Clinical trial results:
A prospective, open-label, multicenter phase-II-trial to evaluate the efficacy and safety of a sequential regimen of bendamustine followed by GA101 (obinutuzumab) and CAL-101 (idelalisib) followed by CAL-101 and GA101 maintenance in CLL patients (CLL2-BCG-trial of the GCLLSG)

Summary

EudraCT number	2014-000582-47
Trial protocol	DE
Global end of trial date	09 May 2022

Results information

Result version number	v2 (current)
This version publication date	01 December 2023
First version publication date	28 March 2023
Version creation reason	• Correction of full data set Corrections of reasons for end of treatment need to be done.

Trial information

Trial identification

Sponsor protocol code	CLL2-BCG

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02445131
WHO universal trial number (UTN)	-
Other trial identifiers	PEI: 2331, Uni Köln: UNI-KOELN-1758

Notes:

Sponsors

Sponsor organisation name	University of Cologne
Sponsor organisation address	Albertus-Magnus-Platz, Cologne, Germany, 50923
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	01 September 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 May 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to evaluate the efficacy of a sequential regimen of two cycles of bendamustine, followed by a combination therapy of GA101 (obinutuzumab) and CAL-101 (idelalisib) followed by CAL-101 and GA101 maintenance in CLL patients.

Protection of trial subjects:

Chapter 8.8 of the most current version of the study protocol includes extended warnings for cytopenias, infections, worsening of cardiac conditions, teratogenicity and mutagenicity, Stevens-Johnson-Syndrome, infusion related reactions, tumor lysis syndrome, hepatitis reactivation, progressive multifocal leukencephalopathy, immunogenicity, gastrointestinal perforation, diarrhea,elevated liver transaminadses, skinreactions,pneumonitis, associated with at least one of the three study drug. The chapters 8.5. include recommendation for concomitant medication, chapter 8.6. include recommendations for dose and schedule modifications.

Background therapy:

The PI3K-inhibitor CAL-101 (idelalisib), was tested in phase-II and III-studies and showed very promising efficacy and a favorable toxicity profile. CAL-101 inhibits the migration and adhesion of CLL cells to the protecting microenvironment and thereby lead to a redistribution and mobilization of these cells to peripheral blood and cause a lymphocytosis. All antibodies, especially the highly effective GA101 may lead to early infusion-related side effects, such as cytokine-release- and tumor lysis-syndromes. In order to avoid additional, overlapping toxicities due to these distinctive features, these two drugs should be started sequentially and a debulking treatment with a mild chemotherapy could reduce the tumor load before the start of these two effective targeted agents. On the other hand, the combination of a drug that leads to a lymphocytosis through a redistribution of leukemic cells to the peripheral blood and a very effective antibody that acts predominantly in the peripheral blood and targets the redistributed cells, is a very attractive treatment approach with a synergistic mechanism of action and might have the potential to eradicate the residual CLL cells.
Previous preclinical data raised concerns that CAL-101 (idelalisib) might have antagonistic effects on rituximab, due to an inhibitory effect of the kinase inhibitors on the immune effector mediated activity. This effect appeared to be less relevant for the combination of CAL-101 and the glycoengineered type-II antibody GA101 (obinutuzumab) as PI3K inhibition with CAL-101 had only minimal impact on the immune effector function of GA101 in vitro as measured in NK cell-mediated ADCC, macrophage-mediated ADCP and whole blood B-cell depletion.The toxicity profile of the combination of idelalisib and obinutuzumab is expected to be similar to the one observed with idelalisib and rituximab and to compare favorably to those of the chemotherapies currently used in the treatment of CLL.

Evidence for comparator:

not applicable

Actual start date of recruitment	02 March 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 48
Worldwide total number of subjects	48
EEA total number of subjects	48

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)	23
From 65 to 84 years	25
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Initially, it was planned to enroll 62 eligible patients . With the entry into force of amendment 2 the first-line stratum was closed after enrolment of 16 previously untreated patients. Due to a slow recruitment rate, the recruitment was closed early after 48 patients were enrolled .

Pre-assignment

Screening details:

A total of 52 pts were screened and 48 pts were enrolled. Screening procedures include central testing , especially immunophenotyping for confirmation of CLL diagnosis. 4 Pts were not enrolled because of missing inclusion or present exclusion criteria.

Pre-assignment period milestones

Number of subjects started	52[1]
Number of subjects completed	48

Pre-assignment subject non-completion reasons

Reason: Number of subjects	missing inclusion or present exclusion criteria: 4

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: A total of 52 pts were screened and 48 pts were enrolled. Screening procedures include central testing, especially immunophenotyping for confirmation of CLL diagnosis. 4 Pts were not enrolled because of missing inclusion or present exclusion criteria.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

not applicable

Arms

Arm title	Bendamustine (optional), idelalisib and obinutuzumab

Arm description:

Two cycles of bendamustine were administered before induction with obinutuzumab and idelalisib unless the patient had a contraindication or a debulking was not clinically indicated. The induction treatment consisted of 6 cycles, each with a duration of 28 days; during the first cycle obinutuzumab was administered intravenously on days 1 (and 2), 8 and 15 as well as on day 1 of the following cycles. The continuous daily administration of idelalisib started in cycle two. On days with administration of both, idelalisib and obinutuzumab, oral intake of idelalisib was followed by intravenous administration of obinutuzumab. Patients received the first dosage of idelalisib on day 1 of the second cycle in clinic/outpatient clinic/private practice before the administration of obinutuzumab was started. Maintenance consisted of a maximum of 8 cycles idelalisib and 3monthly administered obinutuzumab until - 3 months after confirmation of MRD negativity or unacceptable toxicity.

Arm type	Experimental
Investigational medicinal product name	bendamustine
Investigational medicinal product code	
Other name	ribomustin
Pharmaceutical forms	Powder for concentrate and solution for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Bendamustine i.v. infusion:

Cycles 1-2:	Day 1:	bendamustine 70 mg/m² i.v.
	Day 2:	bendamustine 70 mg/m² i.v.

Investigational medicinal product name	Obinutuzumab
Investigational medicinal product code	GA 101
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

GA101 (obinutuzumab) i.v. infusion:

Cycles 1:	Day 1:	GA101 100 mg i.v.
	Day 1 (or 2):	GA101 900 mg i.v.
	Day 8:	GA101 1000 mg i.v.
	Day 15:	GA101 1000 mg i.v.
Cycles 2-6:	Day 1:	GA101 1000 mg i.v.

Investigational medicinal product name	Idelalisib
Investigational medicinal product code	CAL 101
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

CAL-101 (idelalisib) p.o.:

Cycle 1:		--
Cycles 2-6:	Days 1-28:	CAL-101 150 mg (1 tabl.) p.o. 1-0-1

CAL-101 tablets with a strength of 100 mg will be used in case of AEs (as described in the protocol, section 8.6.3 Dose and schedule modifications for CAL-101 (idelalisib).

Number of subjects in period 1	Bendamustine (optional), idelalisib and obinutuzumab
Started	48
Completed	16
Not completed	32
Consent withdrawn by subject	1
Patient refused treatment / did not cooperate	3
Adverse event, non-fatal	6
Death	3
Progressive disease	9
Novel safety data (Amendment 2)	10

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial
Reporting group description:	
All patients enrolled in this trial and who have received at least one dose of study medication are included in the characteristics analysis.	

Reporting group values	Overall Trial	Total	
Number of subjects	48	48	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	23	23	
From 65-84 years	25	25	
85 years and over	0	0	
Age continuous			
median age			
Units: years			
median	66		
inter-quartile range (Q1-Q3)	58.0 to 74.8	-	
Gender categorical			
Units: Subjects			
Female	9	9	
Male	39	39	
Presence of del(17p)			
Cytogenetic risk factor			
Units: Subjects			
Yes	11	11	
No	37	37	
IGHV mutational status			
cytogenetic risk factor			
Units: Subjects			
unmutated	33	33	
mutated	14	14	
missing information	1	1	
CLL-IPI risk group			
International Prognostic Index used for CLL			
Units: Subjects			
low	2	2	
intermediate	7	7	
high	20	20	
very high	18	18	

missing	1	1	
TP53 mutational status			
cytogenetic risk factor			
Units: Subjects			
unmutated	31	31	
mutated	17	17	
Binet stage			
Status of the disease			
Units: Subjects			
Binet A	14	14	
Binet B	12	12	
Binet C	22	22	
Cumulative Illness Rating Scale.			
Validated score to evaluate the comorbidity of included patients			
Units: scores			
median	2		
inter-quartile range (Q1-Q3)	1 to 5	-	
median of previous lines of treatment			
Median number of previous lines of treatment			
Units: numbers			
median	2		
inter-quartile range (Q1-Q3)	1.0 to 3.8	-	
Observation time			
The observation time is defined as time between date of enrolment and time point of last observation or death.			
Units: months			
median	36.9		
inter-quartile range (Q1-Q3)	19.3 to 39.3	-	

Subject analysis sets

Subject analysis set title	First-line safety analysis set
Subject analysis set type	Sub-group analysis

Subject analysis set description:

This analysis set consists of 16 patients included in the trial without previous line of treatment and one dose of any study treatment.

Subject analysis set title	Refractory/relapsed safety analysis set
Subject analysis set type	Sub-group analysis

Subject analysis set description:

This analysis set consists of 32 patients included in the trial with at least one previous line of treatment and at least one dose of any study treatment

Subject analysis set title	Full analysis set
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The primary dataset for efficacy analyses is derived from the full analysis set (FAS). This dataset includes all patients enrolled to the trial who received at least one dose of induction treatment, whether withdrawn prematurely or not. The allocation to the FAS will be determined for every patient according to the previously defined criteria.

Subject analysis set title	First-line analysis set
Subject analysis set type	Sub-group analysis

Subject analysis set description:

This analysis set consists of 10 patients included in the trial without previous line of treatment who have received at least one dose of induction treatment.

Subject analysis set title	Refractory/relapsed analysis set

Subject analysis set type	Sub-group analysis

Subject analysis set description:

This analysis set consists of 30 patients included in the trial with at least one previous line of treatment and at least one dose of induction treatment

Reporting group values	First-line safety analysis set	Refractory/relapsed safety analysis set	Full analysis set
Number of subjects	16	32	40
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	7	16	18
From 65-84 years	9	16	22
85 years and over	0	0	0
Age continuous			
median age			
Units: years			
median	66.5	65.5	67
inter-quartile range (Q1-Q3)	58.3 to 72.8	56.3 to 75.0	57 to 75
Gender categorical			
Units: Subjects			
Female	2	7	8
Male	14	25	32
Presence of del(17p)			
Cytogenetic risk factor			
Units: Subjects			
Yes	0	11	11
No	16	21	29
IGHV mutational status			
cytogenetic risk factor			
Units: Subjects			
unmutated	8	25	28
mutated	8	6	11
missing information	0	1	1
CLL-IPI risk group			
International Prognostic Index used for CLL			
Units: Subjects			
low	1	1	0
intermediate	5	2	5
high	10	10	16
very high	0	18	18
missing	0	1	1
TP53 mutational status			
cytogenetic risk factor			
Units: Subjects			
unmutated	16	15	23

mutated	0	17	17
Binet stage			
Status of the disease			
Units: Subjects			
Binet A	5	9	9
Binet B	5	7	10
Binet C	6	16	21
Cumulative Illness Rating Scale.			
Validated score to evaluate the comorbidity of included patients			
Units: scores			
median	2	3	3
inter-quartile range (Q1-Q3)	1.0 to 2.8	1.3 to 5.8	1 to 6
median of previous lines of treatment			
Median number of previous lines of treatment			
Units: numbers			
median	0	2	0
inter-quartile range (Q1-Q3)	0 to 0	1.0 to 3.8	0 to 0
Observation time			
The observation time is defined as time between date of enrolment and time point of last observation or death.			
Units: months			
median	32.5	37.4	37.4
inter-quartile range (Q1-Q3)	17.1 to 39.6	19.3 to 38.7	28.1 to 39.6

Reporting group values	First-line analysis set	Refractory/relapsed analysis set	
Number of subjects	10	30	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	3	15	
From 65-84 years	7	15	
85 years and over	0	0	
Age continuous			
median age			
Units: years			
median	71	66	
inter-quartile range (Q1-Q3)	60 to 74	56 to 75	
Gender categorical			
Units: Subjects			
Female	1	7	
Male	9	23	
Presence of del(17p)			
Cytogenetic risk factor			
Units: Subjects			
Yes	0	11	

No	10	19	
IGHV mutational status			
cytogenetic risk factor			
Units: Subjects			
unmutated	4	24	
mutated	6	5	
missing information	0	1	
CLL-IPI risk group			
International Prognostic Index used for CLL			
Units: Subjects			
low	0	0	
intermediate	3	2	
high	7	9	
very high	0	18	
missing	0	1	
TP53 mutational status			
cytogenetic risk factor			
Units: Subjects			
unmutated	10	13	
mutated	0	17	
Binet stage			
Status of the disease			
Units: Subjects			
Binet A	1	8	
Binet B	4	6	
Binet C	5	16	
Cumulative Illness Rating Scale.			
Validated score to evaluate the comorbidity of included patients			
Units: scores			
median	2	3	
inter-quartile range (Q1-Q3)	1 to 4	1 to 6	
median of previous lines of treatment			
Median number of previous lines of treatment			
Units: numbers			
median	0	2	
inter-quartile range (Q1-Q3)	0 to 0	1 to 4	
Observation time			
The observation time is defined as time between date of enrolment and time point of last observation or death.			
Units: months			
median	39.3	37.4	
inter-quartile range (Q1-Q3)	32.5 to 39.7	19.3 to 39.0	

End points

End points reporting groups

Reporting group title	Bendamustine (optional), idelalisib and obinutuzumab

Reporting group description:

Two cycles of bendamustine were administered before induction with obinutuzumab and idelalisib unless the patient had a contraindication or a debulking was not clinically indicated. The induction treatment consisted of 6 cycles, each with a duration of 28 days; during the first cycle obinutuzumab was administered intravenously on days 1 (and 2), 8 and 15 as well as on day 1 of the following cycles. The continuous daily administration of idelalisib started in cycle two. On days with administration of both, idelalisib and obinutuzumab, oral intake of idelalisib was followed by intravenous administration of obinutuzumab. Patients received the first dosage of idelalisib on day 1 of the second cycle in clinic/outpatient clinic/private practice before the administration of obinutuzumab was started. Maintenance consisted of a maximum of 8 cycles idelalisib and 3monthly administered obinutuzumab until - 3 months after confirmation of MRD negativity or unacceptable toxicity.

Subject analysis set title	First-line safety analysis set
Subject analysis set type	Sub-group analysis

Subject analysis set description:

This analysis set consists of 16 patients included in the trial without previous line of treatment and one dose of any study treatment.

Subject analysis set title	Refractory/relapsed safety analysis set
Subject analysis set type	Sub-group analysis

Subject analysis set description:

This analysis set consists of 32 patients included in the trial with at least one previous line of treatment and at least one dose of any study treatment

Subject analysis set title	Full analysis set
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The primary dataset for efficacy analyses is derived from the full analysis set (FAS). This dataset includes all patients enrolled to the trial who received at least one dose of induction treatment, whether withdrawn prematurely or not. The allocation to the FAS will be determined for every patient according to the previously defined criteria.

Subject analysis set title	First-line analysis set
Subject analysis set type	Sub-group analysis

Subject analysis set description:

This analysis set consists of 10 patients included in the trial without previous line of treatment who have received at least one dose of induction treatment.

Subject analysis set title	Refractory/relapsed analysis set
Subject analysis set type	Sub-group analysis

Subject analysis set description:

This analysis set consists of 30 patients included in the trial with at least one previous line of treatment and at least one dose of induction treatment

Primary: Response at end of induction treatment

End point title	Response at end of induction treatment[1]

End point description:

Overall response rate (ORR) at final restaging (RE) 12 weeks after start of the last cycle of induction therapy (end of induction treatment response = EOIT) will be used as primary parameter of efficacy. In the ORR all patients achieving a (clinical) complete response (CR) / (clinical) complete response with incomplete recovery of the bone marrow (CRi), partial response (PR) and PR with lymphocytosis will be included. The response will be assessed according to the iwCLL criteria. In 6 patients the response at final restaging was not available at data cut-off: response from interim staging was used for one patient who discontinued treatment early due to adverse event. Initial response was used for 4 patients who discontinued treatment due to progressive disease (n=2) or death (n=2). One patient discontinued treatment due to adverse event before interim staging, so that no response assesment was available.

End point type	Primary

End point timeframe:

12 weeks after start of the last cycle of induction therapy (end of induction treatment response = EOIT)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The evaluation of the primary efficacy variable ORR will be based on the estimation of the ORR and its corresponding exact confidence interval based on the FAS. No inferential test will be performed. The goal is to obtain preliminary estimates. Exact confidence intervals will be calculated using the Clopper-Pearson method. Pairwise comparisons of the strata will be performed descriptively only.

End point values	Full analysis set	First-line analysis set	Refractory/relapsed analysis set	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	40	10	30	
Units: Patients				
Clinical complete remission	6	3	3	
Clinical CR with incomplete bone marrow recovery	1	0	1	
Partial remission	25	7	18	
Stable disease	1	0	1	
Progressive disease	6	0	6	
Missing	1	0	1	

Statistical analyses

No statistical analyses for this end point

Primary: Overall response rate at end of induction

End point title	Overall response rate at end of induction[2]

End point description:

Overall response rate (ORR) at final restaging (RE) 12 weeks after start of the last cycle of induction therapy (end of induction treatment response = EOIT) will be used as primary parameter of efficacy. In the ORR all patients achieving a (clinical) complete response (CR) / (clinical) complete response with incomplete recovery of the bone marrow (CRi), partial response (PR) and PR with lymphocytosis will be included. The response will be assessed according to the iwCLL criteria. In 6 patients the response at final restaging was not available at data cut-off: response from interim staging was used for one patient who discontinued treatment early due to adverse event. Initial response was used for 4 patients who discontinued treatment due to progressive disease (n=2) or death (n=2). One patient discontinued treatment due to adverse event before interim staging, so that no response assesment was available.

End point type	Primary

End point timeframe:

12 weeks after start of the last cycle of induction therapy (end of induction treatment response = EOIT).

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The evaluation of the primary efficacy variable ORR will be based on the estimation of the ORR and its corresponding exact confidence interval based on the FAS. No inferential test will be performed. The goal is to obtain preliminary estimates. Exact confidence intervals will be calculated using the Clopper-Pearson method. Pairwise comparisons of the strata will be performed descriptively only.

End point values	Full analysis set	First-line analysis set	Refractory/relapsed analysis set	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	40	10	30	
Units: Percentage				
number (not applicable)				
Overall response rate	80.0	100.0	73.3	
95% Confidence interval: lower bound	64.4	69.2	54.1	
95% Confidence interval: upper bound	90.9	100.0	87.7	

Statistical analyses

No statistical analyses for this end point

Secondary: Minimal residual disease at end of induction treatment

End point title	Minimal residual disease at end of induction treatment

End point description:

The rate of MRD responses is assessed with four-color-flow cytometry (FACS) and MRD negativity is arbitrarily defined as one CLL cell per 10,000 leukocytes [0.01 %], i.e. <10-4 [1E-4] and patients are defined as MRD negative if their disease burden is below this threshold. MRD in peripheral blood will be analyzed in patients responding to induction treatment at the time point of final restaging.

End point type	Secondary

End point timeframe:

MRD levels of the peripheral blood will be assessed at final restaging in all patients responding to induction treatment

End point values	Full analysis set	First-line analysis set	Refractory/relapsed analysis set	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	40	10	30	
Units: Patients				
Negative (< 10-4)	9	3	6	
Intermediate (>= 10-4 & < 10-2)	15	3	12	
Positive (>= 10-2)	5	1	4	
Missing	11	3	8	

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival

End point title	Progression-free Survival

End point description:

Progression-free survival (PFS) will be calculated until first documented disease progression (determined using standard iwCLL guidelines [2008]) or death, whichever occurs first. Patients for whom no documented event for PFS is available at the time of analysis will be censored at the time point of last follow-up information they were assessed to be event-free. Patients are followed for progression-free survival at each study visit. Analyses of time-to-event endpoints will be performed using Kaplan-Meier methods.

End point type	Secondary

End point timeframe:

Data for this endpoint will be collected from first study visit until last visit of each study subject.

End point values	Full analysis set	First-line analysis set	Refractory/relapsed analysis set	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	40	10	30	
Units: percentage/months				
number (not applicable)				
Median PFS (months)	34.9	44.3	32.3	
3-month survival (%)	97.5	100.0	96.7	
6-month survival (%)	85.0	90.0	83.3	
12-month survival (%)	75.0	90.0	70.0	
24-month survival (%)	61.7	68.6	59.5	
36-month survival (%)	47.6	68.6	40.9	

Statistical analyses

Statistical analysis title	Cox regression regarding progression-free survival

Statistical analysis description:

Progression-free survival was also analyzed separately for first-line patients and refractory/relapsed patients. To compare both groups regarding PFS, a cox regression was performed to test refractory/relapsed patients vs. first-line patients.

Comparison groups	First-line analysis set v Refractory/relapsed analysis set
Number of subjects included in analysis	40
Analysis specification	Post-hoc
Analysis type	other
Parameter estimate	Cox proportional hazard
Point estimate	1.964
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.666
upper limit	5.795

Secondary: Overall survival

End point title	Overall survival

End point description:

Overall survival (OS) will be calculated from the date of enrolment to the date of death due to any cause. Patients who have not yet died at the time of analysis will be censored at the time of last follow-up information they were assessed to be alive. Analyses of time-to-event endpoints will be performed using Kaplan-Meier methods.

End point type	Secondary

End point timeframe:

Data for this endpoint will be collected from first study visit until last visit of each study subject.

End point values	Full analysis set	First-line analysis set	Refractory/relapsed analysis set	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	40	10[3]	30	
Units: percentage/months				
number (not applicable)				
Median OS	46.4	0	46.4	
3-month survival (%)	100.0	100.0	100.0	
6-month survival (%)	92.3	90.0	93.1	
12-month survival (%)	84.1	90.0	81.9	
24-month survival (%)	81.0	90.0	77.6	
36-month survival (%)	81.0	90.0	77.6	

Notes:

[3] - Median overall survival was not reached within this subgroup.

Statistical analyses

Statistical analysis title	Cox regression regarding overall survival

Statistical analysis description:

Overall survival was also analyzed separately for first-line patients and refractory/relapsed patients. To compare both groups regarding OS, a cox regression was performed to test refractory/relapsed patients vs. first-line patients.

Comparison groups	First-line analysis set v Refractory/relapsed analysis set
Number of subjects included in analysis	40
Analysis specification	Post-hoc
Analysis type	other
Parameter estimate	Cox proportional hazard
Point estimate	2.585
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.318
upper limit	21.028

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Timeframe for AE

Adverse event reporting additional description:

AE additional description

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	RR patient

Reporting group description: -

Reporting group title	FL patient

Reporting group description: -

Serious adverse events	RR patient	FL patient	
Total subjects affected by serious adverse events			
subjects affected / exposed	30 / 32 (93.75%)	10 / 16 (62.50%)	
number of deaths (all causes)	8	1	
number of deaths resulting from adverse events	7	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acanthoma	Additional description: Acanthoma		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (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	Additional description: Basal cell carcinoma		
subjects affected / exposed	4 / 32 (12.50%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	1 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign neoplasm of prostate	Additional description: Benign neoplasm of prostate		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bowen's disease	Additional description: Bowen's disease		

subjects affected / exposed	1 / 32 (3.13%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma	Additional description: Malignant melanoma		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal carcinoma	Additional description: Oesophageal carcinoma		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of head and neck	Additional description: Squamous cell carcinoma of head and neck		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma	Additional description: Squamous cell carcinoma		
subjects affected / exposed	3 / 32 (9.38%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin papilloma	Additional description: Skin papilloma		
subjects affected / exposed	0 / 32 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin	Additional description: Squamous cell carcinoma of skin		
subjects affected / exposed	1 / 32 (3.13%)	2 / 16 (12.50%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertensive crisis	Additional description: Hypertensive crisis		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis	Additional description: Thrombosis		

subjects affected / exposed	0 / 32 (0.00%)	1 / 16 (6.25%)	
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			
General physical health deterioration	Additional description: General physical health deterioration		
subjects affected / exposed	0 / 32 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psoriasis	Additional description: Psoriasis		
subjects affected / exposed	0 / 32 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity	Additional description: Hypersensitivity		
subjects affected / exposed	0 / 32 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Graft versus host disease in lung	Additional description: Graft versus host disease in lung		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea at rest	Additional description: Dyspnoea at rest		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea	Additional description: Dyspnoea		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis	Additional description: Pneumonitis		

subjects affected / exposed	2 / 32 (6.25%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism	Additional description: Pulmonary embolism		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety	Additional description: Anxiety		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression	Additional description: Depression		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (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			
Femur fracture	Additional description: Femur fracture		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction	Additional description: Infusion related reaction		
subjects affected / exposed	0 / 32 (0.00%)	2 / 16 (12.50%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris	Additional description: Angina pectoris		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation	Additional description: Atrial fibrillation		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac arrest	Additional description: Cardiac arrest		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure	Additional description: Cardiac failure		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease	Additional description: Coronary artery disease		
subjects affected / exposed	0 / 32 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction	Additional description: Myocardial infarction		
subjects affected / exposed	0 / 32 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Brain hypoxia	Additional description: Brain hypoxia		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke	Additional description: Ischaemic stroke		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope	Additional description: Syncope		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Neutropenia	Additional description: Neutropenia		
subjects affected / exposed	2 / 32 (6.25%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pancytopenia	Additional description: Pancytopenia		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia	Additional description: Thrombocytopenia		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Autoimmune colitis	Additional description: Autoimmune colitis		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma	Additional description: Faecaloma		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis	Additional description: Enterocolitis		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea	Additional description: Diarrhoea		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis	Additional description: Colitis		
subjects affected / exposed	2 / 32 (6.25%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis	Additional description: Cholecystitis		
subjects affected / exposed	0 / 32 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hepatic failure	Additional description: Hepatic failure		
subjects affected / exposed	0 / 32 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Actinic keratosis	Additional description: Actinic keratosis		
subjects affected / exposed	1 / 32 (3.13%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Guttate psoriasis	Additional description: Guttate psoriasis		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Precancerous skin lesion	Additional description: Precancerous skin lesion		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Hydronephrosis	Additional description: Hydronephrosis		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment	Additional description: Renal impairment		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure	Additional description: Renal failure		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction	Additional description: Urinary tract obstruction		
subjects affected / exposed	2 / 32 (6.25%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Endocrine disorders			
Thyroiditis subacute	Additional description: Thyroiditis subacute		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteoarthritis	Additional description: Osteoarthritis		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Atypical pneumonia	Additional description: Atypical pneumonia		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspergillus infection	Additional description: Aspergillus infection		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis	Additional description: Bronchitis		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial infection	Additional description: Bacterial infection		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopulmonary aspergillosis	Additional description: Bronchopulmonary aspergillosis		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile infection	Additional description: Febrile infection		

subjects affected / exposed	1 / 32 (3.13%)	2 / 16 (12.50%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis	Additional description: Escherichia sepsis		
subjects affected / exposed	3 / 32 (9.38%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	2 / 4	0 / 0	
deaths causally related to treatment / all	1 / 3	0 / 0	
Cytomegalovirus infection reactivation	Additional description: Cytomegalovirus infection reactivation		
subjects affected / exposed	2 / 32 (6.25%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic sinusitis	Additional description: Chronic sinusitis		
subjects affected / exposed	0 / 32 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster infection neurological	Additional description: Herpes zoster infection neurological		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasopharyngitis	Additional description: Nasopharyngitis		
subjects affected / exposed	0 / 32 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis	Additional description: Neutropenic sepsis		
subjects affected / exposed	0 / 32 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal candidiasis	Additional description: Oesophageal candidiasis		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral herpes	Additional description: Oral herpes		

subjects affected / exposed	2 / 32 (6.25%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis	Additional description: Pharyngitis		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural infection	Additional description: Pleural infection		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary sepsis	Additional description: Pulmonary sepsis		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia respiratory syncytial viral	Additional description: Pneumonia respiratory syncytial viral		
subjects affected / exposed	0 / 32 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia influenzal	Additional description: Pneumonia influenzal		
subjects affected / exposed	3 / 32 (9.38%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pneumonia	Additional description: Pneumonia		
subjects affected / exposed	5 / 32 (15.63%)	2 / 16 (12.50%)	
occurrences causally related to treatment / all	4 / 7	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia	Additional description: Pneumocystis jirovecii pneumonia		
subjects affected / exposed	2 / 32 (6.25%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Sepsis	Additional description: Sepsis		

subjects affected / exposed	0 / 32 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock	Additional description: Septic shock		
subjects affected / exposed	0 / 32 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Superinfection	Additional description: Superinfection		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic candida	Additional description: Systemic candida		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection	Additional description: Urinary tract infection		
subjects affected / exposed	2 / 32 (6.25%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicella zoster virus infection	Additional description: Varicella zoster virus infection		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection	Additional description: Upper respiratory tract infection		
subjects affected / exposed	2 / 32 (6.25%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyponatraemia	Additional description: Hyponatraemia		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperuricaemia	Additional description: Hyperuricaemia		

subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour lysis syndrome	Additional description: Tumour lysis syndrome		
subjects affected / exposed	4 / 32 (12.50%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	RR patient	FL patient	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	31 / 32 (96.88%)	12 / 16 (75.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acanthoma	Additional description: Acanthoma		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Skin papilloma	Additional description: Skin papilloma		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
Haematoma	Additional description: Haematoma		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Hypertension	Additional description: Hypertension		
subjects affected / exposed	3 / 32 (9.38%)	0 / 16 (0.00%)	
occurrences (all)	3	0	
Hypertensive crisis	Additional description: Hypertensive crisis		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Infarction	Additional description: Infarction		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Pelvic venous thrombosis	Additional description: Pelvic venous thrombosis		

subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Phlebitis	Additional description: Phlebitis		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Thrombophlebitis	Additional description: Thrombophlebitis		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Thrombosis	Additional description: Thrombosis		
subjects affected / exposed	0 / 32 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Chills	Additional description: Chills		
subjects affected / exposed	1 / 32 (3.13%)	1 / 16 (6.25%)	
occurrences (all)	1	1	
Extravasation	Additional description: Extravasation		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Fatigue	Additional description: Fatigue		
subjects affected / exposed	6 / 32 (18.75%)	2 / 16 (12.50%)	
occurrences (all)	10	2	
General physical health deterioration	Additional description: General physical health deterioration		
subjects affected / exposed	2 / 32 (6.25%)	0 / 16 (0.00%)	
occurrences (all)	2	0	
Hernia	Additional description: Hernia		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Malaise	Additional description: Malaise		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Influenza like illness	Additional description: Influenza like illness		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Mucosal inflammation	Additional description: Mucosal inflammation		

subjects affected / exposed	3 / 32 (9.38%)	0 / 16 (0.00%)	
occurrences (all)	3	0	
Oedema	Additional description: Oedema		
subjects affected / exposed	3 / 32 (9.38%)	0 / 16 (0.00%)	
occurrences (all)	3	0	
Oedema peripheral	Additional description: Oedema peripheral		
subjects affected / exposed	3 / 32 (9.38%)	1 / 16 (6.25%)	
occurrences (all)	3	1	
Pyrexia	Additional description: Pyrexia		
subjects affected / exposed	4 / 32 (12.50%)	1 / 16 (6.25%)	
occurrences (all)	4	1	
Immune system disorders			
Allergic reaction to excipient	Additional description: Allergic reaction to excipient		
subjects affected / exposed	0 / 32 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Acute graft versus host disease in skin	Additional description: Acute graft versus host disease in skin		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Allergy to arthropod sting	Additional description: Allergy to arthropod sting		
subjects affected / exposed	0 / 32 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Drug hypersensitivity	Additional description: Drug hypersensitivity		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Immunodeficiency	Additional description: Immunodeficiency		
subjects affected / exposed	2 / 32 (6.25%)	0 / 16 (0.00%)	
occurrences (all)	2	0	
Respiratory, thoracic and mediastinal disorders			
Cough	Additional description: Cough		
subjects affected / exposed	7 / 32 (21.88%)	2 / 16 (12.50%)	
occurrences (all)	9	2	
Bronchospasm	Additional description: Bronchospasm		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Dyspnoea	Additional description: Dyspnoea		

subjects affected / exposed	2 / 32 (6.25%)	1 / 16 (6.25%)	
occurrences (all)	2	1	
Dyspnoea exertional	Additional description: Dyspnoea exertional		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Epistaxis	Additional description: Epistaxis		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Oropharyngeal pain	Additional description: Oropharyngeal pain		
subjects affected / exposed	0 / 32 (0.00%)	2 / 16 (12.50%)	
occurrences (all)	0	2	
Pleural effusion	Additional description: Pleural effusion		
subjects affected / exposed	3 / 32 (9.38%)	0 / 16 (0.00%)	
occurrences (all)	3	0	
Rhinitis allergic	Additional description: Rhinitis allergic		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Disorientation	Additional description: Disorientation		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Depression	Additional description: Depression		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Delirium	Additional description: Delirium		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Insomnia	Additional description: Insomnia		
subjects affected / exposed	2 / 32 (6.25%)	0 / 16 (0.00%)	
occurrences (all)	2	0	
Nervousness	Additional description: Nervousness		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Sleep disorder	Additional description: Sleep disorder		
subjects affected / exposed	0 / 32 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	

Investigations			
Blood creatinine increased	Additional description: Blood creatinine increased		
subjects affected / exposed	3 / 32 (9.38%)	0 / 16 (0.00%)	
occurrences (all)	3	0	
Blood bilirubin increased	Additional description: Blood bilirubin increased		
subjects affected / exposed	0 / 32 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Blood potassium decreased	Additional description: Blood potassium decreased		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Gamma-glutamyltransferase increased	Additional description: Gamma-glutamyltransferase increased		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Immunoglobulins decreased	Additional description: Immunoglobulins decreased		
subjects affected / exposed	3 / 32 (9.38%)	0 / 16 (0.00%)	
occurrences (all)	3	0	
Hepatic enzyme increased	Additional description: Hepatic enzyme increased		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Pneumocystis test positive	Additional description: Pneumocystis test positive		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Serum ferritin decreased	Additional description: Serum ferritin decreased		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Weight decreased	Additional description: Weight decreased		
subjects affected / exposed	0 / 32 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Transaminases increased	Additional description: Transaminases increased		
subjects affected / exposed	3 / 32 (9.38%)	0 / 16 (0.00%)	
occurrences (all)	5	0	
Injury, poisoning and procedural complications			
Arthropod bite	Additional description: Arthropod bite		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Facial bones fracture	Additional description: Facial bones fracture		

subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Fall	Additional description: Fall		
subjects affected / exposed	0 / 32 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Infusion related reaction	Additional description: Infusion related reaction		
subjects affected / exposed	12 / 32 (37.50%)	2 / 16 (12.50%)	
occurrences (all)	13	2	
Joint injury	Additional description: Joint injury		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Nail injury	Additional description: Nail injury		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Arrhythmia	Additional description: Arrhythmia		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Atrial fibrillation	Additional description: Atrial fibrillation		
subjects affected / exposed	1 / 32 (3.13%)	1 / 16 (6.25%)	
occurrences (all)	1	1	
Coronary artery disease	Additional description: Coronary artery disease		
subjects affected / exposed	0 / 32 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Left ventricular failure	Additional description: Left ventricular failure		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Tachycardia	Additional description: Tachycardia		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Carpal tunnel syndrome	Additional description: Carpal tunnel syndrome		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Dysgeusia	Additional description: Dysgeusia		

subjects affected / exposed	0 / 32 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Dizziness	Additional description: Dizziness		
subjects affected / exposed	2 / 32 (6.25%)	0 / 16 (0.00%)	
occurrences (all)	2	0	
Essential tremor	Additional description: Essential tremor		
subjects affected / exposed	0 / 32 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Headache	Additional description: Headache		
subjects affected / exposed	8 / 32 (25.00%)	1 / 16 (6.25%)	
occurrences (all)	10	1	
Parkinson's disease	Additional description: Parkinson's disease		
subjects affected / exposed	0 / 32 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Polyneuropathy	Additional description: Polyneuropathy		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Post herpetic neuralgia	Additional description: Post herpetic neuralgia		
subjects affected / exposed	2 / 32 (6.25%)	0 / 16 (0.00%)	
occurrences (all)	2	0	
Paraesthesia	Additional description: Paraesthesia		
subjects affected / exposed	0 / 32 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Sciatica	Additional description: Sciatica		
subjects affected / exposed	0 / 32 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Taste disorder	Additional description: Taste disorder		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	2	0	
Syncope	Additional description: Syncope		
subjects affected / exposed	0 / 32 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Tremor	Additional description: Tremor		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			

Anaemia	Additional description: Anaemia		
subjects affected / exposed	14 / 32 (43.75%)	2 / 16 (12.50%)	
occurrences (all)	15	2	
Eosinophilia	Additional description: Eosinophilia		
subjects affected / exposed	2 / 32 (6.25%)	0 / 16 (0.00%)	
occurrences (all)	2	0	
Febrile neutropenia	Additional description: Febrile neutropenia		
subjects affected / exposed	3 / 32 (9.38%)	0 / 16 (0.00%)	
occurrences (all)	3	0	
Leukopenia	Additional description: Leukopenia		
subjects affected / exposed	3 / 32 (9.38%)	2 / 16 (12.50%)	
occurrences (all)	6	2	
Lymph node pain	Additional description: Lymph node pain		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Neutropenia	Additional description: Neutropenia		
subjects affected / exposed	13 / 32 (40.63%)	4 / 16 (25.00%)	
occurrences (all)	21	4	
Thrombocytopenia	Additional description: Thrombocytopenia		
subjects affected / exposed	10 / 32 (31.25%)	2 / 16 (12.50%)	
occurrences (all)	16	2	
Ear and labyrinth disorders			
Deafness	Additional description: Deafness		
subjects affected / exposed	0 / 32 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Tinnitus	Additional description: Tinnitus		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Vertigo	Additional description: Vertigo		
subjects affected / exposed	1 / 32 (3.13%)	1 / 16 (6.25%)	
occurrences (all)	1	1	
Eye disorders			
Cataract	Additional description: Cataract		
subjects affected / exposed	0 / 32 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Dry conjunctives	Additional description: Dry conjunctives		

subjects affected / exposed	0 / 32 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Dry eye	Additional description: Dry eye		
subjects affected / exposed	2 / 32 (6.25%)	1 / 16 (6.25%)	
occurrences (all)	2	1	
Eyelid bleeding	Additional description: Eyelid bleeding		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Lacrimation increased	Additional description: Lacrimation increased		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal pain	Additional description: Abdominal pain		
subjects affected / exposed	3 / 32 (9.38%)	1 / 16 (6.25%)	
occurrences (all)	3	1	
Abdominal pain upper	Additional description: Abdominal pain upper		
subjects affected / exposed	2 / 32 (6.25%)	0 / 16 (0.00%)	
occurrences (all)	2	0	
Aphthous ulcer	Additional description: Aphthous ulcer		
subjects affected / exposed	0 / 32 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	2	
Autoimmune colitis	Additional description: Autoimmune colitis		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Colitis	Additional description: Colitis		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Constipation	Additional description: Constipation		
subjects affected / exposed	3 / 32 (9.38%)	1 / 16 (6.25%)	
occurrences (all)	4	2	
Diarrhoea	Additional description: Diarrhoea		
subjects affected / exposed	8 / 32 (25.00%)	1 / 16 (6.25%)	
occurrences (all)	10	2	
Dry mouth	Additional description: Dry mouth		
subjects affected / exposed	2 / 32 (6.25%)	2 / 16 (12.50%)	
occurrences (all)	2	2	

Dysbiosis	Additional description: Dysbiosis		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Dyspepsia	Additional description: Dyspepsia		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Dysphagia	Additional description: Dysphagia		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Faeces soft	Additional description: Faeces soft		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorder	Additional description: Gastrointestinal disorder		
subjects affected / exposed	0 / 32 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Gastrointestinal pain	Additional description: Gastrointestinal pain		
subjects affected / exposed	1 / 32 (3.13%)	1 / 16 (6.25%)	
occurrences (all)	1	1	
Haemorrhoids	Additional description: Haemorrhoids		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Flatulence	Additional description: Flatulence		
subjects affected / exposed	2 / 32 (6.25%)	1 / 16 (6.25%)	
occurrences (all)	2	2	
Nausea	Additional description: Nausea		
subjects affected / exposed	5 / 32 (15.63%)	3 / 16 (18.75%)	
occurrences (all)	5	3	
Oral discharge	Additional description: Oral discharge		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Tongue discomfort	Additional description: Tongue discomfort		
subjects affected / exposed	0 / 32 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Tongue oedema	Additional description: Tongue oedema		
subjects affected / exposed	0 / 32 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	

Tooth loss	Additional description: Tooth loss		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Alopecia	Additional description: Alopecia		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Angioedema	Additional description: Angioedema		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Dry skin	Additional description: Dry skin		
subjects affected / exposed	4 / 32 (12.50%)	2 / 16 (12.50%)	
occurrences (all)	5	2	
Drug eruption	Additional description: Drug eruption		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Dermatosis	Additional description: Dermatosis		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Dermatitis allergic	Additional description: Dermatitis allergic		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Eczema	Additional description: Eczema		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Erythema	Additional description: Erythema		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Hyperhidrosis	Additional description: Hyperhidrosis		
subjects affected / exposed	1 / 32 (3.13%)	1 / 16 (6.25%)	
occurrences (all)	1	1	
Night sweats	Additional description: Night sweats		
subjects affected / exposed	3 / 32 (9.38%)	1 / 16 (6.25%)	
occurrences (all)	5	2	
Pruritus	Additional description: Pruritus		

subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Psoriasis	Additional description: Psoriasis		
subjects affected / exposed	0 / 32 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Rash	Additional description: Rash		
subjects affected / exposed	4 / 32 (12.50%)	6 / 16 (37.50%)	
occurrences (all)	4	6	
Rash maculo-papular	Additional description: Rash maculo-papular		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Skin fissures	Additional description: Skin fissures		
subjects affected / exposed	0 / 32 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	2	
Urticaria	Additional description: Urticaria		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Acute kidney injury	Additional description: Acute kidney injury		
subjects affected / exposed	0 / 32 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Calculus bladder	Additional description: Calculus bladder		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Chronic kidney disease	Additional description: Chronic kidney disease		
subjects affected / exposed	0 / 32 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Haematuria	Additional description: Haematuria		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Prerenal failure	Additional description: Prerenal failure		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Urinary tract obstruction	Additional description: Urinary tract obstruction		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	

Musculoskeletal and connective tissue disorders			
Arthralgia	Additional description: Arthralgia		
subjects affected / exposed	2 / 32 (6.25%)	0 / 16 (0.00%)	
occurrences (all)	2	0	
Back pain	Additional description: Back pain		
subjects affected / exposed	2 / 32 (6.25%)	0 / 16 (0.00%)	
occurrences (all)	2	0	
Bone pain	Additional description: Bone pain		
subjects affected / exposed	3 / 32 (9.38%)	0 / 16 (0.00%)	
occurrences (all)	3	0	
Flank pain	Additional description: Flank pain		
subjects affected / exposed	2 / 32 (6.25%)	0 / 16 (0.00%)	
occurrences (all)	2	0	
Meniscal degeneration	Additional description: Meniscal degeneration		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Muscle spasms	Additional description: Muscle spasms		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Myalgia	Additional description: Myalgia		
subjects affected / exposed	2 / 32 (6.25%)	0 / 16 (0.00%)	
occurrences (all)	3	0	
Neck pain	Additional description: Neck pain		
subjects affected / exposed	2 / 32 (6.25%)	0 / 16 (0.00%)	
occurrences (all)	2	0	
Osteoarthritis	Additional description: Osteoarthritis		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	2	0	
Spondylitis	Additional description: Spondylitis		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Bacterial infection	Additional description: Bacterial infection		
subjects affected / exposed	3 / 32 (9.38%)	0 / 16 (0.00%)	
occurrences (all)	3	0	
Clostridium difficile colitis	Additional description: Clostridium difficile colitis		

subjects affected / exposed	0 / 32 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Conjunctivitis	Additional description: Conjunctivitis		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Candida infection	Additional description: Candida infection		
subjects affected / exposed	2 / 32 (6.25%)	0 / 16 (0.00%)	
occurrences (all)	2	0	
Bronchopulmonary aspergillosis	Additional description: Bronchopulmonary aspergillosis		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Bronchitis	Additional description: Bronchitis		
subjects affected / exposed	6 / 32 (18.75%)	2 / 16 (12.50%)	
occurrences (all)	6	3	
Chronic sinusitis	Additional description: Chronic sinusitis		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Device related infection	Additional description: Device related infection		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Epididymitis	Additional description: Epididymitis		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Erysipelas	Additional description: Erysipelas		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Febrile infection	Additional description: Febrile infection		
subjects affected / exposed	0 / 32 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Fungal skin infection	Additional description: Fungal skin infection		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Gastroenteritis	Additional description: Gastroenteritis		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Gingivitis	Additional description: Gingivitis		

subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Genital herpes	Additional description: Genital herpes		
subjects affected / exposed	1 / 32 (3.13%)	1 / 16 (6.25%)	
occurrences (all)	1	1	
Haemophilus infection	Additional description: Haemophilus infection		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Herpes virus infection	Additional description: Herpes virus infection		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Herpes zoster	Additional description: Herpes zoster		
subjects affected / exposed	4 / 32 (12.50%)	1 / 16 (6.25%)	
occurrences (all)	4	1	
Infection	Additional description: Infection		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Influenza	Additional description: Influenza		
subjects affected / exposed	2 / 32 (6.25%)	0 / 16 (0.00%)	
occurrences (all)	2	0	
Laryngopharyngitis	Additional description: Laryngopharyngitis		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Lip infection	Additional description: Lip infection		
subjects affected / exposed	0 / 32 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Mucosal infection	Additional description: Mucosal infection		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis	Additional description: Nasopharyngitis		
subjects affected / exposed	11 / 32 (34.38%)	4 / 16 (25.00%)	
occurrences (all)	16	6	
Oesophageal candidiasis	Additional description: Oesophageal candidiasis		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Oral candidiasis	Additional description: Oral candidiasis		

subjects affected / exposed	0 / 32 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	2	
Oral fungal infection	Additional description: Oral fungal infection		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Oral herpes	Additional description: Oral herpes		
subjects affected / exposed	4 / 32 (12.50%)	1 / 16 (6.25%)	
occurrences (all)	4	1	
Pneumonia	Additional description: Pneumonia		
subjects affected / exposed	4 / 32 (12.50%)	0 / 16 (0.00%)	
occurrences (all)	4	0	
Pneumonia pneumococcal	Additional description: Pneumonia pneumococcal		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Respiratory tract infection	Additional description: Respiratory tract infection		
subjects affected / exposed	1 / 32 (3.13%)	1 / 16 (6.25%)	
occurrences (all)	1	1	
Rhinitis	Additional description: Rhinitis		
subjects affected / exposed	0 / 32 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Rhinovirus infection	Additional description: Rhinovirus infection		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Sinusitis	Additional description: Sinusitis		
subjects affected / exposed	2 / 32 (6.25%)	0 / 16 (0.00%)	
occurrences (all)	2	0	
Upper respiratory tract infection	Additional description: Upper respiratory tract infection		
subjects affected / exposed	4 / 32 (12.50%)	3 / 16 (18.75%)	
occurrences (all)	4	3	
Urinary tract infection	Additional description: Urinary tract infection		
subjects affected / exposed	2 / 32 (6.25%)	0 / 16 (0.00%)	
occurrences (all)	3	0	
Varicella zoster virus infection	Additional description: Varicella zoster virus infection		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			

Decreased appetite	Additional description: Decreased appetite		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Diabetes mellitus	Additional description: Diabetes mellitus		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Dehydration	Additional description: Dehydration		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Folate deficiency	Additional description: Folate deficiency		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Gout	Additional description: Gout		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Hypercalcaemia	Additional description: Hypercalcaemia		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	3	0	
Hyperkalaemia	Additional description: Hyperkalaemia		
subjects affected / exposed	2 / 32 (6.25%)	1 / 16 (6.25%)	
occurrences (all)	2	1	
Hyperuricaemia	Additional description: Hyperuricaemia		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	2	0	
Hypokalaemia	Additional description: Hypokalaemia		
subjects affected / exposed	2 / 32 (6.25%)	0 / 16 (0.00%)	
occurrences (all)	3	0	
Iron deficiency	Additional description: Iron deficiency		
subjects affected / exposed	2 / 32 (6.25%)	0 / 16 (0.00%)	
occurrences (all)	2	0	
Vitamin D deficiency	Additional description: Vitamin D deficiency		
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 December 2015	A new version of the investigator's brochure for obinutuzumab was submitted aand consequently the informed consent form was emended. ICF v2.1 12.01.2016, 1st extension ICF 1.1 12.01.2016
08 July 2016	Due an unexpected incidence of infections and treatment related mortality in other studies with idelalisib as IMP not under the sponsorship of the university of Cologne, the recruitment for this study was put on hold and competent authority and ethic committees informed about the stopp of recruitment. After evaluation of the new safety information, administration of idelalisib was discontinued in all first-line patients, further recruitment was limited to relapsed/refractory patients with high-risk features (see also chapter 6. Trial population) and a close monitoring with laboratory assessments, including a CMV screening at least every 14 days during the induction treatment with idelalisib (see 7.4.2 Monitoring during treatment with CAL-101 (idelalisib)) was implemented with the second amendment.
18 August 2016	New version of the investigator's brochure for idelalisib and consequently amendment of informed consent form Description and comments: ICF v4.1 23.08.2016, 3rd extension ICF (relapsed/refractory patients) v.1.1 23.08.2016
19 September 2016	New version of the investigator's brochure for idelalisib
08 December 2016	New version of the investigator's brochure for Obinutuzumab and consequently amendment of informed consent form: Description and comments: ICF v5.0 17.11.2016, ICF extension 4. Amendment v1.0 17.11.2016
06 June 2017	addendum to Investigator's brochure for obinutuzumab
15 August 2019	New Safety Reference Documents: Description and comments: ICF v6.0 16.04.2019, ICF extension Amendment 5 v1.0 04.06.2019
18 May 2020	Early closure of recruitment due to low interest of participating sites and to low recruitment. Recruitment was closed after 48 of 62 planned patienst were recruited.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date

16 March 2016	Due an unexpected incidence of infections and treatment related mortality in other studies with idelalisib as IMP not under the sponsorship of the university of Cologne, the recruitment for this study was put on hold and competent authority and ethic committees informed about the stopp of recruitment. After evaluation of the new safety information, administration of idelalisib was discontinued in all first-line patients, further recruitment was limited to relapsed/refractory patients with high-risk features (see also chapter 6. Trial population) and a close monitoring with laboratory assessments, including a CMV screening at least every 14 days during the induction treatment with idelalisib (see 7.4.2 Monitoring during treatment with CAL-101 (idelalisib)) was implemented with the second amendment.	08 July 2016

Notes:

Limitations and caveats

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

In this trial with the combination of obinutuzumab and idelalisib, the known idelalisib toxicities were confirmed. Thus, this combination should be used with caution and only if other treatment options cannot be used.

Notes: