Clinical trial results:
Phase II trial of ofatumumab, dexamethasone and lenalidomide for high-risk CLL (NCRI CLL210).

Summary

EudraCT number	2010-019575-29
Trial protocol	GB
Global end of trial date	07 April 2017

Results information

Result version number	v2 (current)
This version publication date	27 June 2019
First version publication date	27 July 2018
Version creation reason	• New data added to full data set An MHRA audit found that some SAES were downgraded from possibly related to not related following communication with the CI without evidence of clear clinical rationale. A review of downgraded SUSARs was carried out by the PV committee. One of the CLL210 SAEs was downgraded without clinical justification for the downgrade. This requires an update to the SAE dataset
Summary attachment (see zip file)	CLL210 Final Study Report (resubmitted CLL210_Final Clinical Trial Report.pdf)

Trial information

Trial identification

Sponsor protocol code	CLL210 Version 10.1

Additional study identifiers

ISRCTN number	ISRCTN40303610
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Liverpool
Sponsor organisation address	Brownlow Street, Liverpool, United Kingdom, L69 3GL
Public contact	Michael Stackpoole, Liverpool Cancer Trials Unit, 0151 795 7321, mstack@liverpool.ac.uk
Scientific contact	Dr Mel Oates, Molecular and Clinical Cancer Medicine, 0151 706 4845, melly@liv.ac.uk
Sponsor organisation name	Royal Liverpool and Broadgreen University Hospitals NHS Trust
Sponsor organisation address	Prescot Street, Liverpool, United Kingdom, L7 8XP
Public contact	Michael Stackpoole, Liverpool Clinical Trials Unit, 0151 7957321, mstack@liverpool.ac.uk
Scientific contact	Dr Mel Oates, Molecular and Clinical Cancer Medicine, 0151 7064845, melly@liv.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	12 June 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 April 2017
Global end of trial reached?	Yes
Global end of trial date	07 April 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the safety and efficacy of combination induction therapy with ofatumumab, dexamethasone and lenalidomide in patients with high-risk CLL.

Primary:
- CR\CRi and tolerance rate (absence of Grade 3+ infection and no treatment related death) after 6m induction therapy.

Secondary:
- Overall, complete and partial response rates following induction therapy
- Minimal residual disease negativity rate following induction therapy
- Overall survival (from start of study treatment to death)
- PFS (from initiation of study treatment to progression or death)
- Time to treatment failure (from initiation of study treatment to treatment failure defined as progression, death or initiation of alternative treatment due to failure to achieve CR or PR)
- Duration of response (from first achievement of CR or PR to first time of progression or death)
- Toxicity
- Quality of life
- Descriptive summary of PFS and overall survival among transplant-eligible patients

Protection of trial subjects:

Central and on-site monitoring was conducted to help protect patients and to monitor performance relating to trial procedures, trial intervention administration and laboratory/data collection processes. A risk assessment was carried out to determine the level of monitoring required, and subsequently a monitoring plan was developed to document how and when monitoring is conducted and to what extent. Patient safety was also monitored via LCTU pharmacovigilance procedures (reporting and review of adverse event data) and by an ISDMC.

A Trial Management Group regularly reviewed central monitoring reports and advised accordingly.

Following completion of study treatment, routine follow-up assessments were planned every 2 months until disease progression, second-line induction therapy initiated, or until 12 months after the last patient recruited into the study completed induction treatment, whichever was earliest.

Serious adverse events were followed-up until resolution or death.

Annual safety reports were submitted to the national regulatory authorities.

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	06 February 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	6 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 64
Worldwide total number of subjects	64
EEA total number of subjects	64

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)	26
From 65 to 84 years	37
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The CLL210 trial recruited 64 NHS patients from 19 centres across England, Scotland and Wales between 23/01/2012 and 31/10/2015.

Pre-assignment

Screening details:

64 of the 92 patients screened were recruited to the study. Patients provided consent and then a series of screening assessments were performed to determine eligibility, within 42 days prior to the first study treatment.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Baseline

Arm description:

Single arm study followed by randomisation to maintenance treatment/no maintenance treatment for responders.

- Initially the induction treatment regimen included Alemtuzumab instead of Ofatumumab and a subsequent randomisation to lenalidomide maintenance or no further treatment for eligible patients (2 years follow-up). The study was planned to recruit 85 patients but only 16 were recruited before Alemtuzumab was withdrawn. All 16 patients received treatment and were followed-up as per protocol.
- Alemtuzumab was replaced by Ofatumumab; the study was re-initiated with the same design, statistical considerations and recruitment target; 85 more patients were planned to be recruited.
- Recruitment target was reduced to 50 patients resulting in new statistical considerations (increased type I error rate).
- Randomised part of the study was dropped due to very few patients being eligible and follow-up reduced to one instead of two years. This affected only the last two patients.

Arm type	Experimental
Investigational medicinal product name	Alemtuzumab
Investigational medicinal product code	ATC Code: L04AA34
Other name	Campath, MabCampath, Lemtrada
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Prior to its withdrawal, alemtuzumab was sourced commercially by each study centre. Alemtuzumab was administered intravenously in clinic to patients being monitored by research staff.

Alemtuzumab 30mg sc, three times a week, weeks 7-22

Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Dexamethasone was sourced commercially by each study centre, biosimilar products were permitted and could be labelled and stored according to local practice.

Dexamethasone 40mg, po, od, days 1-4, weeks 1, 3, 5, 7, 9, 11, 13, 15

Investigational medicinal product name	Lenalidomide
Investigational medicinal product code	ATC Code: L04AX04
Other name	Revlimid
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Lenalidomide was provided free by Celgene for the CLL210 trial in the form of hard capsules of Revlimid; 5mg and 10mg capsules with an excipient of 147mg and 294mg of anhydrous lactose respectively. Stock was ordered from Celgene, via the LCTU using controlled documentation, and delivered direct to site.

Lenalidomide 5mg, od (weeks 3-4), 10mg od (weeks 5-24)

Investigational medicinal product name	Ofatumumab
Investigational medicinal product code	ATC Code: L01XC10
Other name	Arzerra
Pharmaceutical forms	Solution for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Ofatumumab was supplied free of charge to study centres by GlaxoSmithKline UK (100mg and 1000mg vials for IV infusion).

Ofatumumab 300mg IV day 1 week 7, 1000mg IV d1 weeks 8-15, 17, 19, 21.

Number of subjects in period 1	Baseline
Started	64
Completed	64

Period 2

Period 2 title	Induction Therapy
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Induction therapy

Arm description:

- Initially the induction treatment regimen included Alemtuzumab instead of Ofatumumab and a subsequent randomisation to lenalidomide maintenance or no further treatment for eligible patients (2 years follow-up). The study was planned to recruit 85 patients but only 16 were recruited before Alemtuzumab was withdrawn. All 16 patients received treatment and were followed-up as per protocol.
- Alemtuzumab was replaced by Ofatumumab; the study was re-initiated with the same design, statistical considerations and recruitment target; 85 more patients were planned to be recruited.
- Recruitment target was reduced to 50 patients resulting in new statistical considerations (increased type I error rate).
- Randomised part of the study was dropped due to very few patients being eligible and follow-up reduced to one instead of two years. This affected only the last two patients recruited in the study.

Arm type	Experimental
Investigational medicinal product name	Alemtuzumab
Investigational medicinal product code	ATC Code: L04AA34
Other name	Campath, MabCampath, Lemtrada
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Prior to its withdrawal, alemtuzumab was sourced commercially by each study centre. Alemtuzumab was administered intravenously in clinic to patients being monitored by research staff.

Alemtuzumab 30mg sc, three times a week, weeks 7-22

Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Dexamethasone was sourced commercially by each study centre, biosimilar products were permitted and could be labelled and stored according to local practice.

Dexamethasone 40mg, po, od, days 1-4, weeks 1, 3, 5, 7, 9, 11, 13, 15

Investigational medicinal product name	Lenalidomide
Investigational medicinal product code	ATC Code: L04AX04
Other name	Revlimid
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Lenalidomide was provided free by Celgene for the CLL210 trial in the form of hard capsules of Revlimid; 5mg and 10mg capsules with an excipient of 147mg and 294mg of anhydrous lactose respectively. Stock was ordered from Celgene, via the LCTU using controlled documentation, and delivered direct to site.

Lenalidomide 5mg, od (weeks 3-4), 10mg od (weeks 5-24)

Investigational medicinal product name	Ofatumumab
Investigational medicinal product code	ATC Code: L01XC10
Other name	Arzerra
Pharmaceutical forms	Solution for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Ofatumumab was supplied free of charge to study centres by GlaxoSmithKline UK (100mg and 1000mg vials for IV infusion).

Ofatumumab 300mg IV day 1 week 7, 1000mg IV d1 weeks 8-15, 17, 19, 21.

Number of subjects in period 2	Induction therapy
Started	64
Completed	35
Not completed	29
Adverse event, serious fatal	6
Consent withdrawn by subject	2
Physician decision	1

Change of Diagnosis, and therefore ineligbile	1
Adverse event, non-fatal	3
Toxicity	4
Patient developed ITP at beginning of induction	1
Patient Decision	1
General Condition	1
Reason not known	1
Richters Transformation	1
Disease Progression	7

Period 3

Period 3 title	Maintenance Therapy
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Maintenance Treatment

Arm description:

Patient receive bi-monlthy Lenalidomide for 2 years

Arm type	Experimental
Investigational medicinal product name	Lenalidomide
Investigational medicinal product code	ATC Code: L04AX04
Other name	Revlimid
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

10mg capsules were taken orally, once per day. Patients were dipsensed 5mg and 10mg capsules for their own administration, and a durg diary was kept.

Arm title	No Further treatment

Arm description:

Patient do not receive any further treatment, but are followed up for quality of life and surivival data

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 3[1]	Maintenance Treatment	No Further treatment
Started	11	9
Completed	3	9
Not completed	8	0
Physician decision	1	-
Toxicity	1	-
Progressive Disease	4	-
Later elected for transplant, thus in eligible	1	-
New Primary Malignancy (AML)	1	-

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: The IMP for the study was changed due to the marketing authorisation being wdn for the study disease. Therefore, there are 2 cohorts (17, & 45) of pats listed for induction therapy; though elaborated as to why in the EUDRA-CT data & journal, it was reflected on the system as two inductions arms, even though induction wasn't bifurcated. Further, the maint arm was randomised & only pats who achieved a certain favourable response &had a test for a certain biomarker were eligible for lenalidomide

Baseline characteristics

Reporting groups	
Reporting group title	Baseline

Reporting group description: -

Reporting group values	Baseline	Total	
Number of subjects	64	64	
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)	26	26	
From 65-84 years	37	37	
85 years and over	1	1	
Age continuous Units: years			
median	66		
inter-quartile range (Q1-Q3)	59 to 70	-	
Gender categorical Units: Subjects			
Female	18	18	
Male	46	46	
WHO Performance status Units: Subjects			
PS 0	34	34	
PS 1	24	24	
PS 2	6	6	
Previous Treatment Units: Subjects			
No	29	29	
Yes	35	35	
TP53 defect Units: Subjects			
No	11	11	
Yes	53	53	
CIRS Total Score Units: CIRS Score			
median	2		
inter-quartile range (Q1-Q3)	1 to 4	-	
CIRS Severity Index Units: CIRS Index			
median	1		

inter-quartile range (Q1-Q3)	1 to 1.6	-	

End points

End points reporting groups

Reporting group title	Baseline

Reporting group description:

Single arm study followed by randomisation to maintenance treatment/no maintenance treatment for responders.

- Initially the induction treatment regimen included Alemtuzumab instead of Ofatumumab and a subsequent randomisation to lenalidomide maintenance or no further treatment for eligible patients (2 years follow-up). The study was planned to recruit 85 patients but only 16 were recruited before Alemtuzumab was withdrawn. All 16 patients received treatment and were followed-up as per protocol.
- Alemtuzumab was replaced by Ofatumumab; the study was re-initiated with the same design, statistical considerations and recruitment target; 85 more patients were planned to be recruited.
- Recruitment target was reduced to 50 patients resulting in new statistical considerations (increased type I error rate).
- Randomised part of the study was dropped due to very few patients being eligible and follow-up reduced to one instead of two years. This affected only the last two patients.

Reporting group title	Induction therapy

Reporting group description:

- Initially the induction treatment regimen included Alemtuzumab instead of Ofatumumab and a subsequent randomisation to lenalidomide maintenance or no further treatment for eligible patients (2 years follow-up). The study was planned to recruit 85 patients but only 16 were recruited before Alemtuzumab was withdrawn. All 16 patients received treatment and were followed-up as per protocol.
- Alemtuzumab was replaced by Ofatumumab; the study was re-initiated with the same design, statistical considerations and recruitment target; 85 more patients were planned to be recruited.
- Recruitment target was reduced to 50 patients resulting in new statistical considerations (increased type I error rate).
- Randomised part of the study was dropped due to very few patients being eligible and follow-up reduced to one instead of two years. This affected only the last two patients recruited in the study.

Reporting group title	Maintenance Treatment

Reporting group description:

Patient receive bi-monlthy Lenalidomide for 2 years

Reporting group title	No Further treatment

Reporting group description:

Patient do not receive any further treatment, but are followed up for quality of life and surivival data

Subject analysis set title	Intention to Treat
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All patients recruited into the study

Subject analysis set title	Per Protocol
Subject analysis set type	Per protocol

Subject analysis set description:

Patients with a major protocol deviation removed

Primary: CR/CRi after 6 months of induction therapy

End point title	CR/CRi after 6 months of induction therapy

End point description:

Number of patients reaaching the CR and CRi response criteria following induction therapy.

End point type	Primary

End point timeframe:

Induction therapy - 6 months

End point values	Induction therapy	Intention to Treat		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	47[1]	47[2]		
Units: subjects	2	2		

Notes:

[1] - 17 Patients unevaluable

[2] - 17 Patients unevaluable

Statistical analyses

Statistical analysis title	Complete response rate
Statistical analysis description: Estimate of CR/CRi rate with confidence intervals	
Comparison groups	Induction therapy v Intention to Treat
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	< 0.158
Method	Clopper-Pearsins exact confidence interc
Parameter estimate	Rate
Point estimate	0.043
Confidence interval	
level	Other: 68.4 %
sides	2-sided
lower limit	0.015
upper limit	0.096

Notes:

[3] - Estimation

Primary: Toleration of Therapy

End point title	Toleration of Therapy
End point description:	
End point type	Primary
End point timeframe: Induction period - 6 months	

End point values	Induction therapy	Intention to Treat		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	60[4]	60[5]		
Units: Subjects	27	27		

Notes:
[4] - 4 Unevaluable
[5] - 4 Unevaluable

Statistical analyses

Statistical analysis title	Toleration of therapy
Comparison groups	Induction therapy v Intention to Treat
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.164
Method	Clopper-Pearsins exact confidence interc
Parameter estimate	Rate
Point estimate	0.45
Confidence interval	
level	Other: 67.2 %
sides	2-sided
lower limit	0.38
upper limit	0.521

Secondary: Partial Response Rate

End point title	Partial Response Rate
End point description: Number of patients to achieve PR	
End point type	Secondary
End point timeframe: Induction Treatment - 6 months	

End point values	Induction therapy	Intention to Treat		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	47[6]	47		
Units: Number of	36	36		

Notes:
[6] - 17 unevaluable

Statistical analyses

No statistical analyses for this end point

Secondary: Minimal Residual Disease (MRD) negativity rate following induction therapy

End point title	Minimal Residual Disease (MRD) negativity rate following

	induction therapy

End point description:

The number of patients achieving MRD negativity following complete induction therapy (Measured at WK23 assessment bloods and Bone mrrwo aspirate).

End point type	Secondary

End point timeframe:

Induction Period

End point values	Induction therapy	Intention to Treat		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	24	24		
Units: Subjects	6	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (time from start of study treatment to death)

End point title	Overall survival (time from start of study treatment to death)

End point description:

2 years OS rate with OS defined as the time from recruitment until death by any cause.

End point type	Secondary

End point timeframe:

Duration of the study

End point values	Induction therapy	Intention to Treat		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	64	64		
Units: Time (Months)				
number (confidence interval 95%)	.63 (.52 to .77)	.63 (.52 to .77)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free survival (time from initaiton of study treatment to progression or death)

End point title	Progression-Free survival (time from initaiton of study treatment to progression or death)

End point description:

2 year PFS rate. PFS defined as the time from recruitment until disease progression or death by any cause

End point type	Secondary

End point timeframe:

Duration of Study

End point values	Induction therapy	Intention to Treat		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	64	64		
Units: Time (Months)				
number (confidence interval 95%)	.37 (.26 to .53)	.37 (.26 to .53)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to treatment failure

End point title	Time to treatment failure

End point description:

2 year TTF rate where TTF is defines as the time from recruitment to treatment failure, disease progression or death by any cause.

End point type	Secondary

End point timeframe:

Duration of Study

End point values	Induction therapy	Intention to Treat		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	64	64		
Units: Time (Months)				
number (confidence interval 95%)	.33 (.22 to .48)	.33 (.22 to .48)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate

End point title	Overall Response Rate

End point description:

Number of patients to obtain CR/PR

End point type	Secondary

End point timeframe:

Induction Period - 6 months

End point values	Induction therapy	Intention to Treat		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	47	47		
Units: Subjects	38	38		

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of Life

End point title	Quality of Life

End point description:

Quality of Life measures using the EQ5D QoL form

End point type	Secondary

End point timeframe:

During the induction phase of the study

End point values	Induction therapy	Intention to Treat		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	21	21		
Units: Subjects				
arithmetic mean (standard deviation)	.73 (± .19)	.73 (± .19)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AE/SAEs were reported from Informed Consent until 28 days after last dose of study treatment (or longer if felt to be a long-term side effect of study treatment). Secondary primary malignancies were reported for the duration of the study.

Adverse event reporting additional description:

Participating centres reported AE / SAE to the LCTU. Centres indicated whether there was a causal relationship in their view between the event and study drugs. A Clinical Coordinator then assessed the event on behalf of the Sponsor.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4

Reporting groups

Reporting group title	Alemtuzumab
Reporting group description: -	
Reporting group title	Ofatumumab

Reporting group description: -

Serious adverse events	Alemtuzumab	Ofatumumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 16 (87.50%)	29 / 48 (60.42%)	
number of deaths (all causes)	5	19	
number of deaths resulting from adverse events	1	7	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms benign, malignant, unspec (inc cysts, polyps) - Other			
subjects affected / exposed	3 / 16 (18.75%)	3 / 48 (6.25%)	
occurrences causally related to treatment / all	0 / 5	1 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vascular disorders			
Visceral arterial ischemia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haematoma			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Thromboembolic event			
subjects affected / exposed	0 / 16 (0.00%)	2 / 48 (4.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
General disorders, admin. site conditions - Other			
subjects affected / exposed	1 / 16 (6.25%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	0 / 16 (0.00%)	2 / 48 (4.17%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnea			
subjects affected / exposed	1 / 16 (6.25%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychosis			

subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Creatinine increased			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	1 / 16 (6.25%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders - Other			
subjects affected / exposed	2 / 16 (12.50%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	2 / 16 (12.50%)	3 / 48 (6.25%)	
occurrences causally related to treatment / all	1 / 3	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhea			

subjects affected / exposed	1 / 16 (6.25%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	2 / 16 (12.50%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Enterocolitis infectious			
subjects affected / exposed	1 / 16 (6.25%)	2 / 48 (4.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations - Other			
subjects affected / exposed	3 / 16 (18.75%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	1 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngitis			

subjects affected / exposed	1 / 16 (6.25%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	7 / 16 (43.75%)	11 / 48 (22.92%)	
occurrences causally related to treatment / all	4 / 8	5 / 13	
deaths causally related to treatment / all	0 / 0	1 / 2	
Sepsis			
subjects affected / exposed	5 / 16 (31.25%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	4 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	1 / 16 (6.25%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory infection			
subjects affected / exposed	1 / 16 (6.25%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	2 / 16 (12.50%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anorectal infection			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis infection			

subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Bronchial infection			
subjects affected / exposed	0 / 16 (0.00%)	2 / 48 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metabolism and nutrition disorders			
Hypercalcemia			
subjects affected / exposed	0 / 16 (0.00%)	2 / 48 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Alemtuzumab	Ofatumumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 16 (100.00%)	48 / 48 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms benign, malignant, unspec (inc cysts, polyps) - Other			
subjects affected / exposed	1 / 16 (6.25%)	2 / 48 (4.17%)	
occurrences (all)	2	2	
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Haematoma			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Hypertension			

subjects affected / exposed	0 / 16 (0.00%)	2 / 48 (4.17%)	
occurrences (all)	0	2	
Hot flashes			
subjects affected / exposed	1 / 16 (6.25%)	2 / 48 (4.17%)	
occurrences (all)	1	2	
Hypotension			
subjects affected / exposed	0 / 16 (0.00%)	2 / 48 (4.17%)	
occurrences (all)	0	2	
Thromboembolic event			
subjects affected / exposed	1 / 16 (6.25%)	3 / 48 (6.25%)	
occurrences (all)	1	3	
General disorders and administration site conditions			
Chills			
subjects affected / exposed	2 / 16 (12.50%)	1 / 48 (2.08%)	
occurrences (all)	2	1	
Edema face			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Edema limbs			
subjects affected / exposed	8 / 16 (50.00%)	6 / 48 (12.50%)	
occurrences (all)	13	7	
Fatigue			
subjects affected / exposed	5 / 16 (31.25%)	7 / 48 (14.58%)	
occurrences (all)	9	14	
Facial pain			
subjects affected / exposed	0 / 16 (0.00%)	3 / 48 (6.25%)	
occurrences (all)	0	3	
Fever			
subjects affected / exposed	4 / 16 (25.00%)	7 / 48 (14.58%)	
occurrences (all)	5	9	
Flu like symptoms			
subjects affected / exposed	2 / 16 (12.50%)	4 / 48 (8.33%)	
occurrences (all)	2	5	
Gait disturbance			

subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
General disorders, admin. site conditions - Other			
subjects affected / exposed	2 / 16 (12.50%)	2 / 48 (4.17%)	
occurrences (all)	2	4	
Infusion related reaction			
subjects affected / exposed	0 / 16 (0.00%)	4 / 48 (8.33%)	
occurrences (all)	0	5	
Localized edema			
subjects affected / exposed	2 / 16 (12.50%)	2 / 48 (4.17%)	
occurrences (all)	2	2	
Malaise			
subjects affected / exposed	1 / 16 (6.25%)	1 / 48 (2.08%)	
occurrences (all)	1	1	
Non-cardiac chest pain			
subjects affected / exposed	0 / 16 (0.00%)	2 / 48 (4.17%)	
occurrences (all)	0	2	
Multi-organ failure			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Pain			
subjects affected / exposed	1 / 16 (6.25%)	4 / 48 (8.33%)	
occurrences (all)	1	11	
Immune system disorders			
Autoimmune disorder			
subjects affected / exposed	2 / 16 (12.50%)	0 / 48 (0.00%)	
occurrences (all)	2	0	
Allergic reaction			
subjects affected / exposed	0 / 16 (0.00%)	2 / 48 (4.17%)	
occurrences (all)	0	3	
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Reproductive system and breast disorders - Other			

subjects affected / exposed	1 / 16 (6.25%)	0 / 48 (0.00%)	
occurrences (all)	1	0	
Prostatic obstruction			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	7 / 16 (43.75%)	9 / 48 (18.75%)	
occurrences (all)	16	17	
Atelectasis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Dyspnea			
subjects affected / exposed	6 / 16 (37.50%)	8 / 48 (16.67%)	
occurrences (all)	11	12	
Epistaxis			
subjects affected / exposed	3 / 16 (18.75%)	4 / 48 (8.33%)	
occurrences (all)	5	7	
Hiccups			
subjects affected / exposed	2 / 16 (12.50%)	2 / 48 (4.17%)	
occurrences (all)	4	2	
Hoarseness			
subjects affected / exposed	1 / 16 (6.25%)	1 / 48 (2.08%)	
occurrences (all)	1	1	
Hypoxia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	3	
Laryngeal inflammation			
subjects affected / exposed	2 / 16 (12.50%)	1 / 48 (2.08%)	
occurrences (all)	3	1	
Nasal congestion			
subjects affected / exposed	1 / 16 (6.25%)	0 / 48 (0.00%)	
occurrences (all)	1	0	
Pleural effusion			

subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Postnasal drip			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Productive cough			
subjects affected / exposed	1 / 16 (6.25%)	1 / 48 (2.08%)	
occurrences (all)	1	1	
Respiratory failure			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders - Other			
subjects affected / exposed	1 / 16 (6.25%)	0 / 48 (0.00%)	
occurrences (all)	1	0	
Sore throat			
subjects affected / exposed	2 / 16 (12.50%)	1 / 48 (2.08%)	
occurrences (all)	2	1	
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Confusion			
subjects affected / exposed	1 / 16 (6.25%)	1 / 48 (2.08%)	
occurrences (all)	1	1	
Anxiety			
subjects affected / exposed	0 / 16 (0.00%)	3 / 48 (6.25%)	
occurrences (all)	0	4	
Depression			
subjects affected / exposed	0 / 16 (0.00%)	4 / 48 (8.33%)	
occurrences (all)	0	5	
Euphoria			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Insomnia			

subjects affected / exposed	3 / 16 (18.75%)	10 / 48 (20.83%)	
occurrences (all)	4	10	
Mania			
subjects affected / exposed	0 / 16 (0.00%)	3 / 48 (6.25%)	
occurrences (all)	0	3	
Psychosis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	2	
Psychiatric disorders - Other, specify			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 16 (0.00%)	4 / 48 (8.33%)	
occurrences (all)	0	5	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 16 (0.00%)	3 / 48 (6.25%)	
occurrences (all)	0	4	
Alkaline phosphatase increased			
subjects affected / exposed	0 / 16 (0.00%)	3 / 48 (6.25%)	
occurrences (all)	0	9	
Blood bilirubin increased			
subjects affected / exposed	1 / 16 (6.25%)	2 / 48 (4.17%)	
occurrences (all)	7	27	
GGT increased			
subjects affected / exposed	1 / 16 (6.25%)	1 / 48 (2.08%)	
occurrences (all)	1	2	
Creatinine increased			
subjects affected / exposed	0 / 16 (0.00%)	5 / 48 (10.42%)	
occurrences (all)	0	14	
Investigations - Other, specify			
subjects affected / exposed	0 / 16 (0.00%)	4 / 48 (8.33%)	
occurrences (all)	0	9	
Neutrophil count decreased			

subjects affected / exposed	8 / 16 (50.00%)	20 / 48 (41.67%)	
occurrences (all)	20	86	
Platelet count decreased			
subjects affected / exposed	7 / 16 (43.75%)	11 / 48 (22.92%)	
occurrences (all)	27	58	
Urine output decreased			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
White blood cell decreased			
subjects affected / exposed	2 / 16 (12.50%)	0 / 48 (0.00%)	
occurrences (all)	29	0	
Weight loss			
subjects affected / exposed	2 / 16 (12.50%)	5 / 48 (10.42%)	
occurrences (all)	2	5	
Injury, poisoning and procedural complications			
Bruising			
subjects affected / exposed	4 / 16 (25.00%)	3 / 48 (6.25%)	
occurrences (all)	4	3	
Injury, poisoning, procedural complications - Other			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Fall			
subjects affected / exposed	0 / 16 (0.00%)	4 / 48 (8.33%)	
occurrences (all)	0	5	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Palpitations			
subjects affected / exposed	0 / 16 (0.00%)	2 / 48 (4.17%)	
occurrences (all)	0	2	
Ventricular fibrillation			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Nervous system disorders			

Concentration impairment			
subjects affected / exposed	0 / 16 (0.00%)	2 / 48 (4.17%)	
occurrences (all)	0	2	
Dizziness			
subjects affected / exposed	2 / 16 (12.50%)	6 / 48 (12.50%)	
occurrences (all)	2	11	
Depressed level of consciousness			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Dysarthria			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Dysgeusia			
subjects affected / exposed	4 / 16 (25.00%)	2 / 48 (4.17%)	
occurrences (all)	4	2	
Headache			
subjects affected / exposed	3 / 16 (18.75%)	3 / 48 (6.25%)	
occurrences (all)	4	5	
Neuralgia			
subjects affected / exposed	0 / 16 (0.00%)	2 / 48 (4.17%)	
occurrences (all)	0	2	
Lethargy			
subjects affected / exposed	3 / 16 (18.75%)	7 / 48 (14.58%)	
occurrences (all)	5	15	
Oculomotor nerve disorder			
subjects affected / exposed	1 / 16 (6.25%)	0 / 48 (0.00%)	
occurrences (all)	1	0	
Paresthesia			
subjects affected / exposed	2 / 16 (12.50%)	4 / 48 (8.33%)	
occurrences (all)	3	8	
Peripheral sensory neuropathy			
subjects affected / exposed	2 / 16 (12.50%)	3 / 48 (6.25%)	
occurrences (all)	2	4	
Sinus pain			
subjects affected / exposed	0 / 16 (0.00%)	2 / 48 (4.17%)	
occurrences (all)	0	2	

Presyncope			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Somnolence			
subjects affected / exposed	1 / 16 (6.25%)	0 / 48 (0.00%)	
occurrences (all)	1	0	
Spasticity			
subjects affected / exposed	1 / 16 (6.25%)	0 / 48 (0.00%)	
occurrences (all)	3	0	
Stroke			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Tremor			
subjects affected / exposed	4 / 16 (25.00%)	0 / 48 (0.00%)	
occurrences (all)	5	0	
Vasovagal reaction			
subjects affected / exposed	1 / 16 (6.25%)	0 / 48 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	5 / 16 (31.25%)	12 / 48 (25.00%)	
occurrences (all)	17	70	
Disseminated intravascular coagulation			
subjects affected / exposed	1 / 16 (6.25%)	0 / 48 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders - Other			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Febrile neutropenia			
subjects affected / exposed	1 / 16 (6.25%)	2 / 48 (4.17%)	
occurrences (all)	1	2	
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Haemolysis			

subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Leukocytosis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	2	
Lymph node pain			
subjects affected / exposed	0 / 16 (0.00%)	2 / 48 (4.17%)	
occurrences (all)	0	4	
Ear and labyrinth disorders			
Ear and labyrinth disorders - Other			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Hearing impaired			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Tinnitus			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Vertigo			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Eye disorders			
Blurred vision			
subjects affected / exposed	0 / 16 (0.00%)	2 / 48 (4.17%)	
occurrences (all)	0	2	
Eye disorders - Other, specify			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	2	
Retinal vascular disorder			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Optic nerve disorder			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	2 / 16 (12.50%)	2 / 48 (4.17%)	
occurrences (all)	2	5	
Anal pain			
subjects affected / exposed	0 / 16 (0.00%)	2 / 48 (4.17%)	
occurrences (all)	0	2	
Bloating			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Constipation			
subjects affected / exposed	3 / 16 (18.75%)	9 / 48 (18.75%)	
occurrences (all)	4	12	
Diarrhea			
subjects affected / exposed	12 / 16 (75.00%)	15 / 48 (31.25%)	
occurrences (all)	24	28	
Dry mouth			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Dyspepsia			
subjects affected / exposed	0 / 16 (0.00%)	3 / 48 (6.25%)	
occurrences (all)	0	5	
Flatulence			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Gastritis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Gastroesophageal reflux disease			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Gastrointestinal disorders - Other			
subjects affected / exposed	2 / 16 (12.50%)	4 / 48 (8.33%)	
occurrences (all)	2	5	
Lower Gastrointestinal hemorrhage			
subjects affected / exposed	1 / 16 (6.25%)	0 / 48 (0.00%)	
occurrences (all)	1	0	

Haemorrhoids			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Mucositis oral			
subjects affected / exposed	4 / 16 (25.00%)	3 / 48 (6.25%)	
occurrences (all)	7	4	
Nausea			
subjects affected / exposed	5 / 16 (31.25%)	10 / 48 (20.83%)	
occurrences (all)	7	17	
Oral dysesthesia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Oral pain			
subjects affected / exposed	0 / 16 (0.00%)	2 / 48 (4.17%)	
occurrences (all)	0	2	
Vomiting			
subjects affected / exposed	3 / 16 (18.75%)	6 / 48 (12.50%)	
occurrences (all)	5	13	
Toothache			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	1 / 16 (6.25%)	3 / 48 (6.25%)	
occurrences (all)	1	3	
Alopecia			
subjects affected / exposed	1 / 16 (6.25%)	2 / 48 (4.17%)	
occurrences (all)	1	2	
Hyperhidrosis			
subjects affected / exposed	5 / 16 (31.25%)	3 / 48 (6.25%)	
occurrences (all)	8	3	
Pain of skin			

subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Rash maculo-papular			
subjects affected / exposed	4 / 16 (25.00%)	3 / 48 (6.25%)	
occurrences (all)	5	4	
Rash Papular			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders - Other			
subjects affected / exposed	6 / 16 (37.50%)	7 / 48 (14.58%)	
occurrences (all)	17	10	
Skin ulceration			
subjects affected / exposed	1 / 16 (6.25%)	1 / 48 (2.08%)	
occurrences (all)	1	1	
Urticaria			
subjects affected / exposed	1 / 16 (6.25%)	2 / 48 (4.17%)	
occurrences (all)	2	2	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Cystitis noninfective			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Renal and urinary disorders - Other, specify			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Urinary frequency			
subjects affected / exposed	2 / 16 (12.50%)	0 / 48 (0.00%)	
occurrences (all)	2	0	
Urinary retention			
subjects affected / exposed	1 / 16 (6.25%)	1 / 48 (2.08%)	
occurrences (all)	1	1	
Urinary tract pain			

subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Endocrine disorders			
Cushingoid			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 16 (6.25%)	1 / 48 (2.08%)	
occurrences (all)	1	3	
Arthritis			
subjects affected / exposed	1 / 16 (6.25%)	1 / 48 (2.08%)	
occurrences (all)	2	7	
Back pain			
subjects affected / exposed	2 / 16 (12.50%)	5 / 48 (10.42%)	
occurrences (all)	2	7	
Bone pain			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Chest wall pain			
subjects affected / exposed	1 / 16 (6.25%)	0 / 48 (0.00%)	
occurrences (all)	1	0	
Generalized muscle weakness			
subjects affected / exposed	1 / 16 (6.25%)	0 / 48 (0.00%)	
occurrences (all)	3	0	
Joint range of motion decreased			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Muscle weakness lower limb			
subjects affected / exposed	3 / 16 (18.75%)	3 / 48 (6.25%)	
occurrences (all)	4	3	
Musculoskeletal, connective tissue disorder - Other			
subjects affected / exposed	4 / 16 (25.00%)	5 / 48 (10.42%)	
occurrences (all)	5	8	
Myalgia			

subjects affected / exposed	3 / 16 (18.75%)	1 / 48 (2.08%)	
occurrences (all)	6	1	
Neck pain			
subjects affected / exposed	1 / 16 (6.25%)	1 / 48 (2.08%)	
occurrences (all)	1	1	
Pain in extremity			
subjects affected / exposed	1 / 16 (6.25%)	4 / 48 (8.33%)	
occurrences (all)	3	6	
Infections and infestations			
Anorectal infection			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Bronchial infection			
subjects affected / exposed	2 / 16 (12.50%)	0 / 48 (0.00%)	
occurrences (all)	2	0	
Encephalitis infection			
subjects affected / exposed	1 / 16 (6.25%)	0 / 48 (0.00%)	
occurrences (all)	1	0	
Enterocolitis infectious			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Infections and infestations - Other			
subjects affected / exposed	9 / 16 (56.25%)	11 / 48 (22.92%)	
occurrences (all)	17	19	
Lung infection			
subjects affected / exposed	5 / 16 (31.25%)	6 / 48 (12.50%)	
occurrences (all)	5	7	
Mucosal infection			
subjects affected / exposed	3 / 16 (18.75%)	1 / 48 (2.08%)	
occurrences (all)	4	1	
Pharyngitis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 48 (0.00%)	
occurrences (all)	1	0	
Rash pustular			
subjects affected / exposed	1 / 16 (6.25%)	1 / 48 (2.08%)	
occurrences (all)	1	1	

Sepsis			
subjects affected / exposed	7 / 16 (43.75%)	4 / 48 (8.33%)	
occurrences (all)	9	4	
Skin infection			
subjects affected / exposed	2 / 16 (12.50%)	2 / 48 (4.17%)	
occurrences (all)	3	3	
Sinusitis			
subjects affected / exposed	1 / 16 (6.25%)	1 / 48 (2.08%)	
occurrences (all)	1	1	
Tooth infection			
subjects affected / exposed	1 / 16 (6.25%)	0 / 48 (0.00%)	
occurrences (all)	1	0	
Urinary tract infection			
subjects affected / exposed	0 / 16 (0.00%)	2 / 48 (4.17%)	
occurrences (all)	0	2	
Upper respiratory infection			
subjects affected / exposed	4 / 16 (25.00%)	15 / 48 (31.25%)	
occurrences (all)	6	36	
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	1 / 16 (6.25%)	5 / 48 (10.42%)	
occurrences (all)	1	5	
Dehydration			
subjects affected / exposed	1 / 16 (6.25%)	1 / 48 (2.08%)	
occurrences (all)	1	2	
Glucose intolerance			
subjects affected / exposed	0 / 16 (0.00%)	2 / 48 (4.17%)	
occurrences (all)	0	2	
Hypercalcemia			
subjects affected / exposed	0 / 16 (0.00%)	3 / 48 (6.25%)	
occurrences (all)	0	4	
Hyperglycemia			
subjects affected / exposed	4 / 16 (25.00%)	3 / 48 (6.25%)	
occurrences (all)	4	26	
Hyperkalemia			

subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	2	
Hypermagnesemia			
subjects affected / exposed	1 / 16 (6.25%)	1 / 48 (2.08%)	
occurrences (all)	1	1	
Hyperuricemia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Hypoalbuminemia			
subjects affected / exposed	1 / 16 (6.25%)	3 / 48 (6.25%)	
occurrences (all)	1	10	
Hypocalcemia			
subjects affected / exposed	1 / 16 (6.25%)	9 / 48 (18.75%)	
occurrences (all)	5	29	
Hypoglycemia			
subjects affected / exposed	1 / 16 (6.25%)	2 / 48 (4.17%)	
occurrences (all)	1	3	
Hypokalemia			
subjects affected / exposed	0 / 16 (0.00%)	7 / 48 (14.58%)	
occurrences (all)	0	29	
Hypomagnesemia			
subjects affected / exposed	1 / 16 (6.25%)	2 / 48 (4.17%)	
occurrences (all)	1	2	
Hyponatremia			
subjects affected / exposed	1 / 16 (6.25%)	3 / 48 (6.25%)	
occurrences (all)	1	8	
Hypophosphatemia			
subjects affected / exposed	0 / 16 (0.00%)	4 / 48 (8.33%)	
occurrences (all)	0	27	
Metabolism and nutrition disorders - Other			
subjects affected / exposed	2 / 16 (12.50%)	3 / 48 (6.25%)	
occurrences (all)	2	7	
Tumor lysis syndrome			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 March 2011	Changes made following REC and regulatory review of version 1: o Justification for the use of subcutaneous alemtuzumab added to section 3.2. o Alteration to maintenance phase: trial medication (and pharmacovigilance and follow-up) will continue until disease progression or death for any patients that have not progressed by the time of the primary analysis (2.5 years after the last patient has been recruited). It was intended that Revlimid would continue to be made available to those patients off-trial but they remained on-trial until progression. Changes made to sections 2, 8.4 and 10.1. • Miscellaneous spelling, punctuation and grammar corrections and other minor admin changes.
30 June 2011	• Changes made to translational research to bring it in line with another CLL trial with sample being collected by the UKCLL biobank o Section 7.4 updated to include details of collection of and tests to be performed on translational samples collected at baseline o Section 9.2.4 updated with details of how bone marrow trephine biopsies are to be processed centrally o Section 9.5 updated to emphasise that patients can consent to having baseline and sequential samples taken, or baseline samples only • Miscellaneous spelling, punctuation and grammar corrections and other minor administrative changes.
26 September 2011	• Changes made to contact details and list of TSC members. • Details of specific tests to be performed at study visits added to section 7.1 and section 9 • Added details regarding retention of bone marrow trephine samples for future research to section 7.4. • Updated links and references to CTCAE v4 (rather than v3 which was used previously) • Section 11 (Pharmacovigilance) updated to reflect move to on-line reporting of SAEs and AEs, and annual submission of Development Safety Update Report. • Replace QLQ C30 Questionnaire (Appendix E) with CLL210 Health & Quality of Life Questionnaire, and updated references in protocol. • Miscellaneous spelling, punctuation and grammar corrections and other minor admin changes.
09 February 2012	• Section 2 (and 6.2) - Extra qualification on exclusion criterion "Seropositivity for HIV, HCV or HBV (surface antigen and core antibody)" added. • Section 8.2.4 (and 8.4.4 and 8.5) - Allow sites to give alternative equivalent co-trimoxazole regimens according to local practice. • Section 8.2.4 - Changed days that patient should receive alendronic acid to 70mg on day 1 of weeks 1, 3, 5, 7, 9, 11, 13 and 15 of treatment, on advice from pharmacists. • Section 8.4.2 - Changed references from lenalidomide SPC to lenalidomide IB. • Miscellaneous spelling, punctuation and grammar corrections and other minor admin changes.

25 November 2012	• Changed study title to reflect substitution of alemtuzumab for ofatumumab. • Section 2. Clarified that an estimated 58 patients will be randomised to lenalidomide maintenance versus no further treatment (changed from 54). • Sections 2, 6.1. Qualified inclusion criterion relating to previous treatment episodes for CLL by adding "excluding chlorambucil-based regimen. • Sections 3.1, 3.2. - Rewritten study objectives and rationale and combined into new section. • Section 8 - Major updates to this section to reflect replacement of alemtuzumab with ofatumumab in induction treatment regimen. • Section 10.5.1 - Added futility analysis to stopping guidelines.
19 September 2013	• Update to contact details for Professor Andrew Pettitt and Dr Lukas Smolej • Dr Arvind Arumainathan added as co-investigator • Serum biochemistry assessments chloride, bicarbonate, γGT no longer required. Uric Acid required at baseline only. • Section 8.2.4, 8.4.4 LMW heparin can be given as an alternative to aspirin if patients at high risk of thrombosis.
27 November 2013	• Removed exclusion criterion "Hepatic impairment (serum bilirubin more than twice the upper limit of normal unless due to Gilbert's syndrome)" as already covered by another criterion. • Section 8.2 - Allow local investigators the discretion to extend tapering dexamethasone dose for patients who have steroid withdrawal symptoms, and to allow a tapering dose if patient had grade 3/4 steroid related toxicities prior to starting on study treatment. • Section 8.2.3.1 - Allow lenalidomide to be started and dose increased if low platelet and neutrophil counts are due to underlying CLL.
04 August 2014	• Section 6.1 - Removed the inclusion criterion "No more than 3 previous treatment episodes for CLL (excluding chlorambucil-based regiments)". • Section 9.6 - Added details of Genomics England 10,000 Genomes Project to sub-studies section.
27 October 2014	• Removed references to maintenance part of study from all parts of protocol (including in study title). • Change to protocol to reduce target recruitment from 85 to 50 and remove maintenance part of study. Affects sections 2, 5, 7.3, 8, 10, 12, 14.4.5 • Section 2, 6.2. Changes to the wording of the exclusion criterion relating to women of childbearing potential. • Section 8.5 Updates to the pregnancy prevention plan text. • Update to primary endpoints and major changes to section 10 (statistical considerations), as a result of the above changes. • Section 17.3 Change to timing of ISDMC meetings
07 August 2015	• Section 2, 6.2. Reverted final exclusion criterion to state that women of children bearing potential who do are "unable or unwilling to use adequate contraception from study start to one year after the last dose of protocol" are excluded from the study, instead of "study start to 28 days after the last dose of protocol" as in version 10.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date

11 September 2012	The Original Protocol of the CLL210 trial used Alexmtuzumab in the induction therapy. Marketing Authorisation for the indication of CLL was withdrawn and so the study suspended recruitment. The Study was then restarted using Ofatumumab instead. The study continued from restart to end of study declaration without any further interruption.	-

Notes:

Limitations and caveats

None reported