Clinical trial results:
Efficacy of alternating immunochemotherapy consisting of R-CHOP + R-HAD versus R-CHOP alone, followed by maintenance therapy consisting of additional lenalidomide with rituximab versus rituximab alone for older patients with mantle cell lymphoma

Summary

EudraCT number	2012-002542-20
Trial protocol	FR BE DE NL PT ES PL
Global end of trial date	30 January 2025

Results information

Result version number	v1 (current)
This version publication date	18 February 2026
First version publication date	18 February 2026

Trial information

Trial identification

Sponsor protocol code	MCL-R2 Elderly

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01865110
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	LYSARC
Sponsor organisation address	CH Lyon Sud – Bat 2D, PIERRE-BENITE Cedex, France, 69495
Public contact	Christine STEPHAN, LYSARC, mclr2@lysarc.org
Scientific contact	Vincent Ribrag, LYSA, vincent.ribrag@gustaveroussy.fr

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	30 January 2025
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 January 2025
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the trial is to evaluate whether the addition of lenalidomide to standard rituximab-maintenance improves progression free survival (PFS) compared to standard rituximab maintenance after response to induction chemotherapy in older patients with mantle cell lymphoma not suitable for autologous stem cell transplantation

Protection of trial subjects:

Therapies considered necessary for the subject’s well-being may be administered at the discretion of the Investigator.
Growth factors during induction treatment (e.g. G-CSF, GM-CSF, erythropoietin, etc.) may be prescribed by the Investigator for rescue from severe hematologic events and should be used in accordance with the American Society of Clinical Oncology’s (ASCO) guidelines or the European Society for Medical Oncology (ESMO) guidelines

Background therapy:

Induction treatment with RCHOP followed by R-maintenance

Evidence for comparator:

The European MCL network presented a randomized phase III study including a high number of patients (560 elderly patients). Two induction therapies were compared, 8 cycles of R-CHOP and 6 cycles of R-FC. A second randomization compared rituximab maintenance given every other month to IFN maintenance. Maintenance therapy was continued until progression or recurrence of the lymphoma{Kluin-Nelemans HC, Hoster E, Hermine O et al. Treatment of older patients with mantle cell lymphoma. N Engl J Med. 2012;367(6):520-31}.
Out of 560 patients, 532 could be analyzed according to intention-to-treat for response, whereas 485 were fully evaluable. Median age was 70 yrs. Although complete remission rates were similar after R-FC vs R-CHOP (40% vs 34%, p=0.10), progressive disease was more frequent during R-FC (14% vs 5%). Four-year overall survival was significantly inferior after R-FC (47% vs 62%; p=0.005) with more patients dying in first remission (10% vs 4%).
In 274 of 316 patients randomized for maintenance, rituximab almost doubled the remission duration compared with interferon-alfa (at 4-yr 58% vs 29% in remission; hazard ratio 0.55, 95% CI 0.36-0.87; p=0.0109). Rituximab maintenance significantly improved 4-year overall survival up to 87% vs. 63% on interferon-alfa (p=0.0051) in patients responding to R-CHOP. This study strongly suggests that 8 cycles of R-CHOP followed by rituximab maintenance could now represent a real standard therapy in elderly patients {6}. Still, the percentage of patients obtaining an initial CR is low. Patients who show early progression do not respond upon salvage therapy and die early. These data ask for further improvement of induction therapy. Furthermore, no plateau in remission duration has been observed, suggesting that maintenance with rituximab is not sufficient.

Actual start date of recruitment	04 November 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 75
Country: Number of subjects enrolled	Portugal: 8
Country: Number of subjects enrolled	Spain: 17
Country: Number of subjects enrolled	Belgium: 24
Country: Number of subjects enrolled	France: 412
Country: Number of subjects enrolled	Germany: 74
Country: Number of subjects enrolled	Poland: 10
Worldwide total number of subjects	620
EEA total number of subjects	620

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)	37
From 65 to 84 years	578
85 years and over	5

Subject disposition

Recruitment

Recruitment details:

First patients was randomized in the trial in France on 04/11/2013, in Germany on 11/05/2015, in Belgium on 29/09/2015, in Portugal and the Netherlands on 14/12/2015, in Spain on 13/09/2016 and in Poland on 22/05/2018.
Last patient was randomized for induction part on 05/12/2019 and for maintenance part on 21/08/2020.

Pre-assignment

Screening details:

Previously untreated participants with biopsy-proven mantle cell lymphoma according to WHO classification could be enrolled. From 03/11/2013 to 03/05/2014, patients could be randomized directly for maintenance treatment if they received 8 RCHOP before registration in the trial.
636 patients were screened and 623 randomizedin the trial.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	R-CHOP

Arm description: -

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

Dosage and administration details:

750 mg/m2 at Day 1, compound of standard CHOP chemotherapy, 8 cycles of 21-day cycle

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

Dosage and administration details:

375 mg/m2 at D1 before starting CHOP

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

Dosage and administration details:

50 mg/m2 at Day 1, compound of standard CHOP chemotherapy, 8 cycles of 21-day cycle

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

Dosage and administration details:

1.4 mg/m2 (2mg cap) at Day 1, compound of standard CHOP chemotherapy, 8 cycles of 21-day cycle

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

Dosage and administration details:

100 mg/day at Day 1 to day 5, compound of standard CHOP chemotherapy, 8 cycles of 21-day cycle

Arm title	R-CHOP/R-HAD

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Cytarabine
Investigational medicinal product code	
Other name	Aracytine
Pharmaceutical forms	Solution for injection, Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

1000 mg/m2 at day 1 (twice every 12 to 24 hours), 3 cycles of 28-day cycle for R-HAD alternating with R-CHOP

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

Dosage and administration details:

375 mg/m2 at day 1 (and 4 only during the first 2 cycles of RHAD)

Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection, Tablet
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

20 mg/day at day 1 to 4 of RHAD cycles
The administration route for dexamethasone will be used according to the marketing authorization available in each country for the dose used in the protocol (i.e. oral administration is allowed only in countries where this formulation has a marketing authorization)

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

Dosage and administration details:

750 mg/m2 at Day 1, compound of standard CHOP chemotherapy, 3 cycles of 21-day cycle alternating with R-HAD

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

Dosage and administration details:

50 mg/m2 at Day 1, compound of standard CHOP chemotherapy, 3 cycles of 21-day cycle alternating with R-HAD

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

Dosage and administration details:

1.4 mg/m2 (2mg cap) at Day 1, compound of standard CHOP chemotherapy, 3 cycles of 21-day cycle alternating with R-HAD

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

Dosage and administration details:

100 mg/day at Day 1 to day 5, compound of standard CHOP chemotherapy, 3 cycles of 21-day cycle alternating with R-HAD

Number of subjects in period 1	R-CHOP	R-CHOP/R-HAD
Started	312	308
Completed	259	281
Not completed	53	27
Consent withdrawn by subject	2	2
progression	13	16
Death	6	2
concurrent illness	2	-
Other	9	2
Insufficient response	9	2
Toxicity of study treatment	7	2
Protocol deviation	5	1

Period 2

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

Arms

Are arms mutually exclusive?	Yes

Arm title	R Arm
Arm description: Rituximab	
Arm type	Active comparator
Investigational medicinal product name	rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for injection
Routes of administration	Subcutaneous use
Dosage and administration details: Fixed dose of 1400 mg administered subcutaneously	
Arm title	R2 Arm
Arm description: Rituximab + Lenalidomide	
Arm type	Experimental
Investigational medicinal product name	rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use
Dosage and administration details: Fixed dose of 1400 mg administered subcutaneously	
Investigational medicinal product name	Lenalidomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: lenalidomide 15 mg daily on days 2 to 22 every 4 weeks. starting dose reduced to 10 mg in case of moderate renal insufficiency	

Number of subjects in period 2[1]	R Arm	R2 Arm
Started	248	247
Completed	147	154
Not completed	101	93
Consent withdrawn by subject	2	4
progression	78	42
concurrent illness	5	11
Death	2	2
Other	4	11
Toxicity of study treatment	5	19
Protocol deviation	5	4

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Regarding the second randomization, only patients who had a confirmed or unconfirmed complete response were eligible for randomization

Baseline characteristics

Reporting groups	
Reporting group title	R-CHOP
Reporting group description: -	
Reporting group title	R-CHOP/R-HAD
Reporting group description: -	

Reporting group values	R-CHOP	R-CHOP/R-HAD	Total
Number of subjects	312	308	620
Age categorical			
Three categorises have been defined			
Units: Subjects			
Adults (18-64 years)	19	18	37
From 65-84 years	290	288	578
85 years and over	3	2	5
Age continuous			
Units: years			
arithmetic mean	71.6	71.7	
standard deviation	± 5.22	± 4.77	-
Gender categorical			
Units: Subjects			
Female	91	86	177
Male	221	222	443
Ann arbor stage			
Units: Subjects			
stage I	0	2	2
stage II	12	15	27
stage III	15	16	31
stage IV	284	275	559
Missing	1	0	1
ECOG Performance status			
Units: Subjects			
0-1	287	282	569
>1	23	26	49
Missing	2	0	2
LDH > upper limit			
Units: Subjects			
No	181	174	355
Yes	127	131	258
Missing	4	3	7
MIPI risk group at baseline			
Units: Subjects			
Low risk (<5.7)	21	18	39
Intermediate risk (>=5.7 & <6.2)	137	134	271
High risk (>=6.2)	149	153	302
Missing	5	3	8

Weight			
weight collected in kg			
Units: kg			
arithmetic mean	77.1	76.3	
standard deviation	± 15.13	± 14.93	-
Height			
Units: cm			
arithmetic mean	170.3	170.7	
standard deviation	± 8.52	± 8.84	-
Hemoglobin			
Units: g/dl			
arithmetic mean	12.6	12.2	
standard deviation	± 1.91	± 2.08	-
Leukocytes			
Units: G/L			
arithmetic mean	21.1	17.3	
standard deviation	± 55.14	± 39.75	-
Neutrophils			
Units: G/L			
arithmetic mean	4.9	4.5	
standard deviation	± 3.53	± 2.32	-
Lymphocytes			
Units: G/L			
arithmetic mean	8.2	9.0	
standard deviation	± 27.3	± 36.0	-
Lymphoma cells (%)			
Units: percentage			
arithmetic mean	13	14.2	
standard deviation	± 26.28	± 24.63	-
Platelets			
Units: G/L			
arithmetic mean	198.4	189.3	
standard deviation	± 94.1	± 98.01	-

End points

End points reporting groups	
Reporting group title	R-CHOP
Reporting group description: -	
Reporting group title	R-CHOP/R-HAD
Reporting group description: -	
Reporting group title	R Arm
Reporting group description: Rituximab	
Reporting group title	R2 Arm
Reporting group description: Rituximab + Lenalidomide	

Primary: Progression-Free Survival for maintenance randomisation (PFSm)	
End point title	Progression-Free Survival for maintenance randomisation (PFSm)
End point description: PFS at 2 years	
End point type	Primary
End point timeframe: From the date of maintenance randomization to the date of first documented disease progression, relapse or death from any cause, whichever occurs first or last contact if no event occurs	

End point values	R Arm	R2 Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	248	247		
Units: percentage				
number (confidence interval 95%)	62.3 (55.9 to 68.0)	77.0 (71.2 to 81.8)		

Attachments (see zip file)	Primary analysis -PFS curves/Figure 167002.jpeg

Statistical analyses

Statistical analysis title	PFSm superiority analysis
Comparison groups	R Arm v R2 Arm

Number of subjects included in analysis	495
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.784
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.635
upper limit	0.967

Secondary: Overall Survival since maintenance randomisation (OSm)

End point title	Overall Survival since maintenance randomisation (OSm)

End point description:

End point type	Secondary

End point timeframe:

From maintenance randomisation to death/last visit

End point values	R Arm	R2 Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	248	247		
Units: percent				
number (confidence interval 95%)	85.3 (80.2 to 89.2)	87.7 (82.9 to 91.2)		

Attachments (see zip file)	secondary endpoint -OS curves/Figure 177024.jpeg

Statistical analyses

Statistical analysis title	Overall survival

Statistical analysis description:

Overall survival from maintenance randomisation - Maintenance ITT set

Comparison groups	R Arm v R2 Arm
Number of subjects included in analysis	495
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.02

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.766
upper limit	1.359

Secondary: Overall Survival since induction randomisation (OSi)

End point title	Overall Survival since induction randomisation (OSi)

End point description:

End point type	Secondary

End point timeframe:

From the date of induction randomisation randomization to the date of first documented disease progression, relapse or death
from any cause, whichever occurs first

End point values	R-CHOP	R-CHOP/R-HAD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	312	308		
Units: percent				
number (confidence interval 95%)	83.0 (78.3 to 86.8)	83.2 (78.4 to 86.9)		

Attachments (see zip file)	key secondary analysis -OS curves/Figure 167022.jpeg

Statistical analyses

Statistical analysis title	OS since induction randomisation
Comparison groups	R-CHOP/R-HAD v R-CHOP
Number of subjects included in analysis	620
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.932
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.733
upper limit	1.185

Secondary: Complete Response rate (CR/CRu)

End point title	Complete Response rate (CR/CRu)

End point description:

End point type	Secondary

End point timeframe:

End of induction

End point values	R-CHOP	R-CHOP/R-HAD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	290	300		
Units: percentage				
arithmetic mean (confidence interval 95%)	41 (35.32 to 56.94)	41.3 (35.7 to 47.14)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Patients randomized to receive rituximab and lenalidomide received up to twenty six cycles of lenalidomide 15 mg daily on days 2 to 22 every 4 weeks and up to thirteen injections of rituximab 1400 mg on day 1 every 8 weeks.

Adverse event reporting additional description:

Evaluated for AEs at each visit with the NCI CTCAE v4.0 used as a guide for the grading of severity.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14

Reporting groups

Reporting group title	R Arm

Reporting group description: -

Reporting group title	R2 Arm

Reporting group description: -

Serious adverse events	R Arm	R2 Arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	77 / 250 (30.80%)	101 / 238 (42.44%)	
number of deaths (all causes)	91	93	
number of deaths resulting from adverse events	1	4	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED			
subjects affected / exposed	42 / 250 (16.80%)	48 / 238 (20.17%)	
occurrences causally related to treatment / all	3 / 57	48 / 86	
deaths causally related to treatment / all	0 / 2	4 / 11	
Vascular disorders			
VASCULAR DISORDERS			
subjects affected / exposed	6 / 250 (2.40%)	6 / 238 (2.52%)	
occurrences causally related to treatment / all	0 / 6	3 / 6	
deaths causally related to treatment / all	0 / 1	0 / 0	
Surgical and medical procedures			
SURGICAL AND MEDICAL PROCEDURES			

subjects affected / exposed	2 / 250 (0.80%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
subjects affected / exposed	1 / 250 (0.40%)	4 / 238 (1.68%)	
occurrences causally related to treatment / all	0 / 1	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Immune system disorders			
IMMUNE SYSTEM DISORDER			
subjects affected / exposed	1 / 250 (0.40%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
subjects affected / exposed	3 / 250 (1.20%)	9 / 238 (3.78%)	
occurrences causally related to treatment / all	0 / 5	5 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
PSYCHIATRIC DISORDERS			
subjects affected / exposed	2 / 250 (0.80%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
investigations			
subjects affected / exposed	1 / 250 (0.40%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
subjects affected / exposed	6 / 250 (2.40%)	5 / 238 (2.10%)	
occurrences causally related to treatment / all	0 / 6	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac disorders			
CARDIAC DISORDERS			
subjects affected / exposed	10 / 250 (4.00%)	14 / 238 (5.88%)	
occurrences causally related to treatment / all	1 / 11	7 / 21	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
NERVOUS SYSTEM DISORDERS			
subjects affected / exposed	3 / 250 (1.20%)	3 / 238 (1.26%)	
occurrences causally related to treatment / all	0 / 3	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
subjects affected / exposed	2 / 250 (0.80%)	3 / 238 (1.26%)	
occurrences causally related to treatment / all	1 / 2	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
EAR AND LABYRINTH DISORDERS			
subjects affected / exposed	1 / 250 (0.40%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
EYE DISORDERS			
subjects affected / exposed	2 / 250 (0.80%)	2 / 238 (0.84%)	
occurrences causally related to treatment / all	0 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
GASTROINTESTINAL DISORDERS			
subjects affected / exposed	2 / 250 (0.80%)	7 / 238 (2.94%)	
occurrences causally related to treatment / all	0 / 2	2 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
HEPATOBILIARY DISORDERS			
subjects affected / exposed	3 / 250 (1.20%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			

SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
subjects affected / exposed	0 / 250 (0.00%)	2 / 238 (0.84%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
RENAL AND URINARY DISORDERS			
subjects affected / exposed	0 / 250 (0.00%)	2 / 238 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
subjects affected / exposed	3 / 250 (1.20%)	6 / 238 (2.52%)	
occurrences causally related to treatment / all	0 / 3	4 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
INFECTIONS AND INFESTATIONS			
subjects affected / exposed	10 / 250 (4.00%)	38 / 238 (15.97%)	
occurrences causally related to treatment / all	4 / 11	17 / 46	
deaths causally related to treatment / all	0 / 0	0 / 3	
Metabolism and nutrition disorders			
METABOLISM AND NUTRITION DISORDERS			
subjects affected / exposed	1 / 250 (0.40%)	3 / 238 (1.26%)	
occurrences causally related to treatment / all	1 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	R Arm	R2 Arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	150 / 250 (60.00%)	216 / 238 (90.76%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			

subjects affected / exposed	42 / 250 (16.80%)	48 / 238 (20.17%)	
occurrences (all)	57	87	
Surgical and medical procedures			
SURGICAL AND MEDICAL PROCEDURES			
subjects affected / exposed	2 / 250 (0.80%)	2 / 238 (0.84%)	
occurrences (all)	2	4	
General disorders and administration site conditions			
VASCULAR DISORDERS			
subjects affected / exposed	11 / 250 (4.40%)	11 / 238 (4.62%)	
occurrences (all)	11	11	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
subjects affected / exposed	2 / 250 (0.80%)	26 / 238 (10.92%)	
occurrences (all)	2	29	
Immune system disorders			
IMMUNE SYSTEM DISORDER			
subjects affected / exposed	1 / 250 (0.40%)	2 / 238 (0.84%)	
occurrences (all)	1	2	
Reproductive system and breast disorders			
REPRODUCTIVE SYSTEM AND BREAST DISORDERS			
subjects affected / exposed	0 / 250 (0.00%)	1 / 238 (0.42%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
subjects affected / exposed	8 / 250 (3.20%)	17 / 238 (7.14%)	
occurrences (all)	10	18	
Psychiatric disorders			
PSYCHIATRIC DISORDERS			
subjects affected / exposed	2 / 250 (0.80%)	0 / 238 (0.00%)	
occurrences (all)	2	0	
Investigations			
investigations			
subjects affected / exposed	3 / 250 (1.20%)	5 / 238 (2.10%)	
occurrences (all)	3	5	
Injury, poisoning and procedural complications			

INJURY, POISONING AND PROCEDURAL COMPLICATIONS subjects affected / exposed occurrences (all)	6 / 250 (2.40%) 6	6 / 238 (2.52%) 6	
Cardiac disorders CARDIAC DISORDERS subjects affected / exposed occurrences (all)	14 / 250 (5.60%) 15	20 / 238 (8.40%) 28	
Nervous system disorders NERVOUS SYSTEM DISORDERS subjects affected / exposed occurrences (all)	8 / 250 (3.20%) 8	23 / 238 (9.66%) 25	
Blood and lymphatic system disorders BLOOD AND LYMPHATIC SYSTEM DISORDERS subjects affected / exposed occurrences (all)	70 / 250 (28.00%) 121	144 / 238 (60.50%) 520	
Ear and labyrinth disorders EAR AND LABYRINTH DISORDERS subjects affected / exposed occurrences (all)	2 / 250 (0.80%) 2	5 / 238 (2.10%) 5	
Eye disorders EYE DISORDERS subjects affected / exposed occurrences (all)	4 / 250 (1.60%) 4	2 / 238 (0.84%) 3	
Gastrointestinal disorders GASTROINTESTINAL DISORDERS subjects affected / exposed occurrences (all)	3 / 250 (1.20%) 3	25 / 238 (10.50%) 28	
Hepatobiliary disorders HEPATOBILIARY DISORDERS subjects affected / exposed occurrences (all)	3 / 250 (1.20%) 4	2 / 238 (0.84%) 3	
Skin and subcutaneous tissue disorders SKIN AND SUBCUTANEOUS TISSUE DISORDERS subjects affected / exposed occurrences (all)	0 / 250 (0.00%) 0	30 / 238 (12.61%) 37	
Endocrine disorders			

ENDOCRIN DISORDER subjects affected / exposed occurrences (all)	0 / 250 (0.00%) 0	1 / 238 (0.42%) 1	
Musculoskeletal and connective tissue disorders MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS subjects affected / exposed occurrences (all)	4 / 250 (1.60%) 4	14 / 238 (5.88%) 16	
Infections and infestations INFECTIONS AND INFESTATIONS subjects affected / exposed occurrences (all)	60 / 250 (24.00%) 100	105 / 238 (44.12%) 183	
Metabolism and nutrition disorders METABOLISM AND NUTRITION DISORDERS subjects affected / exposed occurrences (all)	4 / 250 (1.60%) 4	5 / 238 (2.10%) 5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 August 2013	Addition of AE collection of grade >=3 during induction treatment and updates on blood/bone marrow samples collected
17 March 2014	Maintenance treatment: use of rituximab SC instead IV Addition of an exclusion criterion in case of cardiac insufficiency (left ventricular ejection fraction < 50%) on ultrasound Modification of patient stratification rules for maintenance part
14 October 2015	Postponing of the schedule of interim analysis and IDMC review data meeting originally planned after 25 patients had received 6 months of lenalidomide maintenance treatment or no later than 1 year after the first patient was randomized to maintenance treatment, due to a delay in enrollments: will be conducted after 6 months of maintenance treatment for the 25 patients, in order to ensure a minimum number of patients in the analysis and enhance its robustness. Update to the patient and investigator information documents regarding the risks of lenalidomide to the fetus and contraception recommendations (PPP: Pregnancy Prevention Plan).
05 July 2019	Update to storage conditions for subcutaneous rituximab according to the Investigator's Brochure Update to dose reduction measures for lenalidomide Additional safety measures for adverse events such as hepatitis B virus reactivation following recent publications in patients treated with immunochemotherapy, Additional safety measures regarding adverse events such as DRESS syndrome and hypo/hyperthyroidism in accordance with the Investigator's Brochure for lenalidomide Clarifications on the maintenance phase: Clarifications on the duration of reporting adverse events
08 September 2020	Addendum 1 aims to describe the measures taken to adapt the protocol during the pandemic period: postponement of a cycle, possibility of dispensing two cycles of lenalidomide, exceptional authorization to conduct visits by telephone or video to limit travel and patients' exposure to COVID-19; authorization of teleconsultations, authorization to postpone scans; and, if urgent, authorization to use a local imaging center.
13 March 2023	Reduction of the follow-up period by 5 months: end of patient follow-up on January 30, 2025

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported