Clinical trial results:
Positronen-Emissionstomographie-gesteuerte Therapie aggressiver Non-Hodgkin-Lymphome
(Positron emission tomography guided therapy of aggressive non-Hodgkin's lymphomas)

Summary

EudraCT number	2006-001641-33
Trial protocol	DE
Global end of trial date	31 March 2018

Results information

Result version number	v1 (current)
This version publication date	06 June 2022
First version publication date	06 June 2022

Trial information

Trial identification

Sponsor protocol code	PETAL-Studie

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00554164
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University Hospital Essen
Sponsor organisation address	Hufelandstrasse 55, Essen, Germany, 45147
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	31 March 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 March 2018
Global end of trial reached?	Yes
Global end of trial date	31 March 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

First-line therapy for patients with aggressive B-cell or T-cell non-Hodgkin lymphomas
Comparison of treatment results in patients with CD20-positive aggressive non-Hodgkin lymphomas and a good response to 2 cycles of the R-CHOP protocol as assessed by positron emission tomography (interim PET) by randomisation between a further 4 cycles of the R-CHOP protocol or 4 cycles R-CHOP plus 2 additional applications of rituximab (R)
Comparison of treatment results in aggressive non-Hodgkin lymphoma patients with a poor response to 2 cycles of the (R)-CHOP protocol as assessed by interim PET by randomisation between a further 6 cycles of the (R-)CHOP protocol or 6 blocks of the German Burkitt's lymphoma protocol (R restricted to CD20-positive lymphomas)

Protection of trial subjects:

Documentation of adverse events according to CTCAE v3.0

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 November 2007
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	Germany: 363
Worldwide total number of subjects	363
EEA total number of subjects	363

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)	156

From 65 to 84 years	207
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients age 18 to 80 with aggressive B-cell or T-cell non-Hodgkin lymphoma (except Burkitt, lymphoblastic or primary CNS lymphoma) with a positive baseline PET scan and without contraindication to standard first-line treatment
First patient recruited - November 19, 2007
Last patient recruited - December 28, 2012

Pre-assignment

Screening details:

Randomisation was performed after the interim PET. Pre-assigned patients with a negative baseline PET (n=82), not reaching the interim PET (n=129) or presenting with a negative interim PET before or after the randomization period for interim PET-negative patients (n=499) were not treated within the randomized trial

Pre-assignment period milestones

Number of subjects started	1073[1]
Number of subjects completed	363

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Negative baseline PET: 82
Reason: Number of subjects	Histologic misdiagnosis: 41
Reason: Number of subjects	Protocol deviation: 33
Reason: Number of subjects	Technical/logistic PET issues: 13
Reason: Number of subjects	Physician decision: 7
Reason: Number of subjects	Consent withdrawn by subject: 3
Reason: Number of subjects	Miscellaneous reasons: 32
Reason: Number of subjects	Not randomized (interim PET-negative patients): 499

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Randomization required a positive baseline PET and - after two standard treatment cycles - an interim PET based on which the pts were divided into interim PET-negative and interim PET-positive pts. These two groups were independently randomized. The result of the interim PET was not known at pre-assignment. The number of interim-PET negative pts. required for the trial was reached much earlier than that of interim PET-positive pts. Thus, most interim PET-negative pts. were not randomized.

Period 1

Period 1 title	Interim PET-based randomization (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

No blinding.

Arms

Are arms mutually exclusive?	Yes

Arm title	4xR-CHOP

Arm description:

Following 2 cycles of R-CHOP before the interim PET scan, interim PET-negative patients with CD20-positive lymphomas randomized to the active comparator received a further 4 cycles of R-CHOP after the interim PET.

Arm type	Active comparator
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

375 mg/m2, day 1 of each cycle, 4 cycles, every two weeks

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

750 mg/m2, day 1 of each cycle, 4 cycles, every 2 weeks

Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

50 mg/m2, day 1 of each cycle, 4 cycles, every 2 weeks

Investigational medicinal product name	Vincristine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

2 mg, day 1 of each cycle, 4 cycles, every 2 weeks

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

Dosage and administration details:

100 mg, days 1-5 of each cycle, 4 cycles, every 2 weeks

Arm title	4xR-CHOP+2xR

Arm description:

Following 2 cycles of R-CHOP before the interim PET scan, interim PET-negative patients with CD20-positive lymphomas randomized to the experimental arm received a further 4 cycles of R-CHOP plus 2 extra doses of rituximab after the interim PET.

Arm type	Experimental
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:	
375 mg/m2, day 1 of each cycle, 6 cycles, every 2 weeks	
Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details:	
750 mg/m2 day 1 of each cycle, 4 cycles, every 2 weeks	
Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details:	
50 mg/m2, day 1 of each cycle, 4 cycles, every 2 weeks	
Investigational medicinal product name	Vincristine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use
Dosage and administration details:	
2 mg, day 1 of each cycle, 4 cycles, every 2 weeks	
Investigational medicinal product name	Prednisone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
100 mg, days 1-5 of each cycle, 4 cycles, every 2 weeks	
Arm title	6xR-CHOP
Arm description:	
Following 2 cycles of R-CHOP before the interim PET scan, interim PET-positive patients randomized to the active comparator received a further 6 cycles of R-CHOP after the interim PET.	
Arm type	Active comparator
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details:	
375 mg/m2 (only for CD20-positive lymphomas), day 1 of each cycle, 6 cycles, every 2 weeks	
Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details:	
750 mg/m2, day 1 of each cycle, 6 cycles, every 2 weeks	
Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

50 mg/m2, day 1 of each cycle, 6 cycles, every 2 weeks

Investigational medicinal product name	Vincristine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

2 mg, day 1 of each cycle, 6 cycles, every 2 weeks

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

Dosage and administration details:

100 mg, day 1-5 of each cycle, 6 cycles, every 2 weeks

Arm title	6xBurkitt protocol

Arm description:

Following 2 cycles of R-CHOP before the interim PET scan, interim PET-positive patients randomized to the experimental arm received 6 blocks of the German Burkitt's lymphoma protocol after the interim PET.

Arm type	Experimental
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

375 mg/m2 (only for CD20-positive lymphomas), day 1 of each cycle, 6 cycles, every 3 weeks

Investigational medicinal product name	Methotrexate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Age ≤60 years: 1500 mg/m2, age < 60 years: 500 mg/m2, day 2 of each cycle, 6 cycles, every 3 weeks

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

Dosage and administration details:

10 mg, days 2-6 of each cycle, 6 cycles, every 3 weeks

Investigational medicinal product name	Vincristine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details: Age ≤60 years: 2 mg, day 2 of cycles 1, 2, 4 and 5 of six 3-weekly cycles Age >60 years: 1 mg, day 2 of cycles 2, 4 and 6 of six 3-weekly cycles	
Investigational medicinal product name	Vindesine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details: Age ≤60 years: 5 mg, day 2 of cycles 3 and 6 of six 3-weekly cycles	
Investigational medicinal product name	Ifosfamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details: Age ≤60 years: 800 mg/m2, days 2-6 of cycles 1 and 4 of six 3-weekly cycles Age >60 years: 400 mg/m2, days 2-6 of cycles 1, 3 and 5 of six 3-weekly cycles	
Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details: Age ≤60 years: 200 mg/m2, days 2-6 of cycles 2 and 5 of six 3-weekly cycles Age >60 years: 200 mg/m2, days 2-6 of cycles 2, 4 and 6 of six 3-weekly cycles	
Investigational medicinal product name	Cytarabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details: Age ≤60 years: 150 mg/m2 twice daily, days 5-6 of cycles 1 and 4 of six 3-weekly cycles; 2000 mg/m2 twice daily, day 6 of cycles 3 and 6 of six 3-weekly cycles Age >60 years: 60 mg/m2 twice daily, days 5-6 of cycles 1, 3 and 5 of six 3-weekly cycles	
Investigational medicinal product name	Etoposide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details: Age ≤60 years: 100 mg/m2, days 5-6 of cycles 1 and 4 of six 3-weekly cycles; 250 mg/m2, days 5-6 of cycles 3 and 6 of six 3-weekly cycles Age >60 years: 60 mg/m2, days 5-6 of cycles 1, 3 and 5 of six 3-weekly cycles	
Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details: Age ≤60 years: 25 mg/m2, days 5-6 of cycles 2 and 5 of six 3-weekly cycles Age >60 years: 25 mg/m2, days 5-6 of cycles 2, 4 and 6 of six 3-weekly cycles	

Number of subjects in period 1	4xR-CHOP	4xR-CHOP+2xR	6xR-CHOP
Started	129	126	52
Randomization	129	126	52
Completed	129	126	52

Number of subjects in period 1	6xBurkitt protocol
Started	56
Randomization	56
Completed	56

Baseline characteristics

Reporting groups	
Reporting group title	4xR-CHOP
Reporting group description:	
Following 2 cycles of R-CHOP before the interim PET scan, interim PET-negative patients with CD20-positive lymphomas randomized to the active comparator received a further 4 cycles of R-CHOP after the interim PET.	
Reporting group title	4xR-CHOP+2xR
Reporting group description:	
Following 2 cycles of R-CHOP before the interim PET scan, interim PET-negative patients with CD20-positive lymphomas randomized to the experimental arm received a further 4 cycles of R-CHOP plus 2 extra doses of rituximab after the interim PET.	
Reporting group title	6xR-CHOP
Reporting group description:	
Following 2 cycles of R-CHOP before the interim PET scan, interim PET-positive patients randomized to the active comparator received a further 6 cycles of R-CHOP after the interim PET.	
Reporting group title	6xBurkitt protocol
Reporting group description:	
Following 2 cycles of R-CHOP before the interim PET scan, interim PET-positive patients randomized to the experimental arm received 6 blocks of the German Burkitt's lymphoma protocol after the interim PET.	

Reporting group values	4xR-CHOP	4xR-CHOP+2xR	6xR-CHOP
Number of subjects	129	126	52
Age categorical			
The age groups are: 18 to 60 years and >60 to 80 years			
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)	54	52	23
From 65-84 years	75	74	29
85 years and over	0	0	0
Age continuous			
Units: years			
median	63	65	62
full range (min-max)	18 to 80	20 to 78	21 to 77
Gender categorical			
Units: Subjects			
Female	56	56	20
Male	73	70	32
International Prognostic Index			
Units: Subjects			
Low risk	48	47	12
Low-intermediate risk	30	32	14
High-intermediate risk	29	30	16

High risk	21	17	9
Not recorded	1	0	1
Lymphoma entity Units: Subjects			
Diffuse large B-cell lymphoma	97	100	32
Primary mediastinal B-cell lymphoma	9	5	3
Follicular lymphoma grade 3	6	3	1
Other aggressive B-cell lymphoma	5	5	2
T-cell lymphoma	1	2	9
Other entity	11	11	5

Reporting group values	6xBurkitt protocol	Total	
Number of subjects	56	363	
Age categorical			
The age groups are: 18 to 60 years and >60 to 80 years			
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)	27	156	
From 65-84 years	29	207	
85 years and over	0	0	
Age continuous Units: years			
median	61		
full range (min-max)	24 to 78	-	
Gender categorical Units: Subjects			
Female	21	153	
Male	35	210	
International Prognostic Index Units: Subjects			
Low risk	15	122	
Low-intermediate risk	15	91	
High-intermediate risk	14	89	
High risk	11	58	
Not recorded	1	3	
Lymphoma entity Units: Subjects			
Diffuse large B-cell lymphoma	31	260	
Primary mediastinal B-cell lymphoma	2	19	
Follicular lymphoma grade 3	6	16	
Other aggressive B-cell lymphoma	5	17	
T-cell lymphoma	10	22	
Other entity	2	29	

End points

End points reporting groups

Reporting group title	4xR-CHOP
Reporting group description:	
Following 2 cycles of R-CHOP before the interim PET scan, interim PET-negative patients with CD20-positive lymphomas randomized to the active comparator received a further 4 cycles of R-CHOP after the interim PET.	
Reporting group title	4xR-CHOP+2xR
Reporting group description:	
Following 2 cycles of R-CHOP before the interim PET scan, interim PET-negative patients with CD20-positive lymphomas randomized to the experimental arm received a further 4 cycles of R-CHOP plus 2 extra doses of rituximab after the interim PET.	
Reporting group title	6xR-CHOP
Reporting group description:	
Following 2 cycles of R-CHOP before the interim PET scan, interim PET-positive patients randomized to the active comparator received a further 6 cycles of R-CHOP after the interim PET.	
Reporting group title	6xBurkitt protocol
Reporting group description:	
Following 2 cycles of R-CHOP before the interim PET scan, interim PET-positive patients randomized to the experimental arm received 6 blocks of the German Burkitt's lymphoma protocol after the interim PET.	

Primary: Event-free survival rate at 2 years

End point title	Event-free survival rate at 2 years
End point description:	
Kaplan-Meier estimates of the proportion of event-free patients at 2 years Definition of event: Progression, relapse, change to a treatment not specified in the protocol, toxicity-related treatment discontinuation, death from any cause	
End point type	Primary
End point timeframe:	
From randomization to last follow-up (median follow-up: 54 months)	

End point values	4xR-CHOP	4xR-CHOP+2xR	6xR-CHOP	6xBurkitt protocol
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	129	126	52	56
Units: Proportion of patients				
number (confidence interval 95%)	76.4 (68.0 to 84.2)	73.5 (64.8 to 80.4)	42.0 (28.2 to 55.2)	31.6 (19.3 to 44.6)

Attachments (see zip file)	EFS and OS/PETAL-EFS-OS.pdf

Statistical analyses

Statistical analysis title	Event-free survival of interim PET-negative pts
Statistical analysis description:	
Kaplan-Meier analysis of the impact of treatment on event-free survival in patients with a negative interim PET scan after 2 cycles of R-CHOP	
Comparison groups	4xR-CHOP v 4xR-CHOP+2xR
Number of subjects included in analysis	255
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8216
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.689
upper limit	1.598

Statistical analysis title	Event-free survival of interim PET-positive pts
Statistical analysis description:	
Kaplan-Meier analysis of the impact of treatment on event-free survival in patients with a positive interim PET scan after 2 cycles of R-CHOP	
Comparison groups	6xR-CHOP v 6xBurkitt protocol
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0924
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.502
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.931
upper limit	2.424

Secondary: Overall survival rate at 2 years	
End point title	Overall survival rate at 2 years
End point description:	
Kaplan-Meier estimates of the proportion of patients surviving at 2 years	
End point type	Secondary
End point timeframe:	
From randomization to last follow-up	

End point values	4xR-CHOP	4xR-CHOP+2xR	6xR-CHOP	6xBurkitt protocol
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	129	126	52	56
Units: Proportion of patients				
number (confidence interval 95%)	88.2 (81.2 to 92.7)	87.2 (79.9 to 91.9)	63.6 (48.5 to 75.3)	55.4 (40.7 to 67.8)

Statistical analyses

Statistical analysis title	Overall survival of interim PET-negative pts
Statistical analysis description:	
Kaplan-Meier analysis of the impact of treatment on overall survival in patients with a negative interim PET scan after 2 cycles of R-CHOP	
Comparison groups	4xR-CHOP+2xR v 4xR-CHOP
Number of subjects included in analysis	255
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6351
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.876
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.508
upper limit	1.513

Statistical analysis title	Overall survival of interim PET-positive pts
Statistical analysis description:	
Kaplan-Meier analysis of the impact of treatment on overall survival in patients with a positive interim PET scan after 2 cycles of R-CHOP	
Comparison groups	6xR-CHOP v 6xBurkitt protocol
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3085
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.349
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.756
upper limit	2.406

Secondary: Overall response rate	
End point title	Overall response rate
End point description:	

End point type	Secondary
End point timeframe:	
End of treatment specified in the protocol	

End point values	4xR-CHOP	4xR-CHOP+2xR	6xR-CHOP	6xBurkitt protocol
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	119	120	43	35
Units: Patients	111	109	30	24

Statistical analyses

Statistical analysis title	Overall response rate of interim PET-negative pts
Comparison groups	4xR-CHOP v 4xR-CHOP+2xR
Number of subjects included in analysis	239
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.485
Method	Chi-squared

Statistical analysis title	Overall response rate of interim PET-positive pts
Comparison groups	6xR-CHOP v 6xBurkitt protocol
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9094
Method	Chi-squared

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From randomization to 6 weeks after the end of therapy
Only for overall deaths: From randomization to death or last follow-up (median follow-up: 54 months)

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	3.0

Reporting groups

Reporting group title	4xR-CHOP

Reporting group description:

Following 2 cycles of R-CHOP before the interim PET scan, interim PET-negative patients with CD20-positive lymphomas randomized to the active comparator received a further 4 cycles of R-CHOP after the interim PET

Reporting group title	4xR-CHOP+2xR

Reporting group description:

Following 2 cycles of R-CHOP before the interim PET scan, interim PET-negative patients with CD20-positive lymphomas randomized to the experimental arm received a further 4 cycles of R-CHOP plus 2 extra doses of rituximab after the interim PET

Reporting group title	6xR-CHOP

Reporting group description:

Following 2 cycles of R-CHOP before the interim PET scan, interim PET-positive patients randomized to the active comparator received a further 6 cycles of R-CHOP after the interim PET

Reporting group title	6xBurkitt protocol

Reporting group description:

Following 2 cycles of R-CHOP before the interim PET scan, interim PET-positive patients randomized to the experimental arm received 6 blocks of the German Burkitt's lymphoma protocol after the interim PET

Serious adverse events	4xR-CHOP	4xR-CHOP+2xR	6xR-CHOP
Total subjects affected by serious adverse events			
subjects affected / exposed	52 / 129 (40.31%)	30 / 126 (23.81%)	26 / 52 (50.00%)
number of deaths (all causes)	28	23	20
number of deaths resulting from adverse events	5	2	2
Vascular disorders			
Vascular disorders			
subjects affected / exposed	6 / 129 (4.65%)	6 / 126 (4.76%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 6	0 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Treatment-related death			

subjects affected / exposed	5 / 129 (3.88%)	2 / 126 (1.59%)	2 / 52 (3.85%)
occurrences causally related to treatment / all	5 / 5	2 / 2	2 / 2
deaths causally related to treatment / all	5 / 5	2 / 2	2 / 2
Cardiac disorders			
Cardiac disorders			
subjects affected / exposed	11 / 129 (8.53%)	4 / 126 (3.17%)	5 / 52 (9.62%)
occurrences causally related to treatment / all	0 / 11	0 / 4	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Nervous system disorders			
subjects affected / exposed	10 / 129 (7.75%)	9 / 126 (7.14%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	3 / 10	4 / 9	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	11 / 129 (8.53%)	12 / 126 (9.52%)	6 / 52 (11.54%)
occurrences causally related to treatment / all	11 / 11	12 / 12	6 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	8 / 129 (6.20%)	11 / 126 (8.73%)	6 / 52 (11.54%)
occurrences causally related to treatment / all	8 / 8	11 / 11	6 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mucositis			
subjects affected / exposed	3 / 129 (2.33%)	1 / 126 (0.79%)	2 / 52 (3.85%)
occurrences causally related to treatment / all	1 / 3	1 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastrointestinal disorders			
subjects affected / exposed	26 / 129 (20.16%)	14 / 126 (11.11%)	14 / 52 (26.92%)
occurrences causally related to treatment / all	10 / 26	7 / 14	7 / 14
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Respiratory disorders			

subjects affected / exposed	13 / 129 (10.08%)	4 / 126 (3.17%)	3 / 52 (5.77%)
occurrences causally related to treatment / all	2 / 13	2 / 4	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal disorders			
subjects affected / exposed	4 / 129 (3.10%)	2 / 126 (1.59%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Psychiatric disorders			
subjects affected / exposed	2 / 129 (1.55%)	2 / 126 (1.59%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Infection			
subjects affected / exposed	38 / 129 (29.46%)	25 / 126 (19.84%)	19 / 52 (36.54%)
occurrences causally related to treatment / all	38 / 38	25 / 25	19 / 19
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Metabolism disorders			
subjects affected / exposed	8 / 129 (6.20%)	5 / 126 (3.97%)	5 / 52 (9.62%)
occurrences causally related to treatment / all	6 / 8	2 / 5	3 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	6xBurkitt protocol		
Total subjects affected by serious adverse events			
subjects affected / exposed	42 / 56 (75.00%)		
number of deaths (all causes)	27		
number of deaths resulting from adverse events	3		
Vascular disorders			
Vascular disorders			
subjects affected / exposed	3 / 56 (5.36%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Treatment-related death			

subjects affected / exposed	3 / 56 (5.36%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	3 / 3		
Cardiac disorders			
Cardiac disorders			
subjects affected / exposed	4 / 56 (7.14%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Nervous system disorders			
subjects affected / exposed	8 / 56 (14.29%)		
occurrences causally related to treatment / all	4 / 8		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	11 / 56 (19.64%)		
occurrences causally related to treatment / all	11 / 11		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	7 / 56 (12.50%)		
occurrences causally related to treatment / all	7 / 7		
deaths causally related to treatment / all	0 / 0		
Mucositis			
subjects affected / exposed	12 / 56 (21.43%)		
occurrences causally related to treatment / all	12 / 12		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastrointestinal disorders			
subjects affected / exposed	15 / 56 (26.79%)		
occurrences causally related to treatment / all	12 / 15		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Respiratory disorders			

subjects affected / exposed	2 / 56 (3.57%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal disorders			
subjects affected / exposed	2 / 56 (3.57%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Psychiatric disorders			
subjects affected / exposed	3 / 56 (5.36%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Infection			
subjects affected / exposed	26 / 56 (46.43%)		
occurrences causally related to treatment / all	26 / 26		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Metabolism disorders			
subjects affected / exposed	9 / 56 (16.07%)		
occurrences causally related to treatment / all	7 / 9		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	4xR-CHOP	4xR-CHOP+2xR	6xR-CHOP
Total subjects affected by non-serious adverse events			
subjects affected / exposed	129 / 129 (100.00%)	126 / 126 (100.00%)	52 / 52 (100.00%)
Blood and lymphatic system disorders			
Anemia, grade 3 or 4			
subjects affected / exposed	21 / 129 (16.28%)	14 / 126 (11.11%)	13 / 52 (25.00%)
occurrences (all)	21	14	13
Leukopenia, grade 3 or 4			

subjects affected / exposed	70 / 129 (54.26%)	76 / 126 (60.32%)	31 / 52 (59.62%)
occurrences (all)	70	76	31
Neutropenia, grade 3 or 4			
subjects affected / exposed	20 / 129 (15.50%)	30 / 126 (23.81%)	12 / 52 (23.08%)
occurrences (all)	20	30	12
Thrombocytopenia, grade 3 or 4			
subjects affected / exposed	19 / 129 (14.73%)	10 / 126 (7.94%)	11 / 52 (21.15%)
occurrences (all)	19	10	11
Gastrointestinal disorders			
Mucositis, grade 3 or 4			
subjects affected / exposed	2 / 129 (1.55%)	3 / 126 (2.38%)	6 / 52 (11.54%)
occurrences (all)	2	3	6
Diarrhea, grade 3 or 4			
subjects affected / exposed	4 / 129 (3.10%)	1 / 126 (0.79%)	5 / 52 (9.62%)
occurrences (all)	4	1	5
Renal and urinary disorders			
Creatinine increase, grade 3 or 4			
subjects affected / exposed	4 / 129 (3.10%)	1 / 126 (0.79%)	3 / 52 (5.77%)
occurrences (all)	4	1	3
Infections and infestations			
Infection, grade 3 or 4			
subjects affected / exposed	19 / 129 (14.73%)	14 / 126 (11.11%)	11 / 52 (21.15%)
occurrences (all)	19	14	11

Non-serious adverse events	6xBurkitt protocol		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	56 / 56 (100.00%)		
Blood and lymphatic system disorders			
Anemia, grade 3 or 4			
subjects affected / exposed	25 / 56 (44.64%)		
occurrences (all)	25		
Leukopenia, grade 3 or 4			
subjects affected / exposed	45 / 56 (80.36%)		
occurrences (all)	45		
Neutropenia, grade 3 or 4			
subjects affected / exposed	19 / 56 (33.93%)		
occurrences (all)	19		

Thrombocytopenia, grade 3 or 4 subjects affected / exposed occurrences (all)	33 / 56 (58.93%) 33		
Gastrointestinal disorders Mucositis, grade 3 or 4 subjects affected / exposed occurrences (all) Diarrhea, grade 3 or 4 subjects affected / exposed occurrences (all)	 21 / 56 (37.50%) 21 3 / 56 (5.36%) 3		
Renal and urinary disorders Creatinine increase, grade 3 or 4 subjects affected / exposed occurrences (all)	 1 / 56 (1.79%) 1		
Infections and infestations Infection, grade 3 or 4 subjects affected / exposed occurrences (all)	 28 / 56 (50.00%) 28		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 March 2008	Change of interim PET evaluation from a purely visual to a semi-quantitative SUV-based assessment
01 October 2009	Randomization of interim PET-negative patients between a further 4 cycles R-CHOP or 4 cycles R-CHOP plus 2 extra doses rituximab. After reaching the recruitment goal for this randomization, interim PET-negative patients were no longer subjected to randomization within the trial.
16 December 2010	Collection of serum samples for scientific investigations. Otherwise no protocol change.
01 May 2011	Extension of the study period until December 2012 to increase the recruitment of interim PET-positive patients

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.

The effect of 2 extra doses of rituximab on outcome in patients with CD20-positive lymphomas was only tested in interim PET-negative patients.
The recruitment goal for interim PET-positive patients was not reached.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/29750632

http://www.ncbi.nlm.nih.gov/pubmed/30610279

http://www.ncbi.nlm.nih.gov/pubmed/31427567

http://www.ncbi.nlm.nih.gov/pubmed/31710995

http://www.ncbi.nlm.nih.gov/pubmed/31890813

http://www.ncbi.nlm.nih.gov/pubmed/32022621

http://www.ncbi.nlm.nih.gov/pubmed/32067259

http://www.ncbi.nlm.nih.gov/pubmed/32385164

http://www.ncbi.nlm.nih.gov/pubmed/33246974

http://www.ncbi.nlm.nih.gov/pubmed/34523055

http://www.ncbi.nlm.nih.gov/pubmed/34708297