Clinical trial results:
Efficacy and safety of Rituximab, high-dose ARA-C and Dexamethasone (R-HAD) alone or in combination with Bortezomib in patients with relapsed or refractory mantle cell lymphoma
A randomized Phase III Trial of the European MCL Network

Summary

EudraCT number	2005-005144-62
Trial protocol	DE
Global end of trial date	02 April 2020

Results information

Result version number	v1 (current)
This version publication date	25 June 2022
First version publication date	25 June 2022

Trial information

Trial identification

Sponsor protocol code	MCL2005-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01449344
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	LMU Klinikum
Sponsor organisation address	Marchioninistr. 15, München, Germany, 81377
Public contact	Dr. Burkhard Deuß, ClinAssess GmbH, +49 2171363360, info@clinassess.de
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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	19 April 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 April 2020
Global end of trial reached?	Yes
Global end of trial date	02 April 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

This study is a prospective, randomized, multicenter, open-label phase III clinical trial to compare the efficacy and safety of Bortezomib in combination with Rituximab, high-dose Ara-C and dexamethasone (R-HAD) to R-HAD alone in patients with relapsed or refractory MCL after or not eligible for myeloablative treatment. The primary endpoint is time to treatment failure (TTF).

Protection of trial subjects:

The aim of the trial is to compare known standard treatments. Therefore, the therapy of the patients is part of the regular care. To ensure, that only patients with mantle cell lymphoma are included in the trial, the initial diagnosis of all patients enrolled was verified by reference pathologists.

Background therapy:

The objective of this trial is to compare the efficacy and safety of the combination of Rituximab, high-dose Ara-C and dexamethasone (R-HAD) with Bortezomib to R-HAD alone in patients with relapsed or refractory mantle cell lymphoma after 1 to 3 prior lines of therapy and not eligible for myeloablative treatment. The primary trial endpoint is the time to treatment failure (TTF). Study arms will be compared to each other to evaluate the effect of additional Bortezomib.

Patients receive two cycles of Rituximab, Cytarabine and Dexamethasone ± Bortezomib every three weeks. Those patients who respond to the treatment, defined as complete (CR) or partial remission (PR) at midterm staging after two cycles, will receive two additional treatment cycles. In case of stable disease (SD), patients may proceed with the treatment at the investigator’s discretion.

Evidence for comparator:

Cytarabine (AraC) has long been proven to be an effective drug in the treatment of many Non Hodgkin lymphomas (NHL), in the treatment of MCL it is used especially in relapsed or refractory situations after a CHOP like regimen. In nearly all MCLs a high expression of CD20 may be detected, but Rituximab monotherapy has documented only moderate activity in MCL. In contrast, a combined immunochemotherapy approach has been proven to be superior in randomized trials. These results also apply in relapsed MCL.

Actual start date of recruitment	05 May 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Scientific research
Long term follow-up duration	36 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 50
Country: Number of subjects enrolled	Germany: 78
Worldwide total number of subjects	128
EEA total number of subjects	128

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)	33
From 65 to 84 years	93
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

First patient in (randomized): 5 May 2012
Last patient in (randomized): 20 Dec 2016
Stop criterion: sponsor-decided premature stop due to a low recruitment rate

Pre-assignment

Screening details:

Each subject must fulfill all of the inclusion and exclusion criteria as defined in the study protocol before enrollment to the study:
Confirmed pathological diagnosis of MCL
Relapse or progression following 1 to 3 prior lines of anti-neoplastic standard therapy
18 years or older and written informed consent

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-HAD (Arm A)

Arm description:

Rituximab, high-dose Ara-C and dexamethasone

Arm type	No IMP

No investigational medicinal product assigned in this arm

Arm title	R-HAD+Bortezomib (Arm B)

Arm description:

Rituximab, high-dose Ara-C and dexamethasone in combination with Bortezomib

Arm type	Experimental
Investigational medicinal product name	Bortezomib
Investigational medicinal product code	
Other name	Velcade (R)
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Subcutaneous use, Intravenous use

Dosage and administration details:

Bortezomib 1.5 mg/m² was administered additionally to the chemotherapy R-HAD as a intravenous or subcutaneous injection (subcutaneous through the thighs or abdomen) on day 1 at least one hour prior to Rituximab infusion and similarly on day 4. Treatment course will be repeated in 3-week intervals (day 22 + / - 3 days).

Number of subjects in period 1	R-HAD (Arm A)	R-HAD+Bortezomib (Arm B)
Started	64	64
Completed	59	59
Not completed	5	5
Consent withdrawn by subject	1	1
Diagnosis of MCL rejected	-	1

Lost to follow-up	-	1
Protocol deviation	4	2

Baseline characteristics

Reporting groups	
Reporting group title	R-HAD (Arm A)
Reporting group description:	
Rituximab, high-dose Ara-C and dexamethasone	
Reporting group title	R-HAD+Bortezomib (Arm B)
Reporting group description:	
Rituximab, high-dose Ara-C and dexamethasone in combination with Bortezomib	

Reporting group values	R-HAD (Arm A)	R-HAD+Bortezomib (Arm B)	Total
Number of subjects	64	64	128
Age categorical Units: Subjects			
Adults (18-64 years)	13	20	33
From 65-84 years	50	43	93
85 years and over	1	1	2
Age continuous Units: years			
median	71	70	
full range (min-max)	41 to 85	41 to 85	-
Gender categorical Units: Subjects			
Female	13	18	31
Male	51	46	97
Study group Units: Subjects			
LYSA	26	24	50
GLSG	38	40	78
Stage Units: Subjects			
stage I	4	5	9
stage II	6	8	14
stage III	5	9	14
stage IV	49	42	91
ECOG Units: Subjects			
ECOG 0	29	25	54
ECOG 1	29	37	66
ECOG 2	6	2	8
B-symptoms Units: Subjects			
No	50	46	96
Yes	14	18	32
Bone marrow involvement Units: Subjects			
No	25	23	48
Yes	39	41	80

Gastrointestinal involvement Units: Subjects			
No	55	55	110
Yes	9	9	18
Number of other extranodal involvement Units: Subjects			
zero	54	50	104
one	3	12	15
two	4	2	6
three	3	0	3
MIPI Units: Subjects			
Low	11	16	27
Intermediate	22	25	47
High	31	23	54
Previous lines of treatment Units: Subjects			
one	40	51	91
two	17	9	26
three	7	4	11
Previous high-dose cytarabine Units: Subjects			
No	42	40	82
Yes	22	24	46
Previous ASCT Units: Subjects			
Yes	24	26	50
No	40	38	78
Previous remission Units: Subjects			
Yes	61	62	123
No	3	2	5
Primary salvage treatment Units: Subjects			
Yes	1	2	3
No	63	62	125
LDH ratio to ULN Units: ratio			
median	0.95	0.93	
full range (min-max)	0.51 to 5.79	0.57 to 6.74	-
Hb Units: g/L			
median	1.20	1.29	
full range (min-max)	0.64 to 1.66	0.88 to 1.56	-
Leucocytes Units: 10^9/L			
median	7.20	6.96	
full range (min-max)	0.050 to 240.60	1.82 to 374.76	-
Thrombocytes Units: 10^9/L			
median	150	158	

full range (min-max)	20 to 437	24 to 555	-
Neutr. Granulocytes			
Units: 10^9/L			
median	3.79	3.83	
full range (min-max)	0 to 55.44	0.38 to 44.88	-
Lymphocytes			
Units: 10^9/L			
median	1.94	1.38	
full range (min-max)	0.01 to 233.38	0.15 to 363.52	-
Number of Extranodal involvement			
Units: count			
median	1	1	
full range (min-max)	0 to 5	0 to 4	-
MIPI score			
Units: score			
median	6.15	6.05	
full range (min-max)	4.96 to 8.23	4.92 to 7.86	-
Time from first diagnosis			
Units: years			
median	3.7	3.9	
full range (min-max)	0.1 to 14.2	0 to 11.1	-
Time from last relapse/progression			
Units: days			
median	27	31	
full range (min-max)	4 to 1504	2 to 1136	-

Subject analysis sets

Subject analysis set title	mITT
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The modified intention-to-treat (mITT) analysis set comprises all subjects who are randomized, regardless of which treatment they received and whether further protocol violations have occurred. Patients for whom the diagnosis of MCL is rejected by the central pathology review are excluded from the mITT set. The mITT set applies for primary efficacy analysis, secondary efficacy analysis, and subgroup analyses.

Subject analysis set title	PP
Subject analysis set type	Per protocol

Subject analysis set description:

The per protocol (PP) analysis set comprises all subjects of the mITT set who actually received the treatment they were assigned to by randomization and in whom treatment was not stopped prematurely. Thus, patients with progressive (PD) or stable disease (SD) at the end of therapy have to have received at least two cycles and patients with partial (PR, CRu) or complete remission (CR) have to have received the total number of four cycles of therapy. Patients still belong to the PP analysis set if further protocol violations occur. The PP set applies for secondary efficacy analysis

Subject analysis set title	Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety set comprises all randomized subjects who have received at least one cycle of therapy. Patients are evaluated according to the therapy they actually received. The safety set applies for safety analysis.

Reporting group values	mITT	PP	Safety
Number of subjects	127	118	126
Age categorical Units: Subjects			
Adults (18-64 years)	33	30	31
From 65-84 years	92	86	93
85 years and over	2	2	2
Age continuous Units: years			
median	70	70	71
full range (min-max)	41 to 85	41 to 85	41 to 85
Gender categorical Units: Subjects			
Female	31	29	30
Male	96	89	96
Study group Units: Subjects			
LYSA	50	47	50
GLSG	77	71	76
Stage Units: Subjects			
stage I	9	8	9
stage II	14	14	14
stage III	14	13	14
stage IV	90	83	89
ECOG Units: Subjects			
ECOG 0	53	51	54
ECOG 1	66	60	64
ECOG 2	8	7	8
B-symptoms Units: Subjects			
No	95	89	95
Yes	32	29	31
Bone marrow involvement Units: Subjects			
No	48	46	48
Yes	79	72	78
Gastrointestinal involvement Units: Subjects			
No	109	101	109
Yes	18	17	17
Number of other extranodal involvement Units: Subjects			
zero	100	94	100
one	18	16	17
two	6	5	6
three	3	3	3
MIPI Units: Subjects			
Low	27	24	26

Intermediate	46	45	47
High	54	49	53
Previous lines of treatment Units: Subjects			
one	90	84	89
two	26	23	26
three	11	11	11
Previous high-dose cytarabine Units: Subjects			
No	81	75	81
Yes	46	43	45
Previous ASCT Units: Subjects			
Yes	50	47	48
No	77	71	78
Previous remission Units: Subjects			
Yes	122	113	121
No	5	5	5
Primary salvage treatment Units: Subjects			
Yes	3	3	3
No	124	115	123
LDH ratio to ULN Units: ratio			
median	0.95	0.93	0.94
full range (min-max)	0.51 to 6.74	0.51 to 6.74	0.51 to 6.74
Hb Units: g/L			
median	1.27	1.27	1.27
full range (min-max)	0.64 to 1.66	0.78 to 1.66	0.64 to 1.66
Leucocytes Units: 10^9/L			
median	6.98	6.97	6.96
full range (min-max)	0.050 to 374.76	1.82 to 240.60	0.050 to 240.60
Thrombocytes Units: 10^9/L			
median	153	155	153
full range (min-max)	20 to 555	24 to 555	20 to 555
Neutr. Granulocytes Units: 10^9/L			
median	3.84	3.78	3.78
full range (min-max)	0 to 55.44	0.38 to 55.44	0 to 55.44
Lymphocytes Units: 10^9/L			
median	1.60	1.62	1.58
full range (min-max)	0.01 to 363.52	0.15 to 233.38	0.01 to 233.38
Number of Extranodal involvement Units: count			
median	1	1	1
full range (min-max)	0 to 5	0 to 5	0 to 5

MIPI score Units: score median full range (min-max)	 6.08 4.92 to 8.23	 6.08 4.92 to 8.23	 6.08 4.92 to 8.23
Time from first diagnosis Units: years median full range (min-max)	 3.8 0 to 14.2	 3.8 0 to 14.2	 3.8 0 to 14.2
Time from last relapse/progression Units: days median full range (min-max)	 28 2 to 1504	 29 2 to 1504	 29 2 to 1504

End points

End points reporting groups

Reporting group title	R-HAD (Arm A)

Reporting group description:

Rituximab, high-dose Ara-C and dexamethasone

Reporting group title	R-HAD+Bortezomib (Arm B)

Reporting group description:

Rituximab, high-dose Ara-C and dexamethasone in combination with Bortezomib

Subject analysis set title	mITT
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The modified intention-to-treat (mITT) analysis set comprises all subjects who are randomized, regardless of which treatment they received and whether further protocol violations have occurred. Patients for whom the diagnosis of MCL is rejected by the central pathology review are excluded from the mITT set. The mITT set applies for primary efficacy analysis, secondary efficacy analysis, and subgroup analyses.

Subject analysis set title	PP
Subject analysis set type	Per protocol

Subject analysis set description:

The per protocol (PP) analysis set comprises all subjects of the mITT set who actually received the treatment they were assigned to by randomization and in whom treatment was not stopped prematurely. Thus, patients with progressive (PD) or stable disease (SD) at the end of therapy have to have received at least two cycles and patients with partial (PR, CRu) or complete remission (CR) have to have received the total number of four cycles of therapy. Patients still belong to the PP analysis set if further protocol violations occur. The PP set applies for secondary efficacy analysis

Subject analysis set title	Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety set comprises all randomized subjects who have received at least one cycle of therapy. Patients are evaluated according to the therapy they actually received. The safety set applies for safety analysis.

Primary: Time to treatment failure (mITT)

End point title	Time to treatment failure (mITT)

End point description:

The primary endpoint is time to treatment failure (TTF) calculated from the date of randomization. Treatment failure is defined as
– progressive disease (PD) or stable disease (SD) following induction therapy or
– relapse or progression after complete or partial remission (CR, CRu, PR) or
– death from any cause,
whichever occurred first. Response to therapy is defined as the staging result after the last cycle of therapy. If no treatment failure has been observed until the time of analysis, TTF is censored at the day of the last follow-up staging.

End point type	Primary

End point timeframe:

Midterm staging, end of treatment evaluation, follow-up evaluations

End point values	R-HAD (Arm A)	R-HAD+Bortezomib (Arm B)	mITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	64	60[1]	124[2]	
Units: Months				
median (confidence interval 95%)	2.6 (1.9 to 7.1)	12 (6.2 to 21.2)	6.2 (2.7 to 10.6)	

Notes:

[1] - 3 patients were excluded from the analysis because of missing staging result.

[2] - 3 patients from R-HAD+B group were excluded from the analysis because of missing staging result.

Attachments (see zip file)	Primary analysis/PRIMARY ANALYSIS.docx

Statistical analyses

Statistical analysis title	Primary analysis

Statistical analysis description:

The primary statistical comparison between two treatment arms by the log-rank test was performed as underrunning analysis of the sequential test, as no decision boundary was reached. In this underrunning analysis, the p-value and the adjusted maximum-likelihood estimate for the hazard ratio were calculated correcting for the performed interim analyses.

Comparison groups	R-HAD (Arm A) v R-HAD+Bortezomib (Arm B)
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.045 [4]
Method	sequential eval. of Logrank stat.
Parameter estimate	adjusted mle of hazard ratio
Point estimate	0.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	99999

Notes:

[3] - This study was planned as a confirmatory superiority trial. A two-sided log-rank test with a significance level of 5% will be used to compare TTF in two arms. The null hypothesis H0 is TTF(R-HAD) =TTF(R-HAD+B), and the alternative hypothesis H1 is TTF(R-HAD)≠TTF(R-HAD+B).

[4] - P-value from an underrunning analysis of a sequential test.

No valid method for calculation of confidence interval of adjusted mle of hazard ratio is known. Since database does not accept this, (-1 ,999999) was entered for interval.

Statistical analysis title	Sensitivity analysis for primary endpoint

Statistical analysis description:

After the clinical cut-off date of 19 April 2021, an unplanned data update was performed and one more event of treatment failure in the R-HAD+B group was documented. The updated data were analyzed for the primary endpoint as a sensitivity analysis for the primary analysis.

Comparison groups	R-HAD (Arm A) v R-HAD+Bortezomib (Arm B)

Number of subjects included in analysis	124
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.089 [5]
Method	sequential eval. of Logrank stat.
Parameter estimate	adjusted mle of hazard ratio
Point estimate	0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	999999

Notes:

[5] - p value from unterrunning analysis of sequential test.

No valid method for calculation of confidence interval of adjusted mle of hazard ratio is known. Since database does not accept this, (-1 ,999999) was entered for interval.

Secondary: Complete remission rates (mITT)

End point title	Complete remission rates (mITT)

End point description:

Complete remission rate: the rate of complete remissions (CR) after induction therapy. CR including/excluding CRu will be evaluated separately.

End point type	Secondary

End point timeframe:

Midterm staging, end of treatment evaluation

End point values	R-HAD (Arm A)	R-HAD+Bortezomib (Arm B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	60[6]		
Units: patients				
Complete remission (CR)	8	17		
Complete remission (CR+CRu)	12	25		

Notes:

[6] - 3 patients from the mITT set were excluded from the analysis because of missing staging results.

Attachments (see zip file)	Response rates (mITT)/RHAD EudraCT.docx

Statistical analyses

Statistical analysis title	Response rates

Statistical analysis description:

CR- and OR-rate for each treatment arm were calculated with the corresponding 95% confidence intervals, and compared by two-sided Fisher’s exact test.

Comparison groups	R-HAD (Arm A) v R-HAD+Bortezomib (Arm B)

Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.043 [7]
Method	Fisher exact

Notes:

[7] - complete remission (CR): P=0.043
complete remission (CR, CRu): P=0.0062

Secondary: Complete remission rates (PP)

End point title	Complete remission rates (PP)

End point description:

End point type	Secondary

End point timeframe:

Midterm staging, end of treatment evaluation

End point values	R-HAD (Arm A)	R-HAD+Bortezomib (Arm B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58[8]	58[9]		
Units: patients				
Complete remission (CR)	8	17		
Complete remission (CR+CRu)	11	25		

Notes:

[8] - 1 patient was excluded from PP set because of missing staging result.

[9] - 1 patient was excluded from PP set because of missing staging result.

Attachments (see zip file)	Response rates (PP)/RHAD EudraCT.docx

Statistical analyses

Statistical analysis title	Response rates

Statistical analysis description:

CR- and OR-rate for each treatment arm were calculated with the corresponding 95% confidence intervals, and compared by two-sided Fisher’s exact test.

Comparison groups	R-HAD (Arm A) v R-HAD+Bortezomib (Arm B)
Number of subjects included in analysis	116
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.07 [10]
Method	Fisher exact

Notes:

[10] - Complete remission (CR): p=0.070
Complete remission (CR+CRu): p=0.0086

Secondary: Time to treatment failure (PP)

End point title	Time to treatment failure (PP)

End point description:

End point type	Secondary

End point timeframe:

Midterm staging, end of treatment evaluation, follow-up evaluations

End point values	R-HAD (Arm A)	R-HAD+Bortezomib (Arm B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58[11]	58[12]		
Units: Months				
median (confidence interval 95%)	2.6 (1.3 to 6.8)	12.9 (7.6 to 23.2)		

Notes:

[11] - 1 patient was excluded from the PP analysis because of missing staging results during induction.

[12] - 1 patient was excluded from the PP analysis because of missing staging results during induction.

Attachments (see zip file)	TTF (PP)/RHAD EudraCT.docx

Statistical analyses

Statistical analysis title	TTF (PP)

Statistical analysis description:

Kaplan-Meier estimates stratified by treatment groups were calculated with 95% confidence intervals at 12, 24, and 36 months. The hazard ratio of Bortezomib+R-HAD to R-HAD with 95% confidence intervals and the corresponding P values will be calculated from both univariate and multivariate Cox proportional hazards models adjusted for the MIPI prognostic score at trial baseline and time from first diagnosis to randomization, without correction for the sequential design.

Comparison groups	R-HAD (Arm A) v R-HAD+Bortezomib (Arm B)
Number of subjects included in analysis	116
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.017
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.39
upper limit	0.91

Secondary: Progression-free survival (mITT)

End point title	Progression-free survival (mITT)

End point description:

Progression free survival (PFS): time from randomization to first documentation of progression or relapse or death from any cause, whichever occurred first. Patients with no event during follow-up are censored at the day of the last follow-up staging. For per protocol analysis, patients with new lymphoma

treatment before progression will be censored additionally or earlier at treatment start.

End point type	Secondary

End point timeframe:

Midterm staging, end of treatment evaluation, follow-up evaluations

End point values	R-HAD (Arm A)	R-HAD+Bortezomib (Arm B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	60[13]		
Units: Months				
median (confidence interval 95%)	9.2 (6.2 to 14.3)	15.4 (12.0 to 22.0)		

Notes:

[13] - 3 patients were excluded from the analysis because of missing staging results during induction.

Attachments (see zip file)	PFS (mITT)/RHAD EudraCT.docx

Statistical analyses

Statistical analysis title	PFS (mITT)

Statistical analysis description:

Kaplan-Meier estimates at 12, 24, and 36 months were calculated with 95% confidence intervals. PFS was compared between two treatment arms by log-rank test. Hazard ratios with 95% confidence intervals and the corresponding P values were calculated from multivariate Cox proportional hazards models adjusted for the MIPI prognostic score at baseline and time from first diagnosis.

Comparison groups	R-HAD+Bortezomib (Arm B) v R-HAD (Arm A)
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	1.15

Secondary: Progression-free survival (PP)

End point title	Progression-free survival (PP)

End point description:

Progression free survival (PFS): time from randomization to first documentation of progression or relapse or death from any cause, whichever occurred first. Patients with no event during follow-up are censored at the day of the last follow-up staging. For per protocol analysis, patients with new lymphoma treatment before progression will be censored additionally or earlier at treatment start.

End point type	Secondary

End point timeframe:

Midterm staging, end of treatment evaluation, follow-up evaluations

End point values	R-HAD (Arm A)	R-HAD+Bortezomib (Arm B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58[14]	58[15]		
Units: Months				
median (confidence interval 95%)	7.4 (6.2 to 18.8)	16.3 (12.8 to 30.8)		

Notes:

[14] - 1 patient was excluded from the analysis because of missing staging results during induction.

[15] - 1 patient was excluded from the analysis because of missing staging results during induction.

Attachments (see zip file)	PFS (PP)/RHAD EudraCT.docx

Statistical analyses

Statistical analysis title	PFS (PP)

Statistical analysis description:

Kaplan-Meier estimates at 12, 24, and 36 months were calculated with 95% confidence intervals. PFS was compared between two treatment arms by log-rank test. Hazard ratios with 95% confidence intervals and the corresponding P values were calculated from multivariate Cox proportional hazards models adjusted for the MIPI prognostic score at baseline and time from first diagnosis.

Comparison groups	R-HAD (Arm A) v R-HAD+Bortezomib (Arm B)
Number of subjects included in analysis	116
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.021
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.36
upper limit	0.92

Secondary: Response duration (mITT)

End point title	Response duration (mITT)

End point description:

Progression free survival of responders (PFS of responders) or response duration (RD): time from end of successful (CR, CRu, PR) trial therapy to first documentation of progression or relapse or death from any cause, whichever occurred first. Patients with no event during follow-up are censored at the day of the last follow-up staging.

End point type	Secondary

End point timeframe:

Follow-up evaluations

End point values	R-HAD (Arm A)	R-HAD+Bortezomib (Arm B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	38		
Units: Months				
median (confidence interval 95%)	13.5 (8.2 to 33.7)	20.7 (12.2 to 30.9)		

Attachments (see zip file)	RD(mITT)/RHAD EudraCT.docx

Statistical analyses

Statistical analysis title	RD (mITT)

Statistical analysis description:

Kaplan-Meier estimates at 12, 24, and 36 months were calculated with 95% confidence intervals. RD was compared between two treatment arms by log-rank test. Hazard ratios with 95% confidence intervals and the corresponding P values were calculated from multivariate Cox proportional hazards models adjusted for the MIPI prognostic score at baseline and time from first diagnosis.

Comparison groups	R-HAD+Bortezomib (Arm B) v R-HAD (Arm A)
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.62
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	1.52

Secondary: Response duration (PP)

End point title	Response duration (PP)

End point description:

Progression free survival of responders (PFS of responders) or response duration (RD): time from end of successful (CR, CRu, PR) trial therapy to first documentation of progression or relapse or death from any cause, whichever occurred first. Patients with no event during follow-up are censored at the day of the last follow-up staging. For per-protocol analysis, patients with new lymphoma treatment before progression will be censored additionally or earlier at treatment start.

Since upper confidence intervall could not be valid calculated and database does not provide entries like "not reached", the value 999999 was entered.

End point type	Secondary

End point timeframe:

Midterm staging, end of treatment evaluation, follow-up evaluations

End point values	R-HAD (Arm A)	R-HAD+Bortezomib (Arm B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	37		
Units: Months				
median (confidence interval 95%)	17.0 (10.3 to 999999)	21.2 (13.1 to 40.6)		

Attachments (see zip file)	RD(PP)/RHAD EudraCT.docx

Statistical analyses

Statistical analysis title	RD (PP)

Statistical analysis description:

Kaplan-Meier estimates at 12, 24, and 36 months were calculated with 95% confidence intervals. RD was compared between two treatment arms by log-rank test. Hazard ratios with 95% confidence intervals and the corresponding P values were calculated from multivariate Cox proportional hazards models adjusted for the MIPI prognostic score at baseline and time from first diagnosis.

Comparison groups	R-HAD+Bortezomib (Arm B) v R-HAD (Arm A)
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.13
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.32
upper limit	1.17

Secondary: Time to next lymphoma treatment (mITT)

End point title	Time to next lymphoma treatment (mITT)

End point description:

Time to next lymphoma treatment: time from treatment start to the start of next lymphoma treatment outside the protocol. Patients in which no further treatment has been started are censored at the day of the last follow-up staging.

End point type	Secondary

End point timeframe:

Midterm staging, end of treatment evaluation, follow-up evaluations

End point values	R-HAD (Arm A)	R-HAD+Bortezomib (Arm B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	61[16]		
Units: events	19	12		

Notes:

[16] - 2 patients were excluded from the mITT analysis because of missing next lymphoma treatment status.

Attachments (see zip file)	Next lymphoma treatment (mITT)/RHAD EudraCT.docx

Statistical analyses

Statistical analysis title	Next lymphoma treatment (mITT)

Statistical analysis description:

Cumulative incidence of next lymphoma treatment was calculated using cumulative incidence function and compared by Gray's test, treating death without next lymphoma treatment as competing event. Hazard ratio was calculated from proportional subdistribution hazard regression model.

Comparison groups	R-HAD (Arm A) v R-HAD+Bortezomib (Arm B)
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.17
Method	Gray's test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	1.25

Secondary: Time to next lymphoma treatment (PP)

End point title	Time to next lymphoma treatment (PP)

End point description:

Time to next lymphoma treatment: time from treatment start to the start of next lymphoma treatment outside the protocol. Patients in which no further treatment has been started are censored at the day of the last follow-up staging.

End point type	Secondary

End point timeframe:

Midterm staging, end of treatment evaluation, follow-up evaluations

End point values	R-HAD (Arm A)	R-HAD+Bortezomib (Arm B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	59		
Units: events	19	12		

Attachments (see zip file)	Next lymphoma treatment (PP)/RHAD EudraCT.docx

Statistical analyses

Statistical analysis title	Next lymphoma treatment (PP)

Statistical analysis description:

Cumulative incidence of next lymphoma treatment was calculated using cumulative incidence function and compared by Gray’s test, treating death without next lymphoma treatment as competing event. Hazard ratio was calculated from proportional subdistribution hazard regression model.

Comparison groups	R-HAD (Arm A) v R-HAD+Bortezomib (Arm B)
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.14
Method	Gray's test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.29
upper limit	1.2

Secondary: Overall survival (mITT)

End point title	Overall survival (mITT)

End point description:

Overall survival (OS): time from randomization to death. Patients who were alive at the day of the last contact are censored at that time.

Since upper confidence intervall could not be valid calculated and database does not provide entries like "not reached", the value 100 was entered.

End point type	Secondary

End point timeframe:

Midterm staging, end of treatment evaluation, follow-up evaluations

End point values	R-HAD (Arm A)	R-HAD+Bortezomib (Arm B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	63		
Units: Months				
median (confidence interval 95%)	35.0 (21.0 to 71.0)	30.7 (21.5 to 100)		

Attachments (see zip file)	OS (mITT)/RHAD EudraCT.docx

Statistical analyses

Statistical analysis title	OS (mITT)

Statistical analysis description:

Kaplan-Meier estimates at 12, 24, and 36 months were calculated with 95% confidence intervals. OS was compared between two treatment arms by log-rank test. Hazard ratios with 95% confidence intervals and the corresponding P values were calculated from multivariate Cox proportional hazards models adjusted for the MIPI prognostic score at baseline and time from first diagnosis.

Comparison groups	R-HAD (Arm A) v R-HAD+Bortezomib (Arm B)
Number of subjects included in analysis	127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.93
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	1.58

Secondary: Overall survival (PP)

End point title	Overall survival (PP)

End point description:

Overall survival (OS): time from randomization to death. Patients who were alive at the day of the last contact are censored at that time.

Since upper confidence intervall could not be valid calculated and database does not provide entries like "not reached", the value 999999 was entered.

End point type	Secondary

End point timeframe:

Midterm staging, end of treatment evaluation, follow-up evaluations

End point values	R-HAD (Arm A)	R-HAD+Bortezomib (Arm B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	59		
Units: Months				
median (confidence interval 95%)	35.0 (21.0 to 999999)	47.3 (25.8 to 999999)		

Attachments (see zip file)	OS (PP)/RHAD EudraCT.docx

Statistical analyses

Statistical analysis title	OS (PP)

Statistical analysis description:

Kaplan-Meier estimates at 12, 24, and 36 months were calculated with 95% confidence intervals. OS was compared between two treatment arms by log-rank test. Hazard ratios with 95% confidence intervals and the corresponding P values were calculated from multivariate Cox proportional hazards models adjusted for the MIPI prognostic score at baseline and time from first diagnosis.

Comparison groups	R-HAD (Arm A) v R-HAD+Bortezomib (Arm B)
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.45
upper limit	1.48

Secondary: Overall response rate (mITT)

End point title	Overall response rate (mITT)

End point description:

Overall response (OR) rate: the rate of complete, complete unconfirmed, and partial remissions (CR, CRu, PR) after induction therapy.

End point type	Secondary

End point timeframe:

Midterm staging, end of treatment evaluation

End point values	R-HAD (Arm A)	R-HAD+Bortezomib (Arm B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	60[17]		
Units: patients	29	38		

Notes:

[17] - 3 patients from mITT set were excluded from the analysis because of missing staging results.

Statistical analyses

Statistical analysis title	Overall response

Statistical analysis description:

OR-rates for each treatment arm were calculated with the corresponding 95% confidence intervals, and compared by two-sided Fisher’s exact test.

Comparison groups	R-HAD (Arm A) v R-HAD+Bortezomib (Arm B)
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.049
Method	Fisher exact

Secondary: Overall response rate (PP)

End point title	Overall response rate (PP)

End point description:

Overall response (OR) rate: the rate of complete, complete unconfirmed, and partial remissions (CR, CRu, PR) after induction therapy.

End point type	Secondary

End point timeframe:

Midterm staging, end of treatment evaluation

End point values	R-HAD (Arm A)	R-HAD+Bortezomib (Arm B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58[18]	58[19]		
Units: patients	26	37		

Notes:

[18] - 1 patient from PP set was excluded from the analysis because of missing staging result.

[19] - 1 patient from PP set was excluded from the analysis because of missing staging result.

Statistical analyses

Statistical analysis title	Overall response

Statistical analysis description:

OR-rates for each treatment arm were calculated with the corresponding 95% confidence intervals, and compared by two-sided Fisher’s exact test.

Comparison groups	R-HAD+Bortezomib (Arm B) v R-HAD (Arm A)

Number of subjects included in analysis	116
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.062
Method	Fisher exact

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
After each treatment cycle	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups	
Reporting group title	R-HAD
Reporting group description:	
Rituximab, high-dose Ara-C and dexamethasone	
Reporting group title	R-HAD+Bortezomib
Reporting group description:	
Rituximab, high-dose Ara-C and dexamethasone in combination with Bortezomib	

Serious adverse events	R-HAD	R-HAD+Bortezomib	
Total subjects affected by serious adverse events			
subjects affected / exposed	28 / 64 (43.75%)	23 / 64 (35.94%)	
number of deaths (all causes)	62	33	
number of deaths resulting from adverse events	1	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Small cell lung cancer			
subjects affected / exposed	0 / 64 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	0 / 64 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			

subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Mucosal inflammation			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 64 (1.56%)	3 / 64 (4.69%)	
occurrences causally related to treatment / all	0 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	3 / 64 (4.69%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 64 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			

subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 64 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	0 / 64 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic rupture			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	0 / 64 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery insufficiency			

subjects affected / exposed	0 / 64 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Paraesthesia			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 64 (1.56%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Agranulocytosis			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile bone marrow aplasia			

subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	1 / 64 (1.56%)	2 / 64 (3.13%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	3 / 64 (4.69%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 5	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 64 (0.00%)	2 / 64 (3.13%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma			
subjects affected / exposed	0 / 64 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	4 / 64 (6.25%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	0 / 64 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			

subjects affected / exposed	0 / 64 (0.00%)	2 / 64 (3.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 64 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary colic			
subjects affected / exposed	0 / 64 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Atypical pneumonia			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 64 (0.00%)	2 / 64 (3.13%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Candida infection			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 64 (1.56%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 64 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious pleural effusion			

subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	2 / 64 (3.13%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Neutropenic infection			
subjects affected / exposed	0 / 64 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 64 (3.13%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pneumococcal			
subjects affected / exposed	0 / 64 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			

subjects affected / exposed	0 / 64 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection bacterial			
subjects affected / exposed	0 / 64 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 64 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 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-HAD	R-HAD+Bortezomib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	62 / 64 (96.88%)	63 / 64 (98.44%)	
Vascular disorders			
Vena cava thrombosis			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Thrombosis			

subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences (all)	2	0	
Subclavian vein thrombosis			
subjects affected / exposed	0 / 64 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Orthostatic hypotension			
subjects affected / exposed	0 / 64 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Lymphoedema			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Hypotension			
subjects affected / exposed	0 / 64 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Hypokalaemia			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Hypertension			
subjects affected / exposed	1 / 64 (1.56%)	5 / 64 (7.81%)	
occurrences (all)	1	8	
Haemorrhage			
subjects affected / exposed	5 / 64 (7.81%)	2 / 64 (3.13%)	
occurrences (all)	6	3	
Deep vein thrombosis			
subjects affected / exposed	1 / 64 (1.56%)	2 / 64 (3.13%)	
occurrences (all)	1	5	
Angiopathy			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Asthenia			

subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Catheter site inflammation			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences (all)	2	0	
Chills			
subjects affected / exposed	1 / 64 (1.56%)	1 / 64 (1.56%)	
occurrences (all)	1	1	
Fatigue			
subjects affected / exposed	23 / 64 (35.94%)	29 / 64 (45.31%)	
occurrences (all)	41	52	
Malaise			
subjects affected / exposed	0 / 64 (0.00%)	2 / 64 (3.13%)	
occurrences (all)	0	2	
Mucosal inflammation			
subjects affected / exposed	3 / 64 (4.69%)	2 / 64 (3.13%)	
occurrences (all)	4	2	
Oedema			
subjects affected / exposed	7 / 64 (10.94%)	3 / 64 (4.69%)	
occurrences (all)	11	6	
Oedema peripheral			
subjects affected / exposed	6 / 64 (9.38%)	9 / 64 (14.06%)	
occurrences (all)	7	14	
Pain			
subjects affected / exposed	2 / 64 (3.13%)	2 / 64 (3.13%)	
occurrences (all)	2	3	
Pyrexia			
subjects affected / exposed	18 / 64 (28.13%)	19 / 64 (29.69%)	
occurrences (all)	27	23	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	3 / 64 (4.69%)	2 / 64 (3.13%)	
occurrences (all)	3	5	
Anaphylactic reaction			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences (all)	2	0	

Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 64 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Pneumothorax			
subjects affected / exposed	0 / 64 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Pleural effusion			
subjects affected / exposed	0 / 64 (0.00%)	2 / 64 (3.13%)	
occurrences (all)	0	2	
Lung disorder			
subjects affected / exposed	10 / 64 (15.63%)	10 / 64 (15.63%)	
occurrences (all)	12	12	
Hiccups			
subjects affected / exposed	0 / 64 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Epistaxis			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Dyspnoea			
subjects affected / exposed	5 / 64 (7.81%)	2 / 64 (3.13%)	
occurrences (all)	10	2	
Dysphonia			
subjects affected / exposed	0 / 64 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Cough			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences (all)	2	0	
Psychiatric disorders			
Depressed mood			
subjects affected / exposed	4 / 64 (6.25%)	4 / 64 (6.25%)	
occurrences (all)	5	6	
Anxiety			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences (all)	3	0	
Confusional state			

subjects affected / exposed	0 / 64 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	3	
Insomnia			
subjects affected / exposed	0 / 64 (0.00%)	2 / 64 (3.13%)	
occurrences (all)	0	2	
Mental disorder			
subjects affected / exposed	0 / 64 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Obsessive-compulsive disorder			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences (all)	2	0	
Schizophrenia			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Sleep disorder			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Investigations			
Weight increased			
subjects affected / exposed	4 / 64 (6.25%)	1 / 64 (1.56%)	
occurrences (all)	5	2	
Weight decreased			
subjects affected / exposed	11 / 64 (17.19%)	16 / 64 (25.00%)	
occurrences (all)	15	19	
Transaminases			
subjects affected / exposed	18 / 64 (28.13%)	20 / 64 (31.25%)	
occurrences (all)	31	32	
Platelet count increased			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Neutrophil count increased			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences (all)	2	0	
leukocyte count increased			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences (all)	2	0	

Glomerular filtration rate			
subjects affected / exposed	0 / 64 (0.00%)	2 / 64 (3.13%)	
occurrences (all)	0	3	
General physical condition			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Eastern Cooperative Oncology Group performance status worsened			
subjects affected / exposed	0 / 64 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
C-reactive protein increased			
subjects affected / exposed	1 / 64 (1.56%)	3 / 64 (4.69%)	
occurrences (all)	1	3	
Blood urine present			
subjects affected / exposed	0 / 64 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Blood urea increased			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 64 (1.56%)	1 / 64 (1.56%)	
occurrences (all)	2	1	
Blood glucose abnormal			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences (all)	2	0	
Blood creatine			
subjects affected / exposed	18 / 64 (28.13%)	23 / 64 (35.94%)	
occurrences (all)	42	50	
Blood bilirubin abnormal			
subjects affected / exposed	0 / 64 (0.00%)	3 / 64 (4.69%)	
occurrences (all)	0	3	
Blood bilirubin			
subjects affected / exposed	9 / 64 (14.06%)	9 / 64 (14.06%)	
occurrences (all)	15	16	
Blood alkaline phosphatase increased			

subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Subdural haematoma			
subjects affected / exposed	0 / 64 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Spinal fracture			
subjects affected / exposed	0 / 64 (0.00%)	2 / 64 (3.13%)	
occurrences (all)	0	2	
Ligament sprain			
subjects affected / exposed	0 / 64 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	4 / 64 (6.25%)	4 / 64 (6.25%)	
occurrences (all)	7	4	
Cardiac dysfunction			
subjects affected / exposed	4 / 64 (6.25%)	1 / 64 (1.56%)	
occurrences (all)	8	1	
Left ventricular dysfunction			
subjects affected / exposed	0 / 64 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Palpitations			
subjects affected / exposed	0 / 64 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Syncope			
subjects affected / exposed	0 / 64 (0.00%)	2 / 64 (3.13%)	
occurrences (all)	0	3	
Tachycardia			
subjects affected / exposed	0 / 64 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Nervous system disorders			
Transient ischaemic attack			
subjects affected / exposed	0 / 64 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Neuropathy peripheral			

subjects affected / exposed	11 / 64 (17.19%)	16 / 64 (25.00%)	
occurrences (all)	22	28	
Migraine with aura			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences (all)	2	0	
Headache			
subjects affected / exposed	3 / 64 (4.69%)	3 / 64 (4.69%)	
occurrences (all)	4	3	
Dizziness			
subjects affected / exposed	1 / 64 (1.56%)	2 / 64 (3.13%)	
occurrences (all)	1	3	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	59 / 64 (92.19%)	59 / 64 (92.19%)	
occurrences (all)	157	178	
Febrile neutropenia			
subjects affected / exposed	0 / 64 (0.00%)	2 / 64 (3.13%)	
occurrences (all)	0	2	
Leukopenia			
subjects affected / exposed	44 / 64 (68.75%)	46 / 64 (71.88%)	
occurrences (all)	97	120	
Lymphopenia			
subjects affected / exposed	44 / 64 (68.75%)	50 / 64 (78.13%)	
occurrences (all)	102	131	
Neutropenia			
subjects affected / exposed	41 / 64 (64.06%)	48 / 64 (75.00%)	
occurrences (all)	83	113	
Thrombocytopenia			
subjects affected / exposed	56 / 64 (87.50%)	54 / 64 (84.38%)	
occurrences (all)	145	150	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 64 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Eye disorders			

Blepharitis			
subjects affected / exposed	0 / 64 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	2	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 64 (3.13%)	1 / 64 (1.56%)	
occurrences (all)	2	1	
Abdominal pain upper			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Constipation			
subjects affected / exposed	9 / 64 (14.06%)	21 / 64 (32.81%)	
occurrences (all)	12	30	
Diarrhoea			
subjects affected / exposed	6 / 64 (9.38%)	13 / 64 (20.31%)	
occurrences (all)	8	15	
Dyspepsia			
subjects affected / exposed	1 / 64 (1.56%)	1 / 64 (1.56%)	
occurrences (all)	1	1	
Faecaloma			
subjects affected / exposed	0 / 64 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Gastritis			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Large intestine perforation			
subjects affected / exposed	0 / 64 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	8 / 64 (12.50%)	17 / 64 (26.56%)	
occurrences (all)	10	23	
Pancreatitis			

subjects affected / exposed	0 / 64 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Toothache			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	1 / 64 (1.56%)	6 / 64 (9.38%)	
occurrences (all)	1	8	
Skin and subcutaneous tissue disorders			
Skin disorder			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences (all)	4	0	
Rash			
subjects affected / exposed	0 / 64 (0.00%)	3 / 64 (4.69%)	
occurrences (all)	0	3	
Pruritus			
subjects affected / exposed	0 / 64 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	2	
Petechiae			
subjects affected / exposed	1 / 64 (1.56%)	1 / 64 (1.56%)	
occurrences (all)	1	1	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences (all)	2	0	
Night sweats			
subjects affected / exposed	0 / 64 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Hyperhidrosis			
subjects affected / exposed	0 / 64 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Ecchymosis			
subjects affected / exposed	0 / 64 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	3	
Dry skin			

subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences (all)	2	0	
Renal and urinary disorders			
Strangury			
subjects affected / exposed	0 / 64 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Haematuria			
subjects affected / exposed	3 / 64 (4.69%)	0 / 64 (0.00%)	
occurrences (all)	4	0	
Nocturia			
subjects affected / exposed	1 / 64 (1.56%)	2 / 64 (3.13%)	
occurrences (all)	4	4	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	1 / 64 (1.56%)	1 / 64 (1.56%)	
occurrences (all)	1	1	
Myalgia			
subjects affected / exposed	7 / 64 (10.94%)	6 / 64 (9.38%)	
occurrences (all)	9	9	
Musculoskeletal pain			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Muscular weakness			
subjects affected / exposed	0 / 64 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Muscle spasms			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Bone pain			
subjects affected / exposed	2 / 64 (3.13%)	1 / 64 (1.56%)	
occurrences (all)	2	1	
back pain			
subjects affected / exposed	2 / 64 (3.13%)	2 / 64 (3.13%)	
occurrences (all)	3	2	
Infections and infestations			

Bronchitis			
subjects affected / exposed	1 / 64 (1.56%)	1 / 64 (1.56%)	
occurrences (all)	1	1	
Conjunctivitis			
subjects affected / exposed	0 / 64 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	2	
Device related infection			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Herpes zoster			
subjects affected / exposed	0 / 64 (0.00%)	3 / 64 (4.69%)	
occurrences (all)	0	3	
Infection			
subjects affected / exposed	22 / 64 (34.38%)	26 / 64 (40.63%)	
occurrences (all)	28	33	
Localised infection			
subjects affected / exposed	2 / 64 (3.13%)	0 / 64 (0.00%)	
occurrences (all)	3	0	
Nasopharyngitis			
subjects affected / exposed	0 / 64 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Neutropenic infection			
subjects affected / exposed	0 / 64 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Oral candidiasis			
subjects affected / exposed	0 / 64 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Otitis media acute			
subjects affected / exposed	0 / 64 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	2	
Pneumonia			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences (all)	2	0	
Respiratory tract infection			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences (all)	1	0	

Rhinitis			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Schizophrenia			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Sepsis			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Urinary tract infection			
subjects affected / exposed	0 / 64 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Steroid diabetes			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Hyponatraemia			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Hypoglycaemia			
subjects affected / exposed	0 / 64 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Hypocalcaemia			
subjects affected / exposed	0 / 64 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Hyperuricaemia			
subjects affected / exposed	0 / 64 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Hyperglycaemia			
subjects affected / exposed	3 / 64 (4.69%)	6 / 64 (9.38%)	
occurrences (all)	6	9	
Gout			
subjects affected / exposed	0 / 64 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	2	
fluid overload			

subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Diabetes mellitus			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Dehydration			
subjects affected / exposed	0 / 64 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	2	
Decreased appetite			
subjects affected / exposed	1 / 64 (1.56%)	1 / 64 (1.56%)	
occurrences (all)	1	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 November 2010	Deletion of Rituximab as an IMP (only IMP left: Bortezomib), Amendment was implemented before enrollment of first patient
10 April 2012	The Inclusion criterion of prior anthracyclin-containing regimen was deleted
13 January 2015	Switch from Vecalde iv to sc administration Clarification of the Inclusion criterion concerning enrollment of patients who become progressive under Rituximab maintenance Deletion of the Exclusion criterion concerning previous treatment with Bortezomib

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported