Clinical trial results:
Rituximab plus lenalidomide or rituximab monotherapy for untreated patients with follicular lymphoma in need of therapy. A randomized, open-label, multicentre phase II trial.

Summary

EudraCT number	2010-021253-39
Trial protocol	SE DK FI IT
Global end of trial date	26 May 2023

Results information

Result version number	v1 (current)
This version publication date	29 September 2024
First version publication date	29 September 2024

Trial information

Trial identification

Sponsor protocol code	SAKK35/10

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01307605
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Swiss Group for Clinical Cancer Research (SAKK)
Sponsor organisation address	Effingerstrasse 33, Bern, Switzerland, 3008
Public contact	Head Regulatory Affairs, Swiss Group for Clinical Cancer Research SAKK, +41 31389 91 91, sakkcc@sakk.ch
Scientific contact	Head Regulatory Affairs, Swiss Group for Clinical Cancer Research SAKK, +41 31389 91 91, sakkcc@sakk.ch

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 August 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 May 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Main objective of the trial is to determine the activity of the combination of rituximab and lenalidomide given to untreated follicular lymphoma (FL) patients versus rituximab treatment and the safety of both therapy arms.

Protection of trial subjects:

Protection of trial subjects was ensured by Safety Monitoring, i.e. assessment of adverse events, serious adverse events, adverse drug reactions, and the continous assessment of laboratory values and vital signs.

Background therapy:

Not applicable.

Evidence for comparator:

Rituximab in combination with chemotherapy has shown excellent activity as front-line therapy in patients with follicular lymphoma (FL), but it has not been shown to clearly impact overall survival (OS), whilst most combination regimens carry a significant toxicity.
The results of the previous SAKK-trial [PMID: 14976046] and the Nordic-trial [PMID: 18203019] suggest that therapy with rituximab single agent is effective and well tolerated and offers to a subset of FL patients an opportunity to achieve long-term remission and prolonged failure-free survival.

Actual start date of recruitment	12 April 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	10 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Norway: 20
Country: Number of subjects enrolled	Sweden: 25
Country: Number of subjects enrolled	Denmark: 6
Country: Number of subjects enrolled	Finland: 8
Country: Number of subjects enrolled	Italy: 22
Country: Number of subjects enrolled	Switzerland: 73
Worldwide total number of subjects	154
EEA total number of subjects	81

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)	90
From 65 to 84 years	63
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

154 patients at 29 sites in Switzerland (17 sites, 73 patients), Denmark (1 site, 6 patients), Finland (1 site, 8 patients), Italy (2 sites, 22 patients), Norway (3 sites, 20 patients) and Sweden (5 sites, 25 patients) have been enrolled from April 2011 to October 2013.

Pre-assignment

Screening details:

Eligibility criteria of a patient were checked by the investigator. Once a patient fullfils all inclusion criteria and not any of the exclusion criteria, he/she was enrolled.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A - Rituximab Mono

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	MabThera®
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Rituximab was administered for 8 infusions of 375mg/m2 at day 1 of weeks 1, 2, 3, 4, and again at day 1 of weeks 12, 13, 14 and 15.

Arm title	Arm B - Rituximab plus Lenalidomide

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	MabThera®
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Rituximab was administered for 8 infusions of 375mg/m2 at day 1 of weeks 1, 2, 3, 4, and again at day 1 of weeks 12, 13, 14 and 15.

Investigational medicinal product name	Lenalidomide
Investigational medicinal product code	
Other name	Revlimid®
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Lenalidomide was to be administered daily p.o. starting 14 days before the first and stopping 14 days after the last rituximab infusion in addition to rituximab, which was to be given in the same scheme as for Arm A.

Number of subjects in period 1	Arm A - Rituximab Mono	Arm B - Rituximab plus Lenalidomide
Started	77	77
Completed	76	77
Not completed	1	0
No treatment received	1	-

Period 2	
Period 2 title	Treatment Phase
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms	
Are arms mutually exclusive?	Yes
Arm title	Arm A - Rituximab Mono

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	MabThera®
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Rituximab was administered for 8 infusions of 375mg/m2 at day 1 of weeks 1, 2, 3, 4, and again at day 1 of weeks 12, 13, 14 and 15.

Arm title	Arm B - Rituximab plus Lenalidomide

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	MabThera®
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Rituximab was administered for 8 infusions of 375mg/m2 at day 1 of weeks 1, 2, 3, 4, and again at day 1 of weeks 12, 13, 14 and 15.

Investigational medicinal product name	Lenalidomide
Investigational medicinal product code	
Other name	Revlimid®
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Lenalidomide was to be administered daily p.o. starting 14 days before the first and stopping 14 days

after the last rituximab infusion in addition to rituximab, which was to be given in the same scheme as for Arm A.

Number of subjects in period 2	Arm A - Rituximab Mono	Arm B - Rituximab plus Lenalidomide
Started	76	77
Completed	55	58
Not completed	21	19
Relapse	1	-
Consent withdrawn by subject	1	-
Other	2	3
Stopped lenalidomide early due to toxicity	-	13
Stable disease or progressing disease at week 10	16	3
Unacceptabel toxicity	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Arm A - Rituximab Mono
Reporting group description: -	
Reporting group title	Arm B - Rituximab plus Lenalidomide
Reporting group description: -	

Reporting group values	Arm A - Rituximab Mono	Arm B - Rituximab plus Lenalidomide	Total
Number of subjects	77	77	154
Age categorical Units: Subjects			
Adults (18-64 years)	43	47	90
From 65-84 years	33	30	63
85 years and over	1	0	1
Gender categorical Units: Subjects			
Female	40	42	82
Male	37	35	72

End points

End points reporting groups

Reporting group title	Arm A - Rituximab Mono
Reporting group description: -	
Reporting group title	Arm B - Rituximab plus Lenalidomide
Reporting group description: -	
Reporting group title	Arm A - Rituximab Mono
Reporting group description: -	
Reporting group title	Arm B - Rituximab plus Lenalidomide
Reporting group description: -	
Subject analysis set title	Arm A - Rituximab | ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All randomized patients were included in the ITT population.	
Subject analysis set title	Arm B - Rituximab + Lenalidomide | ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All randomized patients were included in the ITT population.	
Subject analysis set title	Arm A - Rituximab | FAS
Subject analysis set type	Full analysis
Subject analysis set description:	
One patient, randomized in arm A, did not start trial treatment and was excluded from the FAS. In addition, for one patient in arm A the diagnosis of FL grade 1, 2 or 3a was unconfirmed by the central pathology review. This patient wasalso excluded from the FAS.	
Subject analysis set title	Arm B - Rituximab + Lenalidomide | FAS
Subject analysis set type	Full analysis
Subject analysis set description:	
Two patients in arm B did not start rituximab and for two additional patients in arm B the diagnosis of FL grade 1, 2 or 3a was unconfirmed by the central pathology review. These four patients were excluded from the FAS.	
Subject analysis set title	Arm A - Rituximab | PPS
Subject analysis set type	Per protocol
Subject analysis set description:	
Ten patients in arm A did not fulfill the criteria defining the PP population and were excluded from the PPS.	
Subject analysis set title	Arm B - Rituximab + Lenalidomide | PPS
Subject analysis set type	Per protocol
Subject analysis set description:	
Twenty patients in arm A did not fulfill the criteria defining the PP population and were excluded from the PPS.	

Primary: PE | Rate of complete remission (CR) at week 23 - ITT

End point title	PE | Rate of complete remission (CR) at week 23 - ITT

End point description:

A success was defined as any patient with a complete remission or CR unconfirmed at the second tumor assessment planned at week 23, regardless of the actual assessment date.

Responses at week 23:
Arm A: CR=9.1%; CRu=15.6%; PR=36.4%; SD=7.8%; PD=2.6%; not done=28.6% | Arm B: CR=18.2%; CRu=18.2%; PR=45.5%; SD=5.2%; PD=3.9%; not done=9.1%.

CR: complete remission, CRu: unconfirmed CR; PR: partial response; SD: stable disease; PD: progressing disease

End point type	Primary

End point timeframe:

At week 23

End point values	Arm A - Rituximab | ITT	Arm B - Rituximab + Lenalidomide | ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	77	77		
Units: % patients with CR/CRu				
number (confidence interval 95%)	24.7 (15.6 to 35.8)	36.4 (25.7 to 48.1)		

Statistical analyses

Statistical analysis title	Z-test
Comparison groups	Arm A - Rituximab | ITT v Arm B - Rituximab + Lenalidomide | ITT
Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.0562
Method	Z-Test

Notes:

[1] - One-sided Z-test with unpooled variance / significance level = 0.10

Primary: PE | Rate of complete remission (CR) at week 23 - FAS

End point title	PE | Rate of complete remission (CR) at week 23 - FAS

End point description:

A success was defined as any patient with a complete remission or CR unconfirmed at the second tumor assessment planned at week 23, regardless of the actual assessment date.

Responses at week 23:
Arm A: CR=9.3%; CRu=16.0%; PR=37.3%; SD=8.0%; PD=2.7%; not done=26.7% | Arm B: CR=19.2%; CRu=19.2%; PR=47.9%; SD=5.5%; PD=4.1%; not done=4.1%.

CR: complete remission, CRu: unconfirmed CR; PR: partial response; SD: stable disease; PD: progressing disease

End point type	Primary

End point timeframe:

At week 23

End point values	Arm A - Rituximab | FAS	Arm B - Rituximab + Lenalidomide | FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	75	73		
Units: % patients with CR/CRu				
number (confidence interval 95%)	25.3 (16.0 to 36.7)	38.4 (27.2 to 50.5)		

Statistical analyses

Statistical analysis title	Z-test
Comparison groups	Arm A - Rituximab | FAS v Arm B - Rituximab + Lenalidomide | FAS
Number of subjects included in analysis	148
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0431 [2]
Method	Z-Test

Notes:

[2] - One-sided Z-test with unpooled variance.

Primary: PE \| Rate of complete remission (CR) at week 23 - PPS

End point title	PE | Rate of complete remission (CR) at week 23 - PPS

End point description:

A success was defined as any patient with a complete remission or CR unconfirmed at the second tumor assessment planned at week 23, regardless of the actual assessment date.

Responses at week 23:
Arm A: CR=9.0%; CRu=17.9%; PR=40.3%; SD=7.5%; PD=3.0%; not done=22.4% | Arm B: CR=19.3%; CRu=21.1%; PR=47.4%; SD=3.5%; PD=5.3%; not done=3.5%.

CR: complete remission, CRu: unconfirmed CR; PR: partial response; SD: stable disease; PD: progressing disease

End point type	Primary

End point timeframe:

At week 23

End point values	Arm A - Rituximab | PPS	Arm B - Rituximab + Lenalidomide | PPS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	67	57		
Units: % patients with CR/CRu				
number (confidence interval 95%)	26.9 (16.8 to 39.1)	40.4 (27.6 to 54.2)		

Statistical analyses

Statistical analysis title	Z-test
Comparison groups	Arm B - Rituximab + Lenalidomide | PPS v Arm A - Rituximab | PPS
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.0554
Method	Z-Test

Notes:

[3] - One-sided Z-test with unpooled variance

Primary: PE | Rate of complete remission (CR) at week 23 - ITT || Sensitivity analysis

End point title	PE | Rate of complete remission (CR) at week 23 - ITT || Sensitivity analysis

End point description:

Response assessment from the independent response review (IRR).

A success was defined as any patient with a complete remission or CR unconfirmed at the second tumor assessment planned at week 23, regardless of the actual assessment date.

Responses at week 23:
Arm A: CR=36.4%; CRu=0.0%; PR=20.8%; SD=9.1%; PD=3.9%; no measurable lesions (week 0 and week 23)=0.0%; not done=29.9% | Arm B: CR=55.8%; CRu=5.2%; PR=16.9%; SD=2.6%; PD=1.3%; no measurable lesions (week 0 and week 23)=5.2%; not done=13.0%.

CR: complete remission, CRu: unconfirmed CR; PR: partial response; SD: stable disease; PD: progressing disease

End point type	Primary

End point timeframe:

At week 23

End point values	Arm A - Rituximab | ITT	Arm B - Rituximab + Lenalidomide | ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	77	77		
Units: % patients with CR/CRu				
number (confidence interval 95%)	36.4 (25.7 to 48.1)	61.0 (49.2 to 72.0)		

Statistical analyses

Statistical analysis title	Z-test
Comparison groups	Arm A - Rituximab | ITT v Arm B - Rituximab + Lenalidomide | ITT
Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	= 0.0008
Method	Z-Test

Notes:

[4] - One-sided Z-test with unpooled variance.

Secondary: SE | Overall response (OR) - ITT

End point title	SE | Overall response (OR) - ITT

End point description:

Responses at week 10:
Arm A: CR=3.9%; CRu=6.5%; PR=35.1%; MR=29.9; SD=16.9%; PD=5.2%; not done=2.6% | Arm B: CR=7.8%; CRu=5.2%; PR=62.3%; MR=18.2%; SD=0.0%; PD=3.9%; not done=2.6%.

Responses at week 23:
see description for primary endpoint.

CR: complete remission, CRu: unconfirmed CR; PR: partial response; MR: minimal response; SD: stable disease; PD: progressing disease

End point type	Secondary

End point timeframe:

At week 10 and week 23.

End point values	Arm A - Rituximab | ITT	Arm B - Rituximab + Lenalidomide | ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	77	77		
Units: % patients with CR/CRu/PR				
number (confidence interval 95%)				
Week 10	45.5 (34.1 to 57.2)	75.3 (64.2 to 84.4)		
Week 23	61.0 (49.2 to 72.0)	81.8 (71.4 to 89.7)		

Statistical analyses

Statistical analysis title	Z-test (week 10)
Comparison groups	Arm A - Rituximab | ITT v Arm B - Rituximab + Lenalidomide | ITT

Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	< 0.0001
Method	Z-Test

Notes:

[5] - One-sided Z-test with unpooled variance.

Statistical analysis title	Z-test (week 23)
Comparison groups	Arm A - Rituximab | ITT v Arm B - Rituximab + Lenalidomide | ITT
Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	= 0.0017
Method	Z-Test

Notes:

[6] - One-sided Z-test with unpooled variance.

Secondary: SE | Complete repsonse or overall response at 30 months - ITT

End point title	SE | Complete repsonse or overall response at 30 months - ITT

End point description:

Response at 30 months:

Arm A: CR=18.2%; CRu=1.3%; PR=9.1%; SD=2.6%; PD=5.2%; not done=63.6% | Arm B: CR=33.8%; CRu=7.8%; PR=7.8%; SD=0.0%; PD=6.5%; not done=44.2%.

CR: complete remission, CRu: unconfirmed CR; PR: partial response; SD: stable disease; PD: progressing disease

End point type	Secondary

End point timeframe:

At 30 months

End point values	Arm A - Rituximab | ITT	Arm B - Rituximab + Lenalidomide | ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	77	77		
Units: % patients with response				
number (confidence interval 95%)				
CR/CRu	19.5 (11.3 to 30.1)	41.6 (30.4 to 53.4)		
CR/CRu/PR	28.6 (18.8 to 40.0)	49.4 (37.8 to 61.0)		

Statistical analyses

Statistical analysis title	Z-test (CR/CRu)
Statistical analysis description: One-sided Z-test with unpooled variance.	
Comparison groups	Arm A - Rituximab | ITT v Arm B - Rituximab + Lenalidomide | ITT
Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0011
Method	Z-Test

Statistical analysis title	Z-test (CR/CRu/PR)
Statistical analysis description: One-sided Z-test with unpooled variance.	
Comparison groups	Arm A - Rituximab | ITT v Arm B - Rituximab + Lenalidomide | ITT
Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0034
Method	Z-Test

Secondary: SE | Duration of CR/CRu - ITT	
End point title	SE | Duration of CR/CRu - ITT
End point description: Kaplan-Meier Analysis for patients with CR/CRu. Note: Median and upper 95%-CI for arm B was not reached; dummy data "99999" entered due to database restrictions. Events | Censored: Arm A, events: 17 (54.8%), censored: 14 (45.2%) | Arm B, events: 14 (28.6%), censored: 35 (71.4%)	
End point type	Secondary
End point timeframe: From baseline until CR/CRu.	

End point values	Arm A - Rituximab | ITT	Arm B - Rituximab + Lenalidomide | ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	31	49		
Units: years				
median (confidence interval 95%)	3.2 (1.6 to 7.6)	99999 (7.4 to 99999)		

Statistical analyses

Statistical analysis title	Log Rank Test / Hazard Ratio
Comparison groups	Arm A - Rituximab | ITT v Arm B - Rituximab + Lenalidomide | ITT
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0143
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.423
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.208
upper limit	0.86

Secondary: SE | Progression free survival - ITT

End point title	SE | Progression free survival - ITT

End point description:

Kaplan-Meier Analysis.

Note: Upper 95%-CI for arm B was not reached; dummy data "99999" entered due to database restrictions.

Events \| Censored:
Arm A, events: 45 (58.4%; [death: 2.2%, progressive disease/relapse: 97.8%]), censored: 32 (41.6%) \| Arm B, events: 36 (46.8% [death, 5.6%; progressive disease/relapse, 94.4%]), censored: 41 (53.2%)

End point type	Secondary

End point timeframe:

From baseline until progression.

End point values	Arm A - Rituximab | ITT	Arm B - Rituximab + Lenalidomide | ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	77	77		
Units: years				
median (confidence interval 95%)	2.3 (1.6 to 3.5)	9.3 (2.5 to 99999)		

Statistical analyses

Statistical analysis title	Log Rank Test / Hazard Ratio
Comparison groups	Arm B - Rituximab + Lenalidomide | ITT v Arm A - Rituximab | ITT
Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0128
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.575
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.37
upper limit	0.894

Secondary: SE | Progression free survival Survival estimates at 2, 3, 5 and 10 years - ITT

End point title	SE | Progression free survival Survival estimates at 2, 3, 5 and 10 years - ITT
End point description:	
End point type	Secondary
End point timeframe:	
At 2, 3, 5 and 10 years.	

End point values	Arm A - Rituximab | ITT	Arm B - Rituximab + Lenalidomide | ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	77	77		
Units: PFS probability (%)				
number (confidence interval 95%)				
2-year PFS	58.8 (45.3 to 70.0)	67.5 (55.2 to 77.1)		
3-year PFS	43.1 (30.3 to 55.2)	57.2 (44.8 to 67.9)		
5-year PFS	33.7 (21.9 to 46.0)	54.0 (41.5 to 64.9)		

10-year PFS	20.9 (10.5 to 33.8)	36.1 (17.7 to 54.9)		

Statistical analyses

Statistical analysis title	2-year PFS (p-value)
Comparison groups	Arm A - Rituximab | ITT v Arm B - Rituximab + Lenalidomide | ITT
Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.303
Method	cloglog (log(-log(.)))

Statistical analysis title	3-year PFS (p-value)
Comparison groups	Arm A - Rituximab | ITT v Arm B - Rituximab + Lenalidomide | ITT
Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1095
Method	cloglog (log(-log(.)))

Statistical analysis title	5-year PFS (p-value)
Comparison groups	Arm A - Rituximab | ITT v Arm B - Rituximab + Lenalidomide | ITT
Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0228
Method	cloglog (log(-log(.)))

Statistical analysis title	10-year PFS (p-value)
Comparison groups	Arm A - Rituximab | ITT v Arm B - Rituximab + Lenalidomide | ITT
Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1921
Method	cloglog (log(-log(.)))

Secondary: SE | Time to first off-trial anti-lymphoma therapy - ITT

End point title	SE | Time to first off-trial anti-lymphoma therapy - ITT

End point description:

Kaplan-Meier Analysis.

Note: Median and upper 95%-CI for arm B was not reached; dummy data "99999" entered due to database restrictions.

Events | Censored:
Arm A, events: 52 (67.5%), censored: 25 (32.5%) | Arm B, events: 30 (39.0%), censored: 47 (61.0%)

End point type	Secondary

End point timeframe:

From baseline until time to first off-trial anti-lymphoma therapy.

End point values	Arm A - Rituximab | ITT	Arm B - Rituximab + Lenalidomide | ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	77	77		
Units: years				
median (confidence interval 95%)	2.1 (1.5 to 3.6)	99999 (4.3 to 99999)		

Statistical analyses

Statistical analysis title	Log-rank test / Hazard Ratio
Comparison groups	Arm A - Rituximab | ITT v Arm B - Rituximab + Lenalidomide | ITT
Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.427
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.272
upper limit	0.672

Secondary: SE | Overall survival - ITT

End point title	SE | Overall survival - ITT

End point description:

Kaplan-Meier Analysis.

Note: Median and 95%-CI for arm A and arm B were not reached; dummy data "99999" entered due to database restrictions.

Events \| Censored:
Arm A, events: 14 (18.2%), censored: 63 (81.8%) \| Arm B, events: 15 (19.5%), censored: 62 (80.5%)

Causes of death:
Arm A, other: 4 (30.8%), tumor: 6 (46.2%), unknown: 3 (23.1%) \| Arm B, other: 3 (20.0%), tumor: 8 (53.3%), unknown: 4 (26.7%)

End point type	Secondary

End point timeframe:

From baseline until death.

End point values	Arm A - Rituximab | ITT	Arm B - Rituximab + Lenalidomide | ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	77	77		
Units: years				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

Statistical analysis title	Log-rank test / Hazard Ratio
Comparison groups	Arm A - Rituximab | ITT v Arm B - Rituximab + Lenalidomide | ITT
Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9609
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.982
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.474
upper limit	2.035

Secondary: SE | Overall survival Survival estimates at 3, 5 and 10 years - ITT

End point title	SE | Overall survival Survival estimates at 3, 5 and 10 years - ITT

End point description:

End point type	Secondary

End point timeframe:

At 3, 5 and 10 years.

End point values	Arm A - Rituximab | ITT	Arm B - Rituximab + Lenalidomide | ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	77	77		
Units: years				
median (confidence interval 95%)				
3-year OS probability	91.8 (82.6 to 96.2)	93.3 (84.7 to 97.2)		
5-year OS probability	90.3 (80.7 to 95.2)	90.6 (81.3 to 95.4)		
10-year OS probability	78.0 (65.4 to 86.4)	76.8 (63.9 to 85.6)		

Statistical analyses

Statistical analysis title	3-year OS (p-value)
Comparison groups	Arm A - Rituximab | ITT v Arm B - Rituximab + Lenalidomide | ITT
Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7187
Method	cloglog (log(-log(.)))

Statistical analysis title	5-year OS (p-value)
Comparison groups	Arm A - Rituximab | ITT v Arm B - Rituximab + Lenalidomide | ITT
Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9419
Method	cloglog (log(-log(.)))

Statistical analysis title	10-year OS (p-value)
Comparison groups	Arm A - Rituximab | ITT v Arm B - Rituximab + Lenalidomide | ITT

Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.881
Method	cloglog (log(-log(.)))

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From randomization until the second restaging at week 23 or until 30 days after end of trial treatment or prior to start of next therapy (whatever was first).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	27.0

Reporting groups

Reporting group title	Arm A - Rituximab | SAF

Reporting group description:

One randomized patient did not receive study treatment and was excluded from the SAF.

Reporting group title	Arm B - Rituximab + Lenalidomide | SAF

Reporting group description: -

Serious adverse events	Arm A - Rituximab | SAF	Arm B - Rituximab + Lenalidomide | SAF	
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 76 (14.47%)	30 / 77 (38.96%)	
number of deaths (all causes)	13	15	
number of deaths resulting from adverse events	0	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm progression	Additional description: One patient death due to neoplasm progression (not related to trial therapy) and the other neoplasm progression and pyrexia.		
subjects affected / exposed	0 / 76 (0.00%)	2 / 77 (2.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute myeloid leukaemia			
subjects affected / exposed	1 / 76 (1.32%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	0 / 76 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diffuse large B-cell lymphoma			

subjects affected / exposed	0 / 76 (0.00%)	2 / 77 (2.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hodgkin's disease			
subjects affected / exposed	2 / 76 (2.63%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-small cell lung cancer	Additional description: One patient with non-small cell lung cancer (adenocarcinoma) and the other with non-small cell lung cancer (lung adenocarcinoma stage 0)		
subjects affected / exposed	0 / 76 (0.00%)	2 / 77 (2.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Primary myelofibrosis			
subjects affected / exposed	1 / 76 (1.32%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	1 / 76 (1.32%)	2 / 77 (2.60%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal cancer			
subjects affected / exposed	0 / 76 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small cell lung cancer			
subjects affected / exposed	0 / 76 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	0 / 76 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin			

subjects affected / exposed	0 / 76 (0.00%)	2 / 77 (2.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Rib fracture	Additional description: Patient with rib fracture complicated by haemothorax.		
subjects affected / exposed	0 / 76 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	0 / 76 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post lumbar puncture syndrome			
subjects affected / exposed	0 / 76 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 76 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation	Additional description: One patient with atrial fibrillation, thrombocytopenia, leukopenia, anaemia and urinary tract infection.		
subjects affected / exposed	0 / 76 (0.00%)	2 / 77 (2.60%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 76 (1.32%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			

subjects affected / exposed	0 / 76 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia	Additional description: One patient with pyrexia and rash.		
subjects affected / exposed	0 / 76 (0.00%)	2 / 77 (2.60%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug withdrawal syndrome	Additional description: Patient with drug withdrawal syndrome manifested in paranoid schizophrenia.		
subjects affected / exposed	0 / 76 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 76 (1.32%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug hypersensitivity			
subjects affected / exposed	0 / 76 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Subileus	Additional description: Patient with subileus and abdominal pain.		
subjects affected / exposed	0 / 76 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal obstruction			
subjects affected / exposed	0 / 76 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis	Additional description: Patient with stomatitis, generalised oedema and urticaria.		

subjects affected / exposed	1 / 76 (1.32%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 76 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 76 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression suicidal			
subjects affected / exposed	0 / 76 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Insomnia			
subjects affected / exposed	0 / 76 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	1 / 76 (1.32%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety	Additional description: Patient with anxiety resulting in dyspnoea.		
subjects affected / exposed	0 / 76 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 76 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Urinary retention			
subjects affected / exposed	0 / 76 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 76 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 76 (1.32%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus infection			
subjects affected / exposed	1 / 76 (1.32%)	0 / 77 (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	Additional description: Patient with urinary tract infection and calculus urinary.		
subjects affected / exposed	0 / 76 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	0 / 76 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Arm A - Rituximab | SAF	Arm B - Rituximab + Lenalidomide | SAF	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	69 / 76 (90.79%)	77 / 77 (100.00%)	
Vascular disorders			

Hot flush			
subjects affected / exposed	3 / 76 (3.95%)	4 / 77 (5.19%)	
occurrences (all)	3	4	
Hypertension			
subjects affected / exposed	13 / 76 (17.11%)	18 / 77 (23.38%)	
occurrences (all)	13	19	
Hypotension			
subjects affected / exposed	3 / 76 (3.95%)	4 / 77 (5.19%)	
occurrences (all)	3	4	
Embolism			
subjects affected / exposed	0 / 76 (0.00%)	4 / 77 (5.19%)	
occurrences (all)	0	4	
General disorders and administration site conditions			
Chills			
subjects affected / exposed	3 / 76 (3.95%)	4 / 77 (5.19%)	
occurrences (all)	4	4	
Oedema peripheral			
subjects affected / exposed	2 / 76 (2.63%)	12 / 77 (15.58%)	
occurrences (all)	2	14	
Fatigue			
subjects affected / exposed	26 / 76 (34.21%)	40 / 77 (51.95%)	
occurrences (all)	28	47	
Pyrexia			
subjects affected / exposed	11 / 76 (14.47%)	12 / 77 (15.58%)	
occurrences (all)	16	13	
Influenza like illness			
subjects affected / exposed	5 / 76 (6.58%)	8 / 77 (10.39%)	
occurrences (all)	5	8	
Pain			
subjects affected / exposed	5 / 76 (6.58%)	3 / 77 (3.90%)	
occurrences (all)	5	3	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	3 / 76 (3.95%)	6 / 77 (7.79%)	
occurrences (all)	3	7	
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	10 / 76 (13.16%)	19 / 77 (24.68%)	
occurrences (all)	10	23	
Dyspnoea			
subjects affected / exposed	6 / 76 (7.89%)	10 / 77 (12.99%)	
occurrences (all)	6	11	
Oropharyngeal pain			
subjects affected / exposed	3 / 76 (3.95%)	5 / 77 (6.49%)	
occurrences (all)	3	7	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	4 / 76 (5.26%)	3 / 77 (3.90%)	
occurrences (all)	4	3	
Investigations			
Blood creatinine increased			
subjects affected / exposed	1 / 76 (1.32%)	6 / 77 (7.79%)	
occurrences (all)	1	7	
Neutrophil count decreased			
subjects affected / exposed	3 / 76 (3.95%)	14 / 77 (18.18%)	
occurrences (all)	3	18	
Weight increased			
subjects affected / exposed	1 / 76 (1.32%)	4 / 77 (5.19%)	
occurrences (all)	1	4	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	11 / 76 (14.47%)	5 / 77 (6.49%)	
occurrences (all)	11	5	
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 76 (2.63%)	9 / 77 (11.69%)	
occurrences (all)	2	9	
Dysgeusia			
subjects affected / exposed	0 / 76 (0.00%)	4 / 77 (5.19%)	
occurrences (all)	0	5	
Headache			

subjects affected / exposed	7 / 76 (9.21%)	12 / 77 (15.58%)	
occurrences (all)	7	12	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	4 / 76 (5.26%)	19 / 77 (24.68%)	
occurrences (all)	4	22	
Constipation			
subjects affected / exposed	12 / 76 (15.79%)	29 / 77 (37.66%)	
occurrences (all)	13	30	
Diarrhoea			
subjects affected / exposed	9 / 76 (11.84%)	19 / 77 (24.68%)	
occurrences (all)	9	28	
Dyspepsia			
subjects affected / exposed	1 / 76 (1.32%)	4 / 77 (5.19%)	
occurrences (all)	1	4	
Nausea			
subjects affected / exposed	10 / 76 (13.16%)	10 / 77 (12.99%)	
occurrences (all)	12	10	
Abdominal pain upper			
subjects affected / exposed	4 / 76 (5.26%)	2 / 77 (2.60%)	
occurrences (all)	4	2	
Vomiting			
subjects affected / exposed	4 / 76 (5.26%)	11 / 77 (14.29%)	
occurrences (all)	5	12	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	1 / 76 (1.32%)	4 / 77 (5.19%)	
occurrences (all)	1	4	
Erythema multiforme			
subjects affected / exposed	1 / 76 (1.32%)	4 / 77 (5.19%)	
occurrences (all)	1	4	
Hyperhidrosis			
subjects affected / exposed	0 / 76 (0.00%)	6 / 77 (7.79%)	
occurrences (all)	0	6	
Pruritus			

subjects affected / exposed	3 / 76 (3.95%)	11 / 77 (14.29%)	
occurrences (all)	3	11	
Dermatitis acneiform			
subjects affected / exposed	2 / 76 (2.63%)	4 / 77 (5.19%)	
occurrences (all)	2	5	
Rash maculo-papular			
subjects affected / exposed	2 / 76 (2.63%)	16 / 77 (20.78%)	
occurrences (all)	3	19	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 76 (2.63%)	6 / 77 (7.79%)	
occurrences (all)	2	6	
Back pain			
subjects affected / exposed	8 / 76 (10.53%)	3 / 77 (3.90%)	
occurrences (all)	8	4	
Myalgia			
subjects affected / exposed	4 / 76 (5.26%)	5 / 77 (6.49%)	
occurrences (all)	5	5	
Pain in extremity			
subjects affected / exposed	2 / 76 (2.63%)	7 / 77 (9.09%)	
occurrences (all)	2	8	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	6 / 76 (7.89%)	3 / 77 (3.90%)	
occurrences (all)	6	3	
Rhinitis			
subjects affected / exposed	1 / 76 (1.32%)	4 / 77 (5.19%)	
occurrences (all)	1	4	
Urinary tract infection			
subjects affected / exposed	2 / 76 (2.63%)	4 / 77 (5.19%)	
occurrences (all)	3	4	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	6 / 76 (7.89%)	13 / 77 (16.88%)	
occurrences (all)	7	14	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 July 2011	Update of section 17 of the protocol 'Translational research' and implementation of administrative changes. In addition the information regarding secondary primary malignancies of lenalidomide were taken into account in the protocol and in the patient information sheet. An additional exclusion criteria regarding compressive syndrome was added as well.

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.

Quality of life and patient reported outcomes could not be assessed, which may be regarded as a potential limitation of this study.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/31101627

http://www.ncbi.nlm.nih.gov/pubmed/32012230