Clinical trial results:
A randomized phase II study of prednisone, vinblastine, doxorubicin, and gemcitabine in patients with intermediate stage Hodgkin's lymphoma

Summary

EudraCT number	2007-003467-48
Trial protocol	DE
Global end of trial date	17 November 2013

Results information

Result version number	v1 (current)
This version publication date	23 April 2020
First version publication date	23 April 2020

Trial information

Trial identification

Sponsor protocol code	Uni-Koeln-949

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00512980
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Cologne
Sponsor organisation address	Albertus Magnus-Platz, Köln, Germany, 50923
Public contact	Trial Coordination Center of the German Hodgkin Study Group (GHSG), German Hodgkin Study Group (GHSG), 0049 22147888200, ghsg@uk-koeln.de
Scientific contact	Trial Coordination Center of the German Hodgkin Study Group (GHSG), German Hodgkin Study Group (GHSG), 0049 22147888200, ghsg@uk-koeln.de

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	05 December 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 November 2013
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of this phase II trial were to assess the toxicity and activity of PVAG-14 in patients with early-stage unfavorable Hodgkin lymphoma.

Protection of trial subjects:

Written informed consent prior to study entry, G-CSF prophylaxis, weekly blood tests during therapy, dose reduction strategy in case of inadequate recovery of blood values

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 November 2008
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 41
Worldwide total number of subjects	41
EEA total number of subjects	41

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)	41
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment started on 17 Nov 2008, was much slower than expected even after increasing the number of trial sites and extending the recruitment period, and was stopped on 13 May 2011 with a total of 41 patients enrolled, because it was deemed unlikely to reach the planned number of 100 patients in a reasonable time.

Pre-assignment

Screening details:

Pre-study assessments should be performed within 28 days prior to enrollment. Main inclusion criteria: previously untreated, histologically confirmed Hodgkin lymphoma; CSI-II with ≥1 risk factor; age 18-60 years. Main exclusion criteria: prior chemo- or radiotherapy; concurrent disease preventing protocol treatment; pregnancy, lactation; ECOG >2.

Period 1

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

Blinding implementation details:

Not applicable

Arms

Are arms mutually exclusive?	Yes
Arm title	8x PVAG-14, Doxo=25mg

Arm description:

Eight cycles of the PVAG chemotherapy regimen with a doxorubicin dose of 25 mg/m² BSA recycled every 14 days; involved-field radiotherapy applied 4-6 weeks after the end of chemotherapy with an overall dose of 30 Gy (1.8-2.0 Gy 5 times per week)

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

Dosage and administration details:

50 mg Prednisone administered on days 1-3 of each 14-day cycle

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

Dosage and administration details:

6 mg Vinblastine per m² BSA administered on day 1 of each 14-day cycle over 10 minutes

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

Dosage and administration details:

25 mg Doxorubicin per m² BSA administered on day 1 of each 14-day cycle over 30 minutes

Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1000 mg Gemcitabine per m² BSA administered on day 1 of each 14-day cycle over 30 minutes

Arm title	8x PVAG-14, Doxo=35mg

Arm description:

Eight cycles of the PVAG chemotherapy regimen with a doxorubicin dose of 35 mg/m² BSA recycled every 14 days; involved-field radiotherapy applied 4-6 weeks after the end of chemotherapy with an overall dose of 30 Gy (1.8-2.0 Gy 5 times per week)

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

Dosage and administration details:

50 mg Prednisone administered on days 1-3 of each 14-day cycle

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

Dosage and administration details:

6 mg Vinblastine per m² BSA administered on day 1 of each 14-day cycle over 10 minutes

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

Dosage and administration details:

35 mg Doxorubicin per m² BSA administered on day 1 of each 14-day cycle over 30 minutes

Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1000 mg Gemcitabine per m² BSA administered on day 1 of each 14-day cycle over 30 minutes

Number of subjects in period 1	8x PVAG-14, Doxo=25mg	8x PVAG-14, Doxo=35mg
Started	21	20
Completed	20	20
Not completed	1	0
Adverse event, non-fatal	1	-

Baseline characteristics

Reporting groups	
Reporting group title	8x PVAG-14, Doxo=25mg
Reporting group description:	
Eight cycles of the PVAG chemotherapy regimen with a doxorubicin dose of 25 mg/m² BSA recycled every 14 days; involved-field radiotherapy applied 4-6 weeks after the end of chemotherapy with an overall dose of 30 Gy (1.8-2.0 Gy 5 times per week)	
Reporting group title	8x PVAG-14, Doxo=35mg
Reporting group description:	
Eight cycles of the PVAG chemotherapy regimen with a doxorubicin dose of 35 mg/m² BSA recycled every 14 days; involved-field radiotherapy applied 4-6 weeks after the end of chemotherapy with an overall dose of 30 Gy (1.8-2.0 Gy 5 times per week)	

Reporting group values	8x PVAG-14, Doxo=25mg	8x PVAG-14, Doxo=35mg	Total
Number of subjects	21	20	41
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)	21	20	41
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
median	33	38.5	
full range (min-max)	18 to 57	19 to 53	-
Gender categorical Units: Subjects			
Female	11	10	21
Male	10	10	20
Ann Arbor Stage Units: Subjects			
IA	0	0	0
IB	0	1	1
IIA	17	14	31
IIB	4	5	9
ECOG performance status Units: Subjects			
ECOG 0	15	16	31
ECOG 1	6	4	10
Large mediastinal mass Units: Subjects			
No	16	17	33

Yes	5	3	8
Extranodal disease Units: Subjects			
No	20	19	39
Yes	1	1	2
Involvement of 3 or more nodal areas Units: Subjects			
No	5	11	16
Yes	16	9	25
Elevated erythrocyte sedimentation rate Units: Subjects			
No	10	10	20
Yes	11	10	21

Subject analysis sets

Subject analysis set title	Pooled treatment groups
Subject analysis set type	Full analysis

Subject analysis set description:

Secondary efficacy endpoints were analyzed in the pooled treatment groups to increase power.

Reporting group values	Pooled treatment groups		
Number of subjects	41		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	41		
From 65-84 years	0		
85 years and over	0		
Age continuous Units: years			
median	38		
full range (min-max)	18 to 57		
Gender categorical Units: Subjects			
Female	21		
Male	20		
Ann Arbor Stage Units: Subjects			
IA	0		
IB	1		
IIA	31		
IIB	9		
ECOG performance status			

Units: Subjects			
ECOG 0	31		
ECOG 1	10		
Large mediastinal mass Units: Subjects			
No	33		
Yes	8		
Extranodal disease Units: Subjects			
No	39		
Yes	2		
Involvement of 3 or more nodal areas Units: Subjects			
No	16		
Yes	25		
Elevated erythrocyte sedimentation rate Units: Subjects			
No	20		
Yes	21		

End points

End points reporting groups

Reporting group title	8x PVAG-14, Doxo=25mg

Reporting group description:

Eight cycles of the PVAG chemotherapy regimen with a doxorubicin dose of 25 mg/m² BSA recycled every 14 days; involved-field radiotherapy applied 4-6 weeks after the end of chemotherapy with an overall dose of 30 Gy (1.8-2.0 Gy 5 times per week)

Reporting group title	8x PVAG-14, Doxo=35mg

Reporting group description:

Eight cycles of the PVAG chemotherapy regimen with a doxorubicin dose of 35 mg/m² BSA recycled every 14 days; involved-field radiotherapy applied 4-6 weeks after the end of chemotherapy with an overall dose of 30 Gy (1.8-2.0 Gy 5 times per week)

Subject analysis set title	Pooled treatment groups
Subject analysis set type	Full analysis

Subject analysis set description:

Secondary efficacy endpoints were analyzed in the pooled treatment groups to increase power.

Primary: Complete remission rate

End point title	Complete remission rate[1]

End point description:

Complete remission rate was assessed in the CT-based definitive restaging 4-6 weeks after completion of radiotherapy.
Two interim analyses and a final analysis were planned. The first interim analysis was scheduled after 19 patients per arm were evaluable. Enrollment was stopped by the time of the interim analyses because of slow recruitment, leaving only 3 patients enrolled in addition to the interim analysis sample. The second interim analysis was thus not done. The final analysis was done descriptively for both arms separately including all enrolled patients.

End point type	Primary

End point timeframe:

4-6 weeks after completion of radiotherapy

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Enrollment was stopped after 41 out of 100 planned patients because of slow recruitment. Due to the small sample size, analysis was done descriptively; no confirmative test, no subgroup analyses and no sensitivity analyses were done. The protocol defines a complete remission rate of 83% as benchmark for insufficient efficacy. The 95% CI for the observed overall complete remission rate of 98% ranged from 87% to 100% and thus exceeded the predefined efficacy benchmark.

End point values	8x PVAG-14, Doxo=25mg	8x PVAG-14, Doxo=35mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	20		
Units: patients				
Partial remission	1	0		
Complete remission	20	20		

Statistical analyses

No statistical analyses for this end point

Primary: Incidence of hematological toxicity grade III/IV

End point title	Incidence of hematological toxicity grade III/IV[2]

End point description:

Hematological toxicity was defined as any case of leukopenia, thrombocytopenia or anemia of CTCAE grade III or IV at any time during chemotherapy.
Two interim analyses and a final analysis were planned. The first interim analysis was scheduled after 19 patients per arm were evaluable. Enrollment was stopped by the time of the interim analyses because of slow recruitment, leaving only 3 patients enrolled in addition to the interim analysis sample. The second interim analysis was thus not done. The final analysis was done descriptively for both arms separately including all enrolled patients.

End point type	Primary

End point timeframe:

During chemotherapy

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Enrollment was stopped after 41 out of 100 planned patients because of slow recruitment. Due to the small sample size, analysis was done descriptively; no confirmative test, no subgroup analyses and no sensitivity analyses were done. The protocol defines a hematological toxicity incidence of 62% as benchmark for inacceptable toxicity. The 95% CI for the observed incidence of 10% ranged from 3% to 23% and was thus below the toxicity benchmark.

End point values	8x PVAG-14, Doxo=25mg	8x PVAG-14, Doxo=35mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	20		
Units: patients				
Hematological toxicity of CTCAE grade III/IV	1	3		
No hematological toxicity of CTCAE grade III/IV	20	17		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival

End point title	Progression-free survival

End point description:

Progression-free survival was calculated from the date of initial staging until progressive disease, relapse, or death from any cause or, if none of these occured, censored at the date of the last determination of continuing remission.

End point type	Secondary

End point timeframe:

Progression-free survival at 2 years

End point values	Pooled treatment groups			
Subject group type	Subject analysis set			
Number of subjects analysed	41			
Units: percent				
number (confidence interval 95%)	94.2 (86.3 to 100)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival

End point description:

Overall survival was calculated from the date of initial staging until death from any cause or, if the patient was alive, censored at the date of the last information about the patient.

End point type	Secondary

End point timeframe:

Overall survival at 2 years

End point values	Pooled treatment groups			
Subject group type	Subject analysis set			
Number of subjects analysed	41			
Units: percent				
number (not applicable)	100			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From start of treatment until 28 days after last study treatment or until AE resolution; AEs beginning >28 days after final study treatment reported only if considered related to study treatment

Adverse event reporting additional description:

All AEs greater than CTCAE grade 2 were to be recorded in the source documents and the CRFs.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10.1

Reporting groups

Reporting group title	8x PVAG-14, Doxo=25mg

Reporting group description:

Eight cycles of the PVAG chemotherapy regimen with a doxorubicin dose of 25 mg/m² BSA recycled every 14 days; involved-field radiotherapy applied 4-6 weeks after the end of chemotherapy with an overall dose of 30 Gy (1.8-2.0 Gy 5 times per week)

Reporting group title	8x PVAG-14, Doxo=35mg

Reporting group description:

Eight cycles of the PVAG chemotherapy regimen with a doxorubicin dose of 35 mg/m² BSA recycled every 14 days; involved-field radiotherapy applied 4-6 weeks after the end of chemotherapy with an overall dose of 30 Gy (1.8-2.0 Gy 5 times per week)

Serious adverse events	8x PVAG-14, Doxo=25mg	8x PVAG-14, Doxo=35mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 21 (19.05%)	2 / 20 (10.00%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
Guillain-Barre syndrome			
subjects affected / exposed	1 / 21 (4.76%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 21 (4.76%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			

subjects affected / exposed	1 / 21 (4.76%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Faecaloma			
subjects affected / exposed	1 / 21 (4.76%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess			
subjects affected / exposed	0 / 21 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scrotal abscess			
subjects affected / exposed	0 / 21 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile infection			
subjects affected / exposed	1 / 21 (4.76%)	0 / 20 (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: 5 %

Non-serious adverse events	8x PVAG-14, Doxo=25mg	8x PVAG-14, Doxo=35mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 21 (33.33%)	8 / 20 (40.00%)	
Nervous system disorders			
Nervous system disorder			
alternative dictionary used: NCI CTCAE 3.0			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 21 (9.52%)	0 / 20 (0.00%)	
occurrences (all)	6	0	
Blood and lymphatic system disorders			

Leukopenia alternative dictionary used: NCI CTCAE 3.0 alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 4	3 / 20 (15.00%) 3	
General disorders and administration site conditions Drug fever alternative dictionary used: NCI CTCAE 3.0 alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1	1 / 20 (5.00%) 1	
Gastrointestinal disorders Nausea or vomiting alternative dictionary used: NCI CTCAE 3.0 alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	2 / 21 (9.52%) 4	1 / 20 (5.00%) 4	
Mucositis alternative dictionary used: NCI CTCAE 3.0 alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1	1 / 20 (5.00%) 2	
Infections and infestations Infection alternative dictionary used: NCI CTCAE 3.0 alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	2 / 21 (9.52%) 2	1 / 20 (5.00%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 May 2011	Premature termination of recruitment

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
13 May 2011	Premature termination of recruitment	-

Notes:

Limitations and caveats

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

Enrollment was stopped after 41 out of 100 planned patients because of slow recruitment. Due to the small sample size, analyses were done descriptively; no confirmative tests, no subgroup analyses and no sensitivity analyses were done.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/25768996