



Clinical trial results:

A phase III multicentre randomised clinical trial comparing rituximab with CHOP given every 14 days and rituximab with CHOP given every 21 days for the treatment of patients with newly diagnosed diffuse large B cell non-Hodgkin's lymphoma

Summary

EudraCT number	2004-002197-34
Trial protocol	GB
Global end of trial date	03 February 2017

Results information

Result version number	v1 (current)
This version publication date	12 August 2018
First version publication date	12 August 2018
Summary attachment (see zip file)	R-CHOP 14vs21 - The Lancet publication 22.04.2013 (RCHOP14 vs 21 paper Lancet 22.04.13.pdf)

Trial information

Trial identification

Sponsor protocol code	BRD/05/122
-----------------------	------------

Additional study identifiers

ISRCTN number	ISRCTN16017947
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University College London
Sponsor organisation address	Joint Research Office, Gower Street, London, United Kingdom, WC1E 6BT
Public contact	Public contact, CRUK and UCL Cancer Trials Centre, ctc.sponsor@ucl.ac.uk
Scientific contact	Scientific contact, CRUK and UCL Cancer Trials Centre, ctc.sponsor@ucl.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	15 February 2012
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	03 February 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the improvement in overall survival of rituximab combined with CHOP given every 14 days (R-CHOP 14) in comparison to rituximab with CHOP given every 21 days (R-CHOP 21).

Protection of trial subjects:

CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) given every 21 days (CHOP-21) has been considered as standard care for all patients with DLBCL for 40 years. Although one arm of the trial altered this regimen to every 14 days, there was anticipated to be little impact on patient safety. Patients were closely monitored for toxicity and the protocol continuation criterion for therapy and dose modification. Supporting medication, lenograstim 263mg/day sc d4-12 was administered if a patient had a BSA < 1.8m² OR 368mg/day sc d4-12 if the BSA was >1.8m². The protocol detailed information on pre-medication and supportive medication for Rituximab.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 March 2005
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: 1080
Worldwide total number of subjects	1080
EEA total number of subjects	1080

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)	679
From 65 to 84 years	399

85 years and over	2
-------------------	---

Subject disposition

Recruitment

Recruitment details:

First patient recruited: 14-MAR-2005

Last patient recruited: 13-NOV-2008

1080 patients recruited across 119 UK sites.

Pre-assignment

Screening details:

Patients were screened for eligibility for inclusion into the study as per the trial protocol and as summarised in the manuscript.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	R-CHOP 14

Arm description:

Six cycles of R-CHOP (Cyclophosphamide 750mg/m², Doxorubicin 50mg/m², Vincristine 2mg, Prednisolone 100mg, Rituximab 375mg/m²) every 14 days (1 cycle). After 6 cycles, two additional infusions of rituximab were given two weeks apart at a dose of 375mg/m² each. This was to ensure equal number of rituximab infusions were given in both arms of the study.

Arm type	Experimental
Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	L01AA01
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Given as part of the following regimen:

R-CHOP 14 (cycle repeats every 14 days for 6 cycles) + Rituximab given for 2 further cycles

Rituximab: 375mg/m² iv day 1

Cyclophosphamide: 750mg/m² iv day 1

Doxorubicin: 50mg/m² iv day 1

Vincristine: 2mg iv day 1

Prednisolone: 100 mg po days 1 to 5

Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	L01DB01
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Given as part of the following regimen:

R-CHOP 14 (cycle repeats every 14 days for 6 cycles) + Rituximab given for 2 further cycles

Rituximab: 375mg/m² iv day 1

Cyclophosphamide: 750mg/m² iv day 1

Doxorubicin: 50mg/m² iv day 1

Vincristine: 2mg iv day 1

Prednisolone: 100 mg po days 1 to 5

Investigational medicinal product name	Vincristine
Investigational medicinal product code	L01CA02
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Given as part of the following regimen:

R-CHOP 14 (cycle repeats every 14 days for 6 cycles) + Rituximab given for 2 further cycles

Rituximab: 375mg/m² iv day 1

Cyclophosphamide: 750mg/m² iv day 1

Doxorubicin: 50mg/m² iv day 1

Vincristine: 2mg iv day 1

Prednisolone: 100 mg po days 1 to 5

Investigational medicinal product name	Rituximab
Investigational medicinal product code	L01XC02
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Given as part of the following regimen:

R-CHOP 14 (cycle repeats every 14 days for 6 cycles) + Rituximab given for 2 further cycles

Rituximab: 375mg/m² iv day 1

Cyclophosphamide: 750mg/m² iv day 1

Doxorubicin: 50mg/m² iv day 1

Vincristine: 2mg iv day 1

Prednisolone: 100 mg po days 1 to 5

Investigational medicinal product name	Prednisolone
Investigational medicinal product code	A07EA01
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Given as part of the following regimen:

R-CHOP 14 (cycle repeats every 14 days for 6 cycles) + Rituximab given for 2 further cycles

Rituximab: 375mg/m² iv day 1

Cyclophosphamide: 750mg/m² iv day 1

Doxorubicin: 50mg/m² iv day 1

Vincristine: 2mg iv day 1

Prednisolone: 100 mg po days 1 to 5

Arm title	R-CHOP 21
------------------	-----------

Arm description:

Six cycles of R-CHOP (Cyclophosphamide 750mg/m², Doxorubicin 50mg/m², Vincristine 1.4mg/m², Prednisolone 40mg/m², Rituximab 375mg/m²) every 21 days (1 cycle). After 6 cycles, two additional infusions of rituximab were given three weeks apart at a dose of 375mg/m² each. This was to ensure equal number of rituximab infusions were given in both arms of the study.

Arm type	Active comparator
Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	L01AA01
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Given as part of the following regimen:

R-CHOP 21 (cycle repeats every 21 days for 6 cycles) + Rituximab given for 2 further cycles.

Rituximab: 375mg/m2 iv day 1
 Cyclophosphamide: 750mg/m2 iv day 1
 Doxorubicin: 50mg/m2 iv day 1
 Vincristine: 1.4mg/m2 iv day 1
 Prednisolone: 40mg/m2 po days 1 to 5

Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	L01DB01
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Given as part of the following regimen:

R-CHOP 21 (cycle repeats every 21 days for 6 cycles) + Rituximab given for 2 further cycles.

Rituximab: 375mg/m2 iv day 1
 Cyclophosphamide: 750mg/m2 iv day 1
 Doxorubicin: 50mg/m2 iv day 1
 Vincristine: 1.4mg/m2 iv day 1
 Prednisolone: 40mg/m2 po days 1 to 5

Investigational medicinal product name	Vincristine
Investigational medicinal product code	L01CA02
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Given as part of the following regimen:

R-CHOP 21 (cycle repeats every 21 days for 6 cycles) + Rituximab given for 2 further cycles.

Rituximab: 375mg/m2 iv day 1
 Cyclophosphamide: 750mg/m2 iv day 1
 Doxorubicin: 50mg/m2 iv day 1
 Vincristine: 1.4mg/m2 iv day 1
 Prednisolone: 40mg/m2 po days 1 to 5

Investigational medicinal product name	Rituximab
Investigational medicinal product code	L01XC02
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Given as part of the following regimen:

R-CHOP 21 (cycle repeats every 21 days for 6 cycles) + Rituximab given for 2 further cycles.

Rituximab: 375mg/m2 iv day 1
 Cyclophosphamide: 750mg/m2 iv day 1
 Doxorubicin: 50mg/m2 iv day 1
 Vincristine: 1.4mg/m2 iv day 1
 Prednisolone: 40mg/m2 po days 1 to 5

Investigational medicinal product name	Prednisolone
Investigational medicinal product code	A07EA01
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Given as part of the following regimen:

R-CHOP 21 (cycle repeats every 21 days for 6 cycles) + Rituximab given for 2 further cycles.

Rituximab: 375mg/m2 iv day 1
 Cyclophosphamide: 750mg/m2 iv day 1
 Doxorubicin: 50mg/m2 iv day 1
 Vincristine: 1.4mg/m2 iv day 1

Number of subjects in period 1	R-CHOP 14	R-CHOP 21
Started	540	540
Completed	536	535
Not completed	4	5
Adverse event, serious fatal	2	2
Consent withdrawn by subject	-	1
LVEF 40–50%	-	1
incorrect diagnosis (CLL)	1	-
incorrect diagnosis (Burkitt's lymphoma)	-	1
coexisting illnesses	1	-

Baseline characteristics

Reporting groups

Reporting group title	R-CHOP 14
Reporting group description: Six cycles of R-CHOP (Cyclophosphamide 750mg/m ² , Doxorubicin 50mg/m ² , Vincristine 2mg, Prednisolone 100mg, Rituximab 375mg/m ²) every 14 days (1 cycle). After 6 cycles, two additional infusions of rituximab were given two weeks apart at a dose of 375mg/m ² each. This was to ensure equal number of rituximab infusions were given in both arms of the study.	
Reporting group title	R-CHOP 21
Reporting group description: Six cycles of R-CHOP (Cyclophosphamide 750mg/m ² , Doxorubicin 50mg/m ² , Vincristine 1.4mg/m ² , Prednisolone 40mg/m ² , Rituximab 375mg/m ²) every 21 days (1 cycle). After 6 cycles, two additional infusions of rituximab were given three weeks apart at a dose of 375mg/m ² each. This was to ensure equal number of rituximab infusions were given in both arms of the study.	

Reporting group values	R-CHOP 14	R-CHOP 21	Total
Number of subjects	540	540	1080
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	339	340	679
From 65-84 years	200	199	399
85 years and over	1	1	2
Age continuous Units: years			
median	61	61	
full range (min-max)	19 to 85	19 to 88	-
Gender categorical Units: Subjects			
Female	251	247	498
Male	289	293	582
WHO performance status Units: Subjects			
Nil (0)	286	258	544
One (1)	182	210	392
Two (2)	72	72	144
Disease Stage Units: Subjects			
Bulky IA	26	20	46
IB	17	16	33
II	157	166	323
III	175	142	317
IV	162	193	355

Unknown	3	3	6
Bulky Disease Units: Subjects			
Bulky Disease	261	272	533
Non-Bulky Disease	279	268	547
International prognostic index score Units: Subjects			
Nil (0)	40	43	83
One (1)	116	117	233
Two (2)	163	143	306
Three (3)	136	143	279
Four (4)	75	79	154
Five (5)	10	15	25
Phenotype Units: Subjects			
Germinal centre	144	145	289
Non-germinal centre	141	130	271
Unknown	255	265	520
Proliferation rate Units: Subjects			
MIB1 ≥80%	106	127	233
MIB1 ≥90%	49	71	120
Other	385	342	727
Other disease types diagnosed at central review Units: Subjects			
Burkitt's lymphoma	1	0	1
B-cell chronic lymphocytic leukaemia	3	1	4
Follicular lymphoma	4	4	8
Marginal zone lymphoma	0	2	2
B-cell non-Hodgkin lymphoma not otherwise classifi	2	0	2
Indolent lymphoma not otherwise classifi ed	0	1	1
Hodgkin's lymphoma	0	2	2
Lymphocyte predominant Hodgkin's lymphoma	0	0	0
Peripheral T-cell lymphoma	1	1	2
No lymphoma	1	0	1
Diffuse large B-cell non-Hodgkin lymphoma	528	529	1057
B Symptoms Units: Subjects			
B Symptoms	251	238	489
No B Symptoms	289	302	591
Elevated Lactate Dehydrogenase Units: Subjects			
Elevated Lactate Dehydrogenase	351	350	701
No Elevated Lactate Dehydrogenase	189	190	379

End points

End points reporting groups

Reporting group title	R-CHOP 14
Reporting group description: Six cycles of R-CHOP (Cyclophosphamide 750mg/m ² , Doxorubicin 50mg/m ² , Vincristine 2mg, Prednisolone 100mg, Rituximab 375mg/m ²) every 14 days (1 cycle). After 6 cycles, two additional infusions of rituximab were given two weeks apart at a dose of 375mg/m ² each. This was to ensure equal number of rituximab infusions were given in both arms of the study.	
Reporting group title	R-CHOP 21
Reporting group description: Six cycles of R-CHOP (Cyclophosphamide 750mg/m ² , Doxorubicin 50mg/m ² , Vincristine 1.4mg/m ² , Prednisolone 40mg/m ² , Rituximab 375mg/m ²) every 21 days (1 cycle). After 6 cycles, two additional infusions of rituximab were given three weeks apart at a dose of 375mg/m ² each. This was to ensure equal number of rituximab infusions were given in both arms of the study.	

Primary: Overall Survival

End point title	Overall Survival
End point description:	
End point type	Primary
End point timeframe: Two years post-trial treatment.	

End point values	R-CHOP 14	R-CHOP 21		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	540	540		
Units: Percentage				
number (not applicable)	82.7	80.8		

Statistical analyses

Statistical analysis title	Overall Survival
Comparison groups	R-CHOP 14 v R-CHOP 21
Number of subjects included in analysis	1080
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	= 0.3763
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.9

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	1.15

Notes:

[1] - hazard ratio 0.90, 95% CI 0.70–1.15; p=0.3763

Secondary: Progression Free Survival

End point title	Progression Free Survival
End point description:	
End point type	Secondary
End point timeframe:	
Two years post-trial treatment.	

End point values	R-CHOP 14	R-CHOP 21		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	540	540		
Units: Percentage				
number (not applicable)	75.4	74.08		

Statistical analyses

Statistical analysis title	Progression Free Survival
Comparison groups	R-CHOP 14 v R-CHOP 21
Number of subjects included in analysis	1080
Analysis specification	Pre-specified
Analysis type	superiority ^[2]
P-value	= 0.5907
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	1.17

Notes:

[2] - hazard ratio 0.94, 95% CI 0.76–1.17; p=0.5907

Secondary: Toxicity

End point title	Toxicity
End point description:	
Toxicity assessed according to CTCAE v3.	

End point type	Secondary
End point timeframe:	
Up to and including 30 days post-trial treatment.	

End point values	R-CHOP 14	R-CHOP 21		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	540	540		
Units: Percentage				
number (not applicable)				
Neutropenia (grade 3 or 4)	31	60		
Thrombocytopenia	9	5		
Febrile Neutropenia	11	5		
Infection	23	18		

Statistical analyses

No statistical analyses for this end point

Secondary: Complete Response Rate

End point title	Complete Response Rate
End point description:	
End point type	Secondary
End point timeframe:	
Post-trial treatment.	

End point values	R-CHOP 14	R-CHOP 21		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	502	500		
Units: Percentage				
number (not applicable)	58	63		

Statistical analyses

Statistical analysis title	Complete Response Rate
Comparison groups	R-CHOP 14 v R-CHOP 21

Number of subjects included in analysis	1002
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.183
Method	Logrank

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported up to 30 days after receiving the last dose of study drug, as per the trial protocol.

Adverse event reporting additional description:

All adverse events were documented on the toxicity page of the Treatment case report form by an appropriately qualified member of staff at each trial site. This documented the severity of the adverse event and causal relationship.

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

Dictionary used

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

Dictionary version	3.0
--------------------	-----

Reporting groups

Reporting group title	R-CHOP 14
-----------------------	-----------

Reporting group description:

Six cycles of R-CHOP (Cyclophosphamide 750mg/m², Doxorubicin 50mg/m², Vincristine 2mg, Prednisolone 100mg, Rituximab 375mg/m²) every 14 days (1 cycle). After 6 cycles, two additional infusions of rituximab were given two weeks apart at a dose of 375mg/m² each. This was to ensure equal number of rituximab infusions were given in both arms of the study.

Reporting group title	R-CHOP 21
-----------------------	-----------

Reporting group description:

Six cycles of R-CHOP (Cyclophosphamide 750mg/m², Doxorubicin 50mg/m², Vincristine 1.4mg/m², Prednisolone 40mg/m², Rituximab 375mg/m²) every 21 days (1 cycle). After 6 cycles, two additional infusions of rituximab were given three weeks apart at a dose of 375mg/m² each. This was to ensure equal number of rituximab infusions were given in both arms of the study.

Serious adverse events	R-CHOP 14	R-CHOP 21	
Total subjects affected by serious adverse events			
subjects affected / exposed	242 / 540 (44.81%)	333 / 540 (61.67%)	
number of deaths (all causes)	177	48	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
CNS Relapse			
subjects affected / exposed	0 / 540 (0.00%)	1 / 540 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 540 (0.19%)	0 / 540 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial ischaemia			

subjects affected / exposed	0 / 540 (0.00%)	1 / 540 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SVC			
subjects affected / exposed	0 / 540 (0.00%)	1 / 540 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Oedema Knee			
subjects affected / exposed	0 / 540 (0.00%)	1 / 540 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema limb			
subjects affected / exposed	0 / 540 (0.00%)	1 / 540 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	2 / 540 (0.37%)	3 / 540 (0.56%)	
occurrences causally related to treatment / all	1 / 2	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fever			
subjects affected / exposed	6 / 540 (1.11%)	10 / 540 (1.85%)	
occurrences causally related to treatment / all	5 / 6	9 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flu like symptoms			
subjects affected / exposed	0 / 540 (0.00%)	3 / 540 (0.56%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
General Symptoms -Initially, Constipation- Post Admission			
subjects affected / exposed	1 / 540 (0.19%)	0 / 540 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injection site reaction			

subjects affected / exposed	1 / 540 (0.19%)	0 / 540 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Other - Pain			
subjects affected / exposed	0 / 540 (0.00%)	1 / 540 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Other - Generally unwell			
subjects affected / exposed	1 / 540 (0.19%)	0 / 540 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound			
subjects affected / exposed	1 / 540 (0.19%)	0 / 540 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic Fever			
subjects affected / exposed	0 / 540 (0.00%)	1 / 540 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rigor			
subjects affected / exposed	4 / 540 (0.74%)	0 / 540 (0.00%)	
occurrences causally related to treatment / all	3 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Allergic reaction			
subjects affected / exposed	3 / 540 (0.56%)	1 / 540 (0.19%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytokine			
subjects affected / exposed	1 / 540 (0.19%)	0 / 540 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			

Pelvic pain			
subjects affected / exposed	2 / 540 (0.37%)	1 / 540 (0.19%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Adult Respiratory Distress Syndrome			
subjects affected / exposed	1 / 540 (0.19%)	0 / 540 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	0 / 540 (0.00%)	2 / 540 (0.37%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia Bronchial			
subjects affected / exposed	1 / 540 (0.19%)	1 / 540 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chylothorax			
subjects affected / exposed	0 / 540 (0.00%)	1 / 540 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	2 / 540 (0.37%)	1 / 540 (0.19%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 540 (0.19%)	0 / 540 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 540 (0.00%)	1 / 540 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hypotension			
subjects affected / exposed	1 / 540 (0.19%)	1 / 540 (0.19%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 540 (0.19%)	2 / 540 (0.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 540 (0.37%)	1 / 540 (0.19%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	3 / 540 (0.56%)	2 / 540 (0.37%)	
occurrences causally related to treatment / all	1 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 540 (0.00%)	1 / 540 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mood altered			
subjects affected / exposed	0 / 540 (0.00%)	1 / 540 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Creatinine			
subjects affected / exposed	1 / 540 (0.19%)	0 / 540 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytes			
subjects affected / exposed	0 / 540 (0.00%)	1 / 540 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Creatinine urine increased			
subjects affected / exposed	1 / 540 (0.19%)	0 / 540 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight Loss			
subjects affected / exposed	1 / 540 (0.19%)	0 / 540 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fracture			
subjects affected / exposed	0 / 540 (0.00%)	7 / 540 (1.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	7 / 540 (1.30%)	6 / 540 (1.11%)	
occurrences causally related to treatment / all	5 / 7	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemia			
subjects affected / exposed	0 / 540 (0.00%)	2 / 540 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Infarction			
subjects affected / exposed	2 / 540 (0.37%)	0 / 540 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	3 / 540 (0.56%)	5 / 540 (0.93%)	
occurrences causally related to treatment / all	2 / 3	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular diastolic dysfunction			
subjects affected / exposed	0 / 540 (0.00%)	1 / 540 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Left Ventricular Systolic Dysfunction			
subjects affected / exposed	1 / 540 (0.19%)	3 / 540 (0.56%)	
occurrences causally related to treatment / all	1 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Other - Cardiac disorders			
subjects affected / exposed	0 / 540 (0.00%)	1 / 540 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pericardial effusion			
subjects affected / exposed	1 / 540 (0.19%)	0 / 540 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular arrhythmia			
subjects affected / exposed	0 / 540 (0.00%)	3 / 540 (0.56%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	0 / 540 (0.00%)	1 / 540 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular systolic dysfunction			
subjects affected / exposed	0 / 540 (0.00%)	1 / 540 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Ischaemia cerebrovascular			
subjects affected / exposed	1 / 540 (0.19%)	0 / 540 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CNS iscenemia			
subjects affected / exposed	1 / 540 (0.19%)	0 / 540 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CNS Ischaemia - Stroke			

subjects affected / exposed	0 / 540 (0.00%)	1 / 540 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dizziness			
subjects affected / exposed	1 / 540 (0.19%)	1 / 540 (0.19%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness and pain			
subjects affected / exposed	0 / 540 (0.00%)	1 / 540 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	2 / 540 (0.37%)	2 / 540 (0.37%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal nerve dysfunction			
subjects affected / exposed	1 / 540 (0.19%)	0 / 540 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lethargy			
subjects affected / exposed	2 / 540 (0.37%)	0 / 540 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy motor			
subjects affected / exposed	3 / 540 (0.56%)	2 / 540 (0.37%)	
occurrences causally related to treatment / all	1 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy Sensory			
subjects affected / exposed	1 / 540 (0.19%)	0 / 540 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Other - Nervous system disorders			

subjects affected / exposed	1 / 540 (0.19%)	1 / 540 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Seizure			
subjects affected / exposed	0 / 540 (0.00%)	2 / 540 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 540 (0.19%)	1 / 540 (0.19%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tremor			
subjects affected / exposed	1 / 540 (0.19%)	0 / 540 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 540 (0.19%)	3 / 540 (0.56%)	
occurrences causally related to treatment / all	1 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophils/granulocytes (ANC/AGC)			
subjects affected / exposed	2 / 540 (0.37%)	0 / 540 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 540 (0.00%)	1 / 540 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile Illness			
subjects affected / exposed	0 / 540 (0.00%)	1 / 540 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			

subjects affected / exposed	30 / 540 (5.56%)	65 / 540 (12.04%)	
occurrences causally related to treatment / all	30 / 30	65 / 65	
deaths causally related to treatment / all	0 / 0	2 / 2	
Haemoglobin anaemia			
subjects affected / exposed	2 / 540 (0.37%)	1 / 540 (0.19%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			
subjects affected / exposed	0 / 540 (0.00%)	1 / 540 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	17 / 540 (3.15%)	27 / 540 (5.00%)	
occurrences causally related to treatment / all	17 / 17	27 / 27	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	2 / 540 (0.37%)	2 / 540 (0.37%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 540 (0.00%)	1 / 540 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	3 / 540 (0.56%)	5 / 540 (0.93%)	
occurrences causally related to treatment / all	2 / 3	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Eye disorders			
Diclofenac Ptosis			
subjects affected / exposed	0 / 540 (0.00%)	1 / 540 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Occular - other			

subjects affected / exposed	0 / 540 (0.00%)	1 / 540 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdomen Pain			
subjects affected / exposed	7 / 540 (1.30%)	4 / 540 (0.74%)	
occurrences causally related to treatment / all	6 / 7	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bleeding GI			
subjects affected / exposed	3 / 540 (0.56%)	1 / 540 (0.19%)	
occurrences causally related to treatment / all	0 / 3	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Constipation			
subjects affected / exposed	2 / 540 (0.37%)	7 / 540 (1.30%)	
occurrences causally related to treatment / all	2 / 2	7 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased oral intake			
subjects affected / exposed	0 / 540 (0.00%)	1 / 540 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	12 / 540 (2.22%)	11 / 540 (2.04%)	
occurrences causally related to treatment / all	12 / 12	7 / 11	
deaths causally related to treatment / all	1 / 1	0 / 0	
Dyspepsia			
subjects affected / exposed	1 / 540 (0.19%)	1 / 540 (0.19%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	0 / 540 (0.00%)	1 / 540 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Esophagitis			

subjects affected / exposed	1 / 540 (0.19%)	1 / 540 (0.19%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Esophagus pain			
subjects affected / exposed	0 / 540 (0.00%)	1 / 540 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fistula Oesophagus			
subjects affected / exposed	1 / 540 (0.19%)	0 / 540 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	2 / 540 (0.37%)	1 / 540 (0.19%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucositis			
subjects affected / exposed	1 / 540 (0.19%)	0 / 540 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	8 / 540 (1.48%)	5 / 540 (0.93%)	
occurrences causally related to treatment / all	5 / 8	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstruction gastric			
subjects affected / exposed	1 / 540 (0.19%)	1 / 540 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Other - Gastrointestinal disorders			
subjects affected / exposed	1 / 540 (0.19%)	0 / 540 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Other - Mouth/throat			

subjects affected / exposed	0 / 540 (0.00%)	1 / 540 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Other - Perforated Caecum			
subjects affected / exposed	0 / 540 (0.00%)	1 / 540 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in Epigastrium and lower abdomen			
subjects affected / exposed	0 / 540 (0.00%)	1 / 540 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perforation			
subjects affected / exposed	1 / 540 (0.19%)	1 / 540 (0.19%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Duodenal ulcer			
subjects affected / exposed	0 / 540 (0.00%)	1 / 540 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	10 / 540 (1.85%)	10 / 540 (1.85%)	
occurrences causally related to treatment / all	7 / 10	10 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Cellulitis			
subjects affected / exposed	2 / 540 (0.37%)	4 / 540 (0.74%)	
occurrences causally related to treatment / all	0 / 2	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	0 / 540 (0.00%)	1 / 540 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shingles			

subjects affected / exposed	0 / 540 (0.00%)	1 / 540 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urticaria			
subjects affected / exposed	0 / 540 (0.00%)	1 / 540 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 540 (0.19%)	1 / 540 (0.19%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic Cystitis			
subjects affected / exposed	1 / 540 (0.19%)	0 / 540 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incontinence, urinary			
subjects affected / exposed	1 / 540 (0.19%)	0 / 540 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 540 (0.19%)	0 / 540 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	2 / 540 (0.37%)	3 / 540 (0.56%)	
occurrences causally related to treatment / all	2 / 2	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	2 / 540 (0.37%)	1 / 540 (0.19%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gout			
subjects affected / exposed	1 / 540 (0.19%)	0 / 540 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			
subjects affected / exposed	2 / 540 (0.37%)	0 / 540 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar pain			
subjects affected / exposed	0 / 540 (0.00%)	1 / 540 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	0 / 540 (0.00%)	1 / 540 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchus			
subjects affected / exposed	0 / 540 (0.00%)	1 / 540 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest Infection			
subjects affected / exposed	5 / 540 (0.93%)	1 / 540 (0.19%)	
occurrences causally related to treatment / all	5 / 5	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	17 / 540 (3.15%)	32 / 540 (5.93%)	
occurrences causally related to treatment / all	14 / 17	32 / 32	
deaths causally related to treatment / all	0 / 0	1 / 1	
Neutropenic sepsis			
subjects affected / exposed	9 / 540 (1.67%)	7 / 540 (1.30%)	
occurrences causally related to treatment / all	9 / 9	7 / 7	
deaths causally related to treatment / all	2 / 2	1 / 1	
Non-neutropenic sepsis			

subjects affected / exposed	1 / 540 (0.19%)	0 / 540 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Other - Infections and infestations			
subjects affected / exposed	1 / 540 (0.19%)	1 / 540 (0.19%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 540 (0.19%)	0 / 540 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 540 (0.19%)	0 / 540 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	2 / 540 (0.37%)	2 / 540 (0.37%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
ADH Hyponatremic			
subjects affected / exposed	0 / 540 (0.00%)	1 / 540 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anorexia			
subjects affected / exposed	1 / 540 (0.19%)	2 / 540 (0.37%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	3 / 540 (0.56%)	1 / 540 (0.19%)	
occurrences causally related to treatment / all	2 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			

subjects affected / exposed	0 / 540 (0.00%)	2 / 540 (0.37%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 540 (0.00%)	1 / 540 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	2 / 540 (0.37%)	0 / 540 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glucose intolerance			
subjects affected / exposed	0 / 540 (0.00%)	1 / 540 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour lysis syndrome			
subjects affected / exposed	1 / 540 (0.19%)	0 / 540 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	R-CHOP 14	R-CHOP 21	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	290 / 540 (53.70%)	380 / 540 (70.37%)	
Cardiac disorders			
Cardiac Toxicity			
subjects affected / exposed	11 / 540 (2.04%)	2 / 540 (0.37%)	
occurrences (all)	11	2	
Nervous system disorders			
Neurological Toxicity			
subjects affected / exposed	53 / 540 (9.81%)	38 / 540 (7.04%)	
occurrences (all)	53	38	
Blood and lymphatic system disorders			

Thrombocytopenia subjects affected / exposed occurrences (all)	50 / 540 (9.26%) 50	28 / 540 (5.19%) 28	
General disorders and administration site conditions All Toxicity subjects affected / exposed occurrences (all)	290 / 540 (53.70%) 290	380 / 540 (70.37%) 380	
Gastrointestinal disorders Mucositis subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	14 / 540 (2.59%) 14 22 / 540 (4.07%) 22 19 / 540 (3.52%) 19	10 / 540 (1.85%) 10 20 / 540 (3.70%) 20 17 / 540 (3.15%) 17	
Infections and infestations Neutropenia subjects affected / exposed occurrences (all) Febrile neutropenia subjects affected / exposed occurrences (all) Infection subjects affected / exposed occurrences (all)	167 / 540 (30.93%) 167 28 / 540 (5.19%) 28 96 / 540 (17.78%) 96	318 / 540 (58.89%) 318 58 / 540 (10.74%) 58 125 / 540 (23.15%) 125	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 August 2005	The protocol was amended to include the following: Page 3. Dr Ian Chau no longer Clinical Coordinator. Any clinical queries should now be directed to Prof. David Cunningham as stated in protocol. Section 6.3 Administration of Rituximab in both treatment arms Page 13. Data on the safe, fast infusion of Rituximab became available. Some hospital trusts are now using this method of administration of Rituximab. This has therefore been incorporated into the protocol. Section 6.6 Central Nervous System (CNS) Prophylaxis Page 14. In keeping with the DOH intrathecal guidance which states "It is not acceptable to inconvenience patients by asking them to attend on two occasions", the protocol has been altered so that intrathecal methotrexate will be given on the same day as CHOP, once the intravenous cytotoxic drugs have been given. Section 14.2 Safety Reporting Page 28. Amendments to the safety reporting have been made to make it clear that expected toxicities with CHOP chemotherapy and Rituximab do not need to be reported as adverse events. Section 14.4 Indemnity and Compensation Page 29. As a legal requirement the role of the sponsor of the trial and definitions of negligent and non-negligent harm are now included in the protocol. Appendix 3 Patient Information Sheet Page 34. CT scans are performed at diagnosis, after 4 cycles and at end of treatment. They are also performed at 3 months and 1 year after treatment. It has been brought to our attention that this final CT scan at 1 year post treatment, although performed routinely in some centres, is not universal practice. Therefore for some patients this is an additional scan and information regarding the implications of this is now incorporated into the patient information sheet. Definitions of negligent and non-negligent harm are now also included in the patient information sheet. Appendix 6 Expected Toxicities. Typographical error - doxorubicin to replace doxycycline. Appendix 7 Trial Management Group -Cathy Burton added
31 July 2006	The protocol was amended to include the addition of a sub-protocol to allow the collection of constitutional DNA from buccal smears. The costs associated with this sub-study (i.e. kits for collecting smears, postage and storage) will be met from a Translational Research in Clinical Trials grant provided by Cancer Research UK. This amendment also included the addition of a second sub-protocol which will prospectively evaluate the prognostic value of PET scanning after 2 cycles of RCHOP chemotherapy. This sub-study will be funded by a subvention from the Department of Health.
19 September 2006	The Lymphoma Trials Office moved premises, so contact details were amended in the protocol.
27 November 2006	The Patient Information Sheet and consent form for the Buccal Smear Substudy were rewritten to make it clearer to patients that this was an add-on to the main trial that they were already taking part in and that any DNA extracted from the samples given would be stored and used anonymously for future research projects. This was not clear in the previous versions, v2.0 of both forms were approved for use in this amendment.

26 July 2007	<p>The protocol and substudy protocol were amended to update a number of contact telephone numbers, fax numbers and email addresses.</p> <p>In addition, the protocol had the following amended:</p> <ul style="list-style-type: none"> - Change length of study from 3 to 4 years (page 5) - Now states that CT scans should be done within 28 days pre-randomisation (page 9) - Stage IB addition into inclusion criteria (page 10) - Update stratification variables (page 11) - Remove request for consent form (page 11) - Reworded when CT scan should be done on 14 arm (page 23) - Complete rewriting of Safety Reporting (page 28) - PIS Replace CERES with CancerBACUP (page 38) - PIS Change of side effects (page 41) - Consent form - Change date and version number of PIS (page 46) - Change in expected toxicities (to fit in with PIS) (page 49) <p>In addition, the substudy protocol had the following amended:</p> <ul style="list-style-type: none"> - PIS Replace CERES with CancerBACUP (page 13) - Addition of Appendix 4. Stating PET centres involved (page 18)
26 August 2008	<p>This substantial amendment allowed for an extension to the R-CHOP 14 vs 21 study. This was in the form of a single arm registration phase, post the initial 1080 patients randomised into the study. This was designed to enable the PET sub study to recruit its full 200 patients. Only patients that can be recruited onto the PET substudy were consented onto the registration phase of R-CHOP 14 vs 21. On the 4th August 2008, 60 patients had been entered onto the PET substudy, so it was estimated 75 patients would be enrolled at the close of the randomisation section of the protocol. Therefore, it was expected that the registration phase was to be for a further 125 patients.</p> <p>The registration phase was single arm. This was initially R-CHOP 21 as this is the standard arm. When analysis of the 1080 patients was complete and the results are known treatment could change, this is laid out on pages 11 and 12 of the main protocol. This enabled the study to react to any change in standard treatment in the UK. Patients will be treated as per protocol.</p> <p>Both the R-CHOP and the PET protocol had a new Patient Information Sheet and consent form when the registration phase began, replacing the previous PISs and CFs post 1080 patients.</p> <p>The Trial Management Group felt that the PET sub-study is a decisive trial in answering how patients should be treated in the future, and we needed to be able to recruit the full number of patients set out in the protocol.</p>
30 March 2010	<p>This substantial amendment allowed for the number of CHOP cycles in the control arm (R-CHOP 21) to be reduced from 8 to 6 cycles. The following documents were amended to reflect this change:</p> <ol style="list-style-type: none"> 1. Protocol (version 6.0) 2. Patient Information Sheet for registration (version 5.0) 3. Consent Form for registration (version 5.0) 4. GP letter for registration (version 4.0) 5. PET sub-study Protocol (version 5.0) 6. PET sub-study Patient Information Sheet for registration (version 4.0) 7. PET sub-study Consent Form for registration (version 4.0) <p>In addition, contact details were updated in both the protocol and sub-study protocol.</p> <p>There was also a new site added to the trial and changes in PI at two sites: NEW SITE: Dr Naheed Mir - The Lewisham Hospital NHS Trust CHANGE IN PIs: Dr Toby Nicholson (was Dr Gnanam Satchi) - Whiston Hospital Dr Humayun Ahmad (Dr Adrian Smith) – Queens Hospital, Burton-on-Trent</p>

11 January 2011	<p>This amendment was primarily to amend an error in the GP letter. Version 4.0 of the GP letter referred to Version 4.0 (dated 30/03/2010) of the protocol. This is an error, and should read version 6.0 (dated 30/03/2010) of the protocol. This was corrected and version 4.1 was approved in this amendment.</p> <p>Also approved in this amendment, North Cheshire NHS Trust (Warrington Hospital & Halton Hospital, PI Dr Peter Clark) had not recruited any patients into the trial and requested that they were closed in order to archive.</p> <p>Hannah Farrant left the UCL CTC and was replaced by Jo Gambell, the REC was asked to update their contact details to reflect this.</p>
17 March 2011	<p>This substantial amendment allowed for an additional assessment of the response by PET scan using new criteria. The response using this new criteria was compared with the original criteria.</p> <p>This substantial amendment also allowed for analysis of the effect of cell proliferation, as measured by MIB1.</p> <p>The protocol and substudy protocol were amended to reflect this.</p>
15 July 2011	<p>This amendment was to correct an error in the GP letter. Version 4.0 of the GP letter referred to Version 4.0 (dated 30/03/2010) of the protocol. This was an error, and should have read version 6.0 (dated 30/03/2010) of the protocol.</p> <p>North Cheshire NHS Trust (Warrington Hospital & Halton Hospital) had not recruited any patients into the trial and requested that they could close in order to archive.</p> <p>Lastly, Hannah Farrant had left the Haematology Trials Group and was replaced by Jo Gambell, so the REC were informed of a change in contact information for the trial.</p>
29 October 2012	<p>This substantial amendment was made to provide clarification of the methods of pathology review. An additional paragraph was added to section 9.0 of the trial protocol to clarify the methods of pathology review already approved within this clinical trial. The contact details of the UCL Cancer Trials Centre were also updated on page 3.</p>

29 February 2016	<p>This amendment was made to the trial protocol to allow trial data to be shared with the German High Grade Lymphoma Group and with the SEAL project, there was no scope to do this in the previously approved version.</p> <p>The entirety of 'Section 18 – Data Sharing' was new and reads as follows:</p> <p>"In accordance with Cancer Research UK data sharing policy which states that "Cancer Research UK is committed to ensuring that the data generated through its funding should be put to maximum use by the cancer research community and, whenever possible, is translated to deliver patient benefit. It is therefore our policy that all data generated as a result of our funding be considered for sharing and made as widely and freely accessible as possible whilst safeguarding intellectual property, the privacy of patients and confidential data." All requests for data sharing will be considered by the Trial Management Group. If they approve the request data will be provided in a confidential and secure manner i.e. no patient identifiable material will be sent and data will be sent in an encrypted format.</p> <p>As of February 2016 two requests to share data have been received. The first project is in collaboration with the German High Grade Lymphoma group and they have requested data from this trial to try to confirm that the outcome of treatment with rituximab differs between the sexes because the drug is metabolised differently in men and women.</p> <p>The second project (SEAL) is in collaboration with an international consortium and will explore whether progression-free survival can be used as a surrogate endpoint for overall survival in this patient population. The analysis for this project will be done in America and the results of the analysis will be made available to the pharmaceutical company, Celgene.</p> <p>Release of data for these projects was approved by London – Hampstead NRES committee. Any further requests for data will require separate ethical approval."</p>
------------------	--

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Non-serious AEs: 'Occurrences all number' cannot be provided, highest grade experienced collected on CRF; 'subjects affected number' listed instead. Serious AEs and non-serious AEs are listed under non-serious adverse events (only grade 3-4 reported).

Notes: