Clinical trial results:
Comparing two schedules of rituximab maintenance in rituximab-responding patients with untreated, chemotherapy resistant or relapsed follicular lymphoma: A randomized phase III trial

Summary

EudraCT number	2004-002859-13
Trial protocol	IT SK
Global end of trial date	19 December 2017

Results information

Result version number	v1 (current)
This version publication date	15 December 2022
First version publication date	15 December 2022

Trial information

Trial identification

Sponsor protocol code	SAKK 35/03

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00227695
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, +41 31389 91 91, sakkcc@sakk.ch
Scientific contact	Head Regulatory Affairs, Swiss Group for Clinical Cancer, +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	10 September 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 December 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this trial was to investigate if maintenance with rituximab for 5 years or until relapse/progression, unacceptable toxicity or death is superior to 4 times maintenance with rituximab.

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:

None

Evidence for comparator:

Not applicable; no comparator was used. The study evaluated the impact of different rituximab maintenance schedules.

Actual start date of recruitment	05 August 2004
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	Slovakia: 2
Country: Number of subjects enrolled	Italy: 53
Country: Number of subjects enrolled	Brazil: 7
Country: Number of subjects enrolled	North Macedonia: 10
Country: Number of subjects enrolled	Serbia: 4
Country: Number of subjects enrolled	South Africa: 16
Country: Number of subjects enrolled	Switzerland: 73
Worldwide total number of subjects	165
EEA total number of subjects	55

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)	119
From 65 to 84 years	46
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between August 2004 and September 2007, 270 patients were included into the trial at 19 centers in Switzerland, 2 centers in South Africa, 1 center each in Brazil, Italy, Macedonia, Serbia and Slovakia.

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. Of the 270 registered patients, 165 patients were randomized.

Pre-assignment period milestones

Number of subjects started	270[1]
Number of subjects completed	165

Pre-assignment subject non-completion reasons

Reason: Number of subjects	PD / Relapse: 17
Reason: Number of subjects	Toxicity: 2
Reason: Number of subjects	Consent withdrawn by subject: 1
Reason: Number of subjects	SD: 75
Reason: Number of subjects	Other: 10

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: It was planned to enroll 270 patients into the induction phase and then randomize a total of about 135 patients, in order to observe the required number of 99 events.

Period 1

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

Blinding implementation details:

n/a

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A

Arm description:

Rituximab 375 mg/m2 | every 2 months x 4

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

Dosage and administration details:

Inductionphase: Rituximab 375 mg/m2 weekly x 4 || Maintenance phase: Rituximab 375 mg/m2 every 2 months x 4

Arm title	Arm B

Arm description:	
Rituximab 375 mg/m2 | every 2 months for 5 years or until PD, relapse or unacceptable toxicity	
Arm type	Experimental
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	MabThera®
Pharmaceutical forms	Infusion
Routes of administration	Infusion

Dosage and administration details:

Inductionphase: Rituximab 375 mg/m2 weekly x4 || Maintenance phase: Rituximab 375 mg/m2 every 2 months for 5 years or until PD, relapse or unacceptable toxicity.

Number of subjects in period 1	Arm A	Arm B
Started	82	83
Completed	82	83

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

Arm description:

Rituximab 375 mg/m2 \| every 2 months x 4

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

Dosage and administration details:

Inductionphase: Rituximab 375 mg/m2 weekly x 4 || Maintenance phase: Rituximab 375 mg/m2 every 2 months x 4

Arm title	Arm B

Arm description:

Rituximab 375 mg/m2 \| every 2 months for 5 years or until PD, relapse or unacceptable toxicity

Arm type	Experimental

Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	MabThera®
Pharmaceutical forms	Infusion
Routes of administration	Infusion

Dosage and administration details:

Inductionphase: Rituximab 375 mg/m2 weekly x4 || Maintenance phase: Rituximab 375 mg/m2 every 2 months for 5 years or until PD, relapse or unacceptable toxicity.

Number of subjects in period 2	Arm A	Arm B
Started	82	83
Completed	80	46
Not completed	2	37
Relapse	-	5
Consent withdrawn by subject	-	3
Progressive disease (PD)	2	21
Death	-	1
Other	-	2
2nd tumour	-	2
Unacceptable toxicity	-	3

Period 3

Period 3 title	Follow-up 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

Arm description:

Rituximab 375 mg/m2 | every 2 months x 4

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

Dosage and administration details:

Inductionphase: Rituximab 375 mg/m2 weekly x 4 || Maintenance phase: Rituximab 375 mg/m2 every 2 months x 4

Arm title	Arm B

Arm description:

Rituximab 375 mg/m2 | every 2 months for 5 years or until PD, relapse or unacceptable toxicity

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

Dosage and administration details:

Inductionphase: Rituximab 375 mg/m2 weekly x4 || Maintenance phase: Rituximab 375 mg/m2 every 2 months for 5 years or until PD, relapse or unacceptable toxicity.

Number of subjects in period 3	Arm A	Arm B
Started	80	46
Completed	42	16
Not completed	38	30
Death	17	16
Lost to follow-up	21	14

Baseline characteristics

Reporting groups	
Reporting group title	Arm A
Reporting group description: Rituximab 375 mg/m2 | every 2 months x 4	
Reporting group title	Arm B
Reporting group description: Rituximab 375 mg/m2 | every 2 months for 5 years or until PD, relapse or unacceptable toxicity	

Reporting group values	Arm A	Arm B	Total
Number of subjects	82	83	165
Age categorical Units: Subjects			
Adults (18-64 years)	59	60	119
From 65-84 years	23	23	46
Gender categorical Units: Subjects			
Female	44	57	101
Male	38	26	64

End points

End points reporting groups

Reporting group title	Arm A
Reporting group description: Rituximab 375 mg/m2 | every 2 months x 4	
Reporting group title	Arm B
Reporting group description: Rituximab 375 mg/m2 | every 2 months for 5 years or until PD, relapse or unacceptable toxicity	
Reporting group title	Arm A
Reporting group description: Rituximab 375 mg/m2 | every 2 months x 4	
Reporting group title	Arm B
Reporting group description: Rituximab 375 mg/m2 | every 2 months for 5 years or until PD, relapse or unacceptable toxicity	
Reporting group title	Arm A
Reporting group description: Rituximab 375 mg/m2 | every 2 months x 4	
Reporting group title	Arm B
Reporting group description: Rituximab 375 mg/m2 | every 2 months for 5 years or until PD, relapse or unacceptable toxicity	
Subject analysis set title	Arm A - ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description: Patients in Arm A (ITT population)	
Subject analysis set title	Arm B - ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description: Patients in Arm B (ITT population)	
Subject analysis set title	Arm A - PPS
Subject analysis set type	Per protocol
Subject analysis set description: PPS is a subset of patients in the ITT population (patients who took at least one dose of the trial treatment after randomization) who comply with the requirements of the protocol: (1) patients without any major protocol violation regarding inclusion/exclusion criteria for registration and randomization, (2) patients with a CR or PR as assessed by the central re-assessment at re-staging following the induction treatment, (3) centrally reviewed PD shall be considered as PD instead of PD as recorded by the centers. Reverse cases where the center assessed the patient as being PD as supposed to CR / PR / SD by the central review will be censored at this time.	
Subject analysis set title	Arm B - PPS
Subject analysis set type	Per protocol
Subject analysis set description: PPS is a subset of patients in the ITT population (patients who took at least one dose of the trial treatment after randomization) who comply with the requirements of the protocol: (1) patients without any major protocol violation regarding inclusion/exclusion criteria for registration and randomization, (2) patients with a CR or PR as assessed by the central re-assessment at re-staging following the induction treatment, (3) centrally reviewed PD shall be considered as PD instead of PD as recorded by the centers. Reverse cases where the center assessed the patient as being PD as supposed to CR / PR / SD by the central review will be censored at this time.	
Subject analysis set title	Prognostic CRP value - short term maintenance arm
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients with baseline CRP levels (in short term maintenance).

Subject analysis set title	Prognostic CRP value - long term maintenance arm
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients with baseline CRP levels (in long term maintenance).

Primary: Primary Endpoint | Event-free survival (EFS)

End point title	Primary Endpoint | Event-free survival (EFS)

End point description:

EFS was defined as the period from randomization for the maintenance until one of the following events occurred: PD or relapse, unacceptable toxicity, death from any cause, initiation of non-protocol anticancer treatment or concomitant steroids introduced because of lymphoma symptoms or concomitant radiotherapy, or secondary malignancy.

NOTE: UPPER VALUES FOR 95% CONFIDENCE INTERVAL FOR ARM B (ITT AND PPS) ARE "N/A". HOWEVER, DUE TO DATABASE RESTRICTIONS VALUE = "999" WAS ENTERED.

End point type	Primary

End point timeframe:

EFS was defined as the period from randomization for the maintenance until event occurence.

End point values	Arm A - ITT	Arm B - ITT	Arm A - PPS	Arm B - PPS
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	82	83	69	71
Units: EFS (months)				
median (confidence interval 95%)	3.4 (2.1 to 5.3)	5.3 (3.5 to 999)	3.4 (2.1 to 5.9)	5.6 (3.4 to 999)

Statistical analyses

Statistical analysis title	KM Analysis EFS | Log rank test (ITT)
Comparison groups	Arm A - ITT v Arm B - ITT
Number of subjects included in analysis	165
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1436
Method	Logrank

Statistical analysis title	KM Analysis EFS | Log rank test (PPS)
Comparison groups	Arm A - PPS v Arm B - PPS

Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3041
Method	Logrank

Secondary: Secondary Endpoint | Progression free survival (PFS)

End point title	Secondary Endpoint | Progression free survival (PFS)

End point description:

Patients not experiencing an event were censored at the last known time they were alive without PD or relapse (i.e. last date of tumor assessment).

NOTE: UPPER VALUES FOR 95% CI ARE "N/A". HOWEVER, DUE TO DATABASE RESTRICTIONS VALUE "999" WAS ENTERED.

End point type	Secondary

End point timeframe:

Time from randomization to relapse/progression or death from NHL (Non-Hodgkin’s Lymphoma).

End point values	Arm A - ITT	Arm B - ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	82	83		
Units: PFS (months)				
median (confidence interval 95%)	3.5 (2.1 to 5.9)	7.4 (5.1 to 999)		

Statistical analyses

Statistical analysis title	KM Analysis PFS | Log rank test (ITT)
Comparison groups	Arm A - ITT v Arm B - ITT
Number of subjects included in analysis	165
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0388
Method	Logrank

Secondary: Secondary Endpoint | Overall survival (OS)

End point title	Secondary Endpoint | Overall survival (OS)

End point description:

Patients not experiencing an event were censored at the last known time they were alive.

NOTE: UPPER VALUES FOR 95% CI ARE "N/A". HOWEVER, DUE TO DATABASE RESTRICTIONS VALUE "999" WAS ENTERED.

End point type	Secondary

End point timeframe:

OS was calculated from randomization until death from any cause.

End point values	Arm A - ITT	Arm B - ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	82	83		
Units: OS (months)				
median (confidence interval 95%)	8.1 (8.1 to 999)	7.8 (7.8 to 999)		

Statistical analyses

Statistical analysis title	KM Analysis OS | Log rank test (ITT)
Comparison groups	Arm A - ITT v Arm B - ITT
Number of subjects included in analysis	165
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6336
Method	Logrank

Secondary: Secondary Endpoint | Objective Response (OR)

End point title	Secondary Endpoint | Objective Response (OR)

End point description:

Objective response (OR) was defined as the observed best response (CR [complete response], CRu [complete unconfirmed response], PR [partial response], SD [stable disease], PD [progressive disease]) as assessed following the criteria of Cheson et al 1999 (1) after randomization and before switching to another treatment.

End point type	Secondary

End point timeframe:

From randomization until switching to another treatment.

End point values	Arm A - ITT	Arm B - ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	82	82[1]		
Units: Pts with best response CR, CRu or PR (%)				
number (confidence interval 95%)	93.9 (86.3 to 98.0)	87.8 (78.7 to 94.0)		

Notes:

[1] - One patient did not have post-randomization tumor assessment.

Statistical analyses

Statistical analysis title	OR | Fisher's exact test (ITT)
Comparison groups	Arm A - ITT v Arm B - ITT
Number of subjects included in analysis	164
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2784
Method	Fisher exact

Secondary: Secondary Endpoint | Prognostic value of baseline CRP for EFS (ITT)	
End point title	Secondary Endpoint | Prognostic value of baseline CRP for EFS (ITT)
End point description:	
Prognostic value of baseline CRP for EFS (only patients still at risk after 8 months from randomization) and PFS.	
End point type	Secondary
End point timeframe:	
From randomization until event (see EFS and PFS for details).	

End point values	Prognostic CRP value - short term maintenance arm	Prognostic CRP value - long term maintenance arm		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	68	62		
Units: Patients (n)				
CRP elevated	12	7		
CRP not elevated	56	55		

Statistical analyses

Statistical analysis title	Hazard ratio (baseline CRP) - EFS
Statistical analysis description:	
Hazard ratio (baseline CRP elevated vs not elevated)	
Comparison groups	Prognostic CRP value - short term maintenance arm v Prognostic CRP value - long term maintenance arm
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2022
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.462

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.816
upper limit	2.621

Statistical analysis title	Hazard ratio (treatment) - EFS
Statistical analysis description:	
Hazard ratio (treatment long term maintenance vs short term maintenance)	
Comparison groups	Prognostic CRP value - short term maintenance arm v Prognostic CRP value - long term maintenance arm
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0665
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.658
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	1.029

Statistical analysis title	Hazard ratio (baseline CRP) - PFS
Statistical analysis description:	
Hazard ratio (baseline CRP elevated vs not elevated)	
Comparison groups	Prognostic CRP value - short term maintenance arm v Prognostic CRP value - long term maintenance arm
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0188
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.863
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.109
upper limit	3.13

Statistical analysis title	Copy of Hazard ratio (treatment) - PFS

Statistical analysis description:	
Hazard ratio (treatment long term maintenance vs short term maintenance)	
Comparison groups	Prognostic CRP value - short term maintenance arm v Prognostic CRP value - long term maintenance arm
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1667
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.736
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.477
upper limit	1.136

Secondary: Secondary Endpoint | Molecular remission (Swiss centers only)

End point title	Secondary Endpoint | Molecular remission (Swiss centers only)

End point description:

Blood (PB): The absence of t(14;18) positive cells in blood, in patients with a positive result before registration, after induction treatment with rituximab, at 6 and 12 months since randomization during maintenance treatment and every 12 months after the end of the treatment until relapse/progression.
Bone marrow (BM): The absence of t(14;18) positive cells in bone marrow, in patients with a positive result before registration, after induction treatment with rituximab, at 12 months since randomization during maintenance treatment and every 12 months after the end of the treatment until relapse/progression.
Duration of molecular remission was calculated from the first demonstration of t(14;18) negativity in bone marrow and peripheral blood until the demonstration of t(14;18) positivity for patients who were positive prior to registration.

End point type	Secondary

End point timeframe:

After induction of treatment until relapse/progression.

End point values	Arm A - ITT	Arm B - ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	37[2]	36[3]		
Units: patients || days				
number (not applicable)				
PB: t(14;18) positive cells at BSL (pts.)	17	19		
PB: t(14;18) negativity (pts.)	16	19		
PB: Median time to MR (days)	85.5	91		
PB: Molecular relapse (pts.)	1	2		
BM: t(14;18) positive cells at BSL (pts.)	10	9		
BM: t(14;18) negativity (pts.)	8	7		
BM: Median time to MR (days)	456	433		
BM: Molecular relapse (pts.)	1	0		

Notes:

[2] - Only patiens at swiss centers.

[3] - Only patients at swiss centers.

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary Endpoint |Immunophenotyping analysis (Swiss centers only)	
End point title	Secondary Endpoint |Immunophenotyping analysis (Swiss centers only)

End point description:

The evolution over time of the concentration of CD19+ B-lymphocytes in the peripheral blood.

End point type	Secondary

End point timeframe:

From randomization at various time points.

End point values	Arm A - ITT	Arm B - ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	37[4]	36[5]		
Units: Samples, n	37	36		

Notes:

[4] - Patients from swiss centers only.

[5] - Patients from swiss centers only.

Attachments (see zip file)	CD19+ B lymphocytes (cells/µl)/SAKK3503_CD19.png

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Primary Endpoint | Event-free survival (EFS) at 3 and 5 years	
End point title	Primary Endpoint | Event-free survival (EFS) at 3 and 5 years

End point description:

End point type	Other pre-specified

End point timeframe:

EFS probability at 3 years and 5 years.

End point values	Arm A - ITT	Arm B - ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	82	83		
Units: EFS probability (%)				
number (confidence interval 95%)				
3-year EFS probability	54.5 (42.9 to 64.8)	62.7 (51.3 to 72.1)		
5-year EFS probability	41.8 (30.5 to 52.6)	52.8 (41.5 to 62.9)		

Statistical analyses

Statistical analysis title	3-year EFS probability
Comparison groups	Arm A - ITT v Arm B - ITT
Number of subjects included in analysis	165
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	= 0.2958
Method	cloglog

Notes:

[6] - cloglog-Test

Statistical analysis title	5-year EFS probability
Comparison groups	Arm A - ITT v Arm B - ITT
Number of subjects included in analysis	165
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	= 0.1657
Method	cloglog

Notes:

[7] - cloglog-Test

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Events are reported from time of randomization until end of study.	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	25.0
Reporting groups	
Reporting group title	Arm A
Reporting group description: Rituximab 375 mg/m2 | every 2 months x4	
Reporting group title	Arm B
Reporting group description: Rituximab 375 mg/m2 | every 2 months for 5 years or until PD, relapse or unacceptable toxicity	

Serious adverse events	Arm A	Arm B	
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 82 (13.41%)	20 / 83 (24.10%)	
number of deaths (all causes)	17	16	
number of deaths resulting from adverse events	3	3	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Prostate cancer			
subjects affected / exposed	2 / 82 (2.44%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Basal cell carcinoma	Additional description: One of these events (Arm B): Cutaneous basal cell carcinoma (face) with curative complete resection		
subjects affected / exposed	1 / 82 (1.22%)	2 / 83 (2.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	0 / 82 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hodgkin's disease stage IV			

subjects affected / exposed	1 / 82 (1.22%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hodgkin's disease			
subjects affected / exposed	1 / 82 (1.22%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma in situ			
subjects affected / exposed	1 / 82 (1.22%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive breast carcinoma	Additional description: One of these events (Arm B): Invasive breast carcinoma and mastectomy		
subjects affected / exposed	1 / 82 (1.22%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive ductal breast carcinoma	Additional description: One of these events (Arm B): Hormone receptor positive invasive ductal breast cancer		
subjects affected / exposed	1 / 82 (1.22%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	0 / 82 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma			
subjects affected / exposed	1 / 82 (1.22%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelodysplastic syndrome			
subjects affected / exposed	0 / 82 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Sarcoma	Additional description: Sarcoma and sarcoma excision		

subjects affected / exposed	0 / 82 (0.00%)	1 / 83 (1.20%)	
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	1 / 82 (1.22%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Colorectal adenocarcinoma			
subjects affected / exposed	0 / 82 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis	Additional description: Inguinal pain, deep vein thrombosis (v. femoris profunda) and local infection with normal absolute neutrophil count		
subjects affected / exposed	0 / 82 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Meniscus removal			
subjects affected / exposed	0 / 82 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 82 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 82 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central nervous system haemorrhage			

subjects affected / exposed	0 / 82 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine	Additional description: Headache, migraine		
subjects affected / exposed	0 / 82 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 82 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Prostatitis	Additional description: Cystitis, epididymitis, prostatitis		
subjects affected / exposed	1 / 82 (1.22%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Ileus	Additional description: Ileus, acute abdomen and peritonitis		
subjects affected / exposed	0 / 82 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Abdominal pain upper			
subjects affected / exposed	1 / 82 (1.22%)	0 / 83 (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			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 82 (1.22%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Non-cirrhotic portal hypertension	Additional description: Idiopathic portal hypertension (IPH) and hepatopathy		

subjects affected / exposed	0 / 82 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cytomegalovirus infection			
subjects affected / exposed	1 / 82 (1.22%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 82 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Progressive multifocal leukoencephalopathy			
subjects affected / exposed	0 / 82 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Skin infection			
subjects affected / exposed	0 / 82 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia mycoplasmal			
subjects affected / exposed	0 / 82 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia	Additional description: One of these events (Arm B): Pneumonia with fever		
subjects affected / exposed	0 / 82 (0.00%)	2 / 83 (2.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pneumococcal			
subjects affected / exposed	1 / 82 (1.22%)	0 / 83 (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: 5 %

Non-serious adverse events	Arm A	Arm B	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	41 / 82 (50.00%)	63 / 83 (75.90%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 82 (0.00%)	8 / 83 (9.64%)	
occurrences (all)	0	9	
Hot flush			
subjects affected / exposed	2 / 82 (2.44%)	8 / 83 (9.64%)	
occurrences (all)	2	16	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 82 (1.22%)	7 / 83 (8.43%)	
occurrences (all)	1	7	
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 82 (0.00%)	7 / 83 (8.43%)	
occurrences (all)	0	7	
Headache			
subjects affected / exposed	2 / 82 (2.44%)	6 / 83 (7.23%)	
occurrences (all)	2	12	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	7 / 82 (8.54%)	20 / 83 (24.10%)	
occurrences (all)	8	28	
Pyrexia			
subjects affected / exposed	3 / 82 (3.66%)	8 / 83 (9.64%)	
occurrences (all)	3	10	
Oedema peripheral			
subjects affected / exposed	3 / 82 (3.66%)	6 / 83 (7.23%)	
occurrences (all)	3	8	
Influenza like illness			
subjects affected / exposed	1 / 82 (1.22%)	14 / 83 (16.87%)	
occurrences (all)	1	16	
Gastrointestinal disorders			

Diarrhoea			
subjects affected / exposed	2 / 82 (2.44%)	13 / 83 (15.66%)	
occurrences (all)	2	19	
Nausea			
subjects affected / exposed	5 / 82 (6.10%)	6 / 83 (7.23%)	
occurrences (all)	5	8	
Abdominal pain			
subjects affected / exposed	2 / 82 (2.44%)	10 / 83 (12.05%)	
occurrences (all)	2	14	
Respiratory, thoracic and mediastinal disorders			
Laryngeal pain			
subjects affected / exposed	1 / 82 (1.22%)	6 / 83 (7.23%)	
occurrences (all)	1	8	
Cough			
subjects affected / exposed	6 / 82 (7.32%)	24 / 83 (28.92%)	
occurrences (all)	6	34	
Dyspnoea			
subjects affected / exposed	2 / 82 (2.44%)	5 / 83 (6.02%)	
occurrences (all)	2	7	
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	3 / 82 (3.66%)	9 / 83 (10.84%)	
occurrences (all)	3	10	
Rash			
subjects affected / exposed	2 / 82 (2.44%)	7 / 83 (8.43%)	
occurrences (all)	2	8	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	2 / 82 (2.44%)	6 / 83 (7.23%)	
occurrences (all)	2	6	
Depression			
subjects affected / exposed	2 / 82 (2.44%)	5 / 83 (6.02%)	
occurrences (all)	2	6	
Musculoskeletal and connective tissue disorders			
Back pain			

subjects affected / exposed	2 / 82 (2.44%)	9 / 83 (10.84%)	
occurrences (all)	2	10	
Pain in extremity			
subjects affected / exposed	3 / 82 (3.66%)	9 / 83 (10.84%)	
occurrences (all)	3	11	
Arthralgia			
subjects affected / exposed	5 / 82 (6.10%)	12 / 83 (14.46%)	
occurrences (all)	5	13	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 82 (0.00%)	8 / 83 (9.64%)	
occurrences (all)	0	9	
Influenza			
subjects affected / exposed	2 / 82 (2.44%)	6 / 83 (7.23%)	
occurrences (all)	2	8	
Sinusitis			
subjects affected / exposed	0 / 82 (0.00%)	5 / 83 (6.02%)	
occurrences (all)	0	5	
Upper respiratory tract infection			
subjects affected / exposed	2 / 82 (2.44%)	8 / 83 (9.64%)	
occurrences (all)	2	11	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/26712227

http://www.ncbi.nlm.nih.gov/pubmed/33275769