mantle Cell Lymphoma.

Summary

EudraCT number	2007-005472-13
Trial protocol	GB
Global end of trial date	16 December 2016

Results information

Result version number	v1 (current)
This version publication date	21 September 2019
First version publication date	21 September 2019

Trial information

Trial identification

Sponsor protocol code	Ply-5013

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	IRAS number: 4140, REC reference: 08/H0203/152

Notes:

Sponsors

Sponsor organisation name	University Hospitals Plymouth NHS Trust (formerly Plymouth Hospitals NHS Trust)
Sponsor organisation address	Research Office, L2 MSCP, Bircham Park Offices, 1 Roscoff Rise, Derriford, Plymouth, United Kingdom, PL6 5FP
Public contact	Dr Chris Rollinson, Research Governance Manager, University Hospitals Plymouth NHS Trust, Research Development and Innovation, 01752 432842, c.rollinson@nhs.net
Scientific contact	Prof Simon Rule, Consultant Haematologist, University Hospitals Plymouth NHS Trust, Haematology Department, 01752 517505, simon.rule@nhs.net

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	31 March 2010
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 March 2010
Global end of trial reached?	Yes
Global end of trial date	16 December 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the rates of overall response to lenalidomide in terms of complete response, complete response unconfirmed and partial response

Protection of trial subjects:

The study is approved by the MHRA and the South West - Cornwall & Plymouth (formerly Cornwall and Plymouth) Research Ethics Committee (NRES). 20% source data verification, as well as 100% verification of patient consent and central monitoring of data was carried out throughout the trial. Study monitoring is conducted by Peninsula CTU (Pen CTU).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 November 2008
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: 26
Worldwide total number of subjects	26
EEA total number of subjects	26

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)	9
From 65 to 84 years	17

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study population will comprise of patients with refractory mantle cell lymphoma and patients who have relapsed after completion of two or more treatment regimens.

Pre-assignment

Screening details:

Screening assessments (medical history, previous lymphoma history, date of diagnosis, prior treatment & responses, date & duration of responses, other significant illnesses); Demographics; Physical examination; CT scan (neck, thorax abdomen & pelvis); Bone marrow tests; Blood tests; ECG (heart trace); Pregnancy tests (all female patients).

Pre-assignment period milestones

Number of subjects started	26
Number of subjects completed	26

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Lenalidomide
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Lenalidomide
Investigational medicinal product code	
Other name	Revlimid
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants were enrolled on a dose of 25mg per day for 21 days in a 28 day cycle for six cycles, then reduce to 15mg per day for 21 out of 28 days for a maintenance period.

Number of subjects in period 1	Lenalidomide
Started	26
Completed	15
Not completed	11
Consent withdrawn by subject	2
Adverse events	4
Withdrew due to progressive disease	5

Baseline characteristics

Reporting groups	
Reporting group title	Lenalidomide

Reporting group description: -

Reporting group values	Lenalidomide	Total	
Number of subjects	26	26	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
median	66		
full range (min-max)	45 to 81	-	
Gender categorical Units: Subjects			
Female	7	7	
Male	19	19	
Ann Arbor stage			
At study entry.			
Units: Subjects			
III-IV	26	26	
Bone marrow involvement? Y/N			
At study entry.			
Units: Subjects			
Yes	14	14	
No	12	12	
Lymphocytosis? Y/N			
At study entry.			
Units: Subjects			
Yes	8	8	
No	18	18	
Blastic histology? Y/N Units: Subjects			
Yes	4	4	
No	22	22	
ECOG (Performance Status) Units: Subjects			

Grade 0	11	11	
Grade 1	11	11	
Grade 2	4	4	
Prior therapy: Rituximab (Y/N) Units: Subjects			
Yes	19	19	
No	7	7	
Prior therapy: Bortezomib (Y/N) Units: Subjects			
Yes	8	8	
No	18	18	
Prior therapy: Thalidomide (Y/N) Units: Subjects			
Yes	2	2	
No	24	24	
Prior therapy: Stem cell transplantation (Y/N) Units: Subjects			
Yes	6	6	
No	20	20	
Prior therapy: Purine analogue (Y/N) Units: Subjects			
Yes	19	19	
No	7	7	
Prior therapy: Anthracycline (Y/N) Units: Subjects			
Yes	18	18	
No	8	8	
Prior therapy: Alkylating agent (Y/N) Units: Subjects			
Yes	25	25	
No	1	1	
Refractory to last treatment Units: Subjects			
Refractory	6	6	
Not refractory	20	20	
Time from diagnosis Units: Years			
median	3.9		
full range (min-max)	0.3 to 12.9	-	
Prior therapies Units: Number			
median	3		
full range (min-max)	2 to 7	-	

End points

End points reporting groups

Reporting group title	Lenalidomide

Reporting group description: -

Primary: Overall Response Rate (ORR)

End point title	Overall Response Rate (ORR)[1]

End point description:

The primary endpoint was ORR, defined as the proportion of patients with partial response (PR), complete response unconfirmed (CRu), or complete response (CR).

End point type	Primary

End point timeframe:

Response assessments - study visits took place at the beginning of each cycle. Response was evaluated using International Working Group criteria for NHL after 3 and 6 cycles of lenalidomide, and thereafter as clinically indicated.

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: The statistical analyses data was not available to the EudraCT Data Inputter. However, the statistical analysis and results have been published. A link to the publication is provided in the 'Online references' section.

End point values	Lenalidomide			
Subject group type	Reporting group			
Number of subjects analysed	26			
Units: Months				
median (confidence interval 95%)	22.2 (0.0 to 53.6)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

PI's make initial report describing the event and possible causality, to coordinating centre, within 24 hours. Initial reports must be followed by more detailed information as soon as it becomes available.

Adverse event reporting additional description:

PI to sign/date SAEs reported. In PI's absence a designated medically qualified person may sign report, but PI to countersign on return. Countersigned form must be sent to trial coordinator ASAP. Notifications for MHRA/ REC are generated from these reports. All investigators will receive SAEs/SUSARS notifications occurring during the study.

Assessment type	Systematic

Dictionary used

Dictionary name	None
Dictionary version	0

Reporting groups

Reporting group title	Lenalidomide

Reporting group description: -

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: The non-serious adverse events data was not available to the EudraCT Data Inputter.

Serious adverse events	Lenalidomide		
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 26 (61.54%)		
number of deaths (all causes)	5		
number of deaths resulting from adverse events	4		
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
General disorders and administration site conditions			
Spleen disorder	Additional description: Left loin pain, possible tumour flare - enlarged spleen.		
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Fatigue	Additional description: Increased pain from leg lesion.		
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Febrile infection	Additional description: Febrile illness following flu vaccination.		

subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pain	Additional description: Abdominal and back pain - general deterioration in condition.		
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Thrombocytopenia	Additional description: Thrombocytopenia and deterioration in condition.		
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Pyrexia			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Pancytopenia			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	3 / 26 (11.54%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 2		
Neutropenia			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Neutropenic sepsis			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			

Vomiting	Additional description: Vomiting and dehydration.		
subjects affected / exposed	2 / 26 (7.69%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	3 / 26 (11.54%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pneumonia			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 1		
Plural effusion			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Dyspnea			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Respiratory tract infection			
subjects affected / exposed	4 / 26 (15.38%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 1		
Cough			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		

Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Laryngitis	Additional description: Grade 3		
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory tract infection			
subjects affected / exposed	3 / 26 (11.54%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	1 / 1		
Neutropenic sepsis			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Lenalidomide		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 26 (0.00%)		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 May 2009	Protocol V2, 12 Mar 2009: Changes in the information regarding adverse reactions associated with Lenalidomide supplied by Celgene Ltd following publication of an updated IB. Most significant are: Tumour Lysis Syndrome, Tumour Flare Reaction, Allergic reactions (angioedema & serious dermatological reactions).
25 March 2010	Protocol V3, 6 Jan 2010: Changes in the information regarding adverse reactions associated with Lenalidomide supplied by Celgene Ltd following publication of an updated IB. Addition to the exclusion criteria and changes to the dose modification for haematological toxicity in cycles one and two.
24 December 2010	Protocol V4, 4 Oct 2010: Following a review by the Data Monitoring Committee a change has been made in the dosing schedule for the patients enrolled. The haematological entry criteria was also changed to allow patients with a previous treatment related compromised bone marrow to be enrolled into the trial. Increase the recruitment target by a further 10 participants as the initial recruitment target of 25 has been reached. Finally, changes to the dose modification for haematology toxicity in line with the changes to the dosing schedule.
17 August 2011	Protocol V5, 20 Jun 2011: Change to the entry criterion, in relation to platelet counts and the number of previous therapies the potential patients need to be eligible. Request for the addition of two biopsies to assess the mechanisms of the actions of Lenalidomide and the potential for biomarkers to be isolated. As a result of a revised IB, the protocol has been updated with two additional warnings and precautions.
12 December 2011	Protocol V6, 19 Oct 2011: Information relating to the potential for Lenalidomide to increase the patients risk of developing a second cancer. Change in the drug supply process and a change to the drug labels.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/22881386