Clinical trial results:
Combination of ibrutinib and bortezomib followed by ibrutinib maintenance to treat patients with relapsed and refractory mantle cell lymphoma; a multicenter Phase I/II trial

Summary

EudraCT number	2014-003893-17
Trial protocol	DE IT
Global end of trial date	30 March 2021

Results information

Result version number	v1 (current)
This version publication date	14 August 2022
First version publication date	14 August 2022

Trial information

Trial identification

Sponsor protocol code	SAKK36/13

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02356458
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	Swiss Group for Clinical Cancer, Head Regulatory Affairs, +41 31389 91 91, sakkcc@sakk.ch
Scientific contact	Swiss Group for Clinical Cancer, Head Regulatory Affairs, +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	22 November 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 March 2021
Global end of trial reached?	Yes
Global end of trial date	30 March 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the phase I (dose escalation of ibrutinib) is to establish the recommended phase II dose (RP2D) of ibrutinib in combination with bortezomib in patients with relapsed or refractory Mantle cell Lymphoma (MCL).
The primary objective of the phase II is to define the efficacy of ibrutinib in combination with bortezomib in patients with relapsed or
refractory Mantle cell Lymphoma.

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:

none

Actual start date of recruitment	31 August 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: 15
Country: Number of subjects enrolled	Italy: 9
Country: Number of subjects enrolled	Switzerland: 31
Worldwide total number of subjects	55
EEA total number of subjects	24

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)	13
From 65 to 84 years	41
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The recruitment phase started on 31-Aug-2015 and and ended on 30-Mar-2021 after the recruitment of 58 patients (including three patients being enrolled in Phase I, receiving the lower study drug dose and thus not passing over to Phase II). Patients were enrolled at three sites in Germany, three sites in Italy and nine sites in Switzerland.

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. One patient was deemed a screening failure and not included into the trial.

Period 1

Period 1 title	Phase I - Dose Finding
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Group [1]

Arm description:

Dose level 1 (lower dose of Ibrutinib)

Arm type	Experimental
Investigational medicinal product name	Bortezomib
Investigational medicinal product code	
Other name	Velcade®
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

1.3 mg/m2 on day 1, 4, 8, 11

Investigational medicinal product name	Ibrutinib
Investigational medicinal product code	
Other name	Imbruvica®
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

420 mg/day

Arm title	Group [2]

Arm description:

Dose level 2 (higher dose of Ibrutinib)

Arm type	Experimental
Investigational medicinal product name	Bortezomib
Investigational medicinal product code	
Other name	Velcade®
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

1.3 mg/m2 on day 1, 4, 8, 11

Investigational medicinal product name	Ibrutinib
Investigational medicinal product code	
Other name	Imbruvica®
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

560 mg/day

Number of subjects in period 1	Group [1]	Group [2]
Started	3	6
Completed	0	6
Not completed	3	0
Receipt of lower dose of ibrutinib in Phase I	3	-

Period 2

Period 2 title	Phase II - Enrollment
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	RP2D

Arm description:

Recommended dose for Phase II from Phase I dose finding

Arm type	Experimental
Investigational medicinal product name	Bortezomib
Investigational medicinal product code	
Other name	Velcade®
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

1.3 mg/m2 on day 1, 4, 8, 11

Investigational medicinal product name	Ibrutinib
Investigational medicinal product code	
Other name	Imbruvica®
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

560 mg/day

Number of subjects in period 2	RP2D
Started	6
Completed	55

Joined	49
Phase II Enrollment	49

Period 3	
Period 3 title	Phase II - Baseline
Is this the baseline period?	Yes[1]
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	RP2D
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Bortezomib
Investigational medicinal product code	
Other name	Velcade®
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Subcutaneous use
Dosage and administration details: 1.3 mg/m2 on day 1, 4, 8, 11	
Investigational medicinal product name	Ibrutinib
Investigational medicinal product code	
Other name	Imbruvica®
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: 560 mg/day	

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: This was a combined Phase I/Phase II study.

Number of subjects in period 3	RP2D
Started	55
Completed	55

Period 4	
Period 4 title	Phase II - Combination Therapy
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms	
Arm title	RP2D - Combination Therapy
Arm description: 6 cycles of 21 days each	
Arm type	Experimental
Investigational medicinal product name	Bortezomib
Investigational medicinal product code	
Other name	Velcade®
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Subcutaneous use
Dosage and administration details: 1.3 mg/m2 on day 1, 4, 8, 11	
Investigational medicinal product name	Ibrutinib
Investigational medicinal product code	
Other name	Imbruvica®
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: 560 mg/day	

Number of subjects in period 4	RP2D - Combination Therapy
Started	55
Completed	42
Not completed	13
Consent withdrawn by subject	3
Unacceptable toxicity	3
Progressive disease	6
Protocol deviation	1

Period 5

Period 5 title	Phase II - Maintenance therapy
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	RP2D - Ibrutinib Monotherapy

Arm description:

Courses of ibrutinib were repeated every 28-days in the absence of disease progression or unacceptable toxicity.

Arm type	Experimental
Investigational medicinal product name	Ibrutinib
Investigational medicinal product code	
Other name	Imbruvica®
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

560 mg/day

Number of subjects in period 5	RP2D - Ibrutinib Monotherapy
Started	42
Completed	0
Not completed	42
Stem cell transplantation	1
Consent withdrawn by subject	1
Unacceptable toxicity	1
Study termination by sponsor	19
Progressive disease	15
Protocol deviation	5

Baseline characteristics

Reporting groups	
Reporting group title	RP2D

Reporting group description: -

Reporting group values	RP2D	Total	
Number of subjects	55	55	
Age categorical Units: Subjects			
Adults (18-64 years)	13	13	
From 65-84 years	41	41	
85 years and over	1	1	
Gender categorical Units: Subjects			
Female	12	12	
Male	43	43	

End points

End points reporting groups

Reporting group title	Group [1]
Reporting group description:	
Dose level 1 (lower dose of Ibrutinib)	
Reporting group title	Group [2]
Reporting group description:	
Dose level 2 (higher dose of Ibrutinib)	
Reporting group title	RP2D
Reporting group description:	
Recommended dose for Phase II from Phase I dose finding	
Reporting group title	RP2D
Reporting group description: -	
Reporting group title	RP2D - Combination Therapy
Reporting group description:	
6 cycles of 21 days each	
Reporting group title	RP2D - Ibrutinib Monotherapy
Reporting group description:	
Courses of ibrutinib were repeated every 28-days in the absence of disease progression or unacceptable toxicity.	
Subject analysis set title	FAS (Phase II)
Subject analysis set type	Full analysis
Subject analysis set description:	
The phase II full analysis set was defined as all patients registered in phase II and patients from phase I treated with the RP2D, excluding patients who (i) failed to satisfy major eligibility criteria or (ii) failed to receive at least one dose of both ibrutinib AND bortezomib. Patients excluded from the phase II full analysis set were replaced.	

Primary: Phase II | Primary endpoint (OR during combination therapy) - 1/2

End point title	Phase II | Primary endpoint (OR during combination therapy) - 1/2[1]
End point description:	
ORR defined as the proportion of patients whose best overall response, is either complete response (CR), complete response unconfirmed (CRu) or partial response (PR) according to the International Working group criteria for NHL. The primary endpoint of phase II is OR observed during the combination therapy. Tumor assessments until 21 days after the end of the last treatment cycle started with both trial drugs, were considered. [CR: 16.4%; CRu: 5.5%; PR: 60.0%; SD: 9.1%; PD: 7.3%; not assessed: 1.8%]	
End point type	Primary
End point timeframe:	
Start of trial treatment up to 14 days (tolerance +7 days) after end of last cycle.	

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: This was a single arm study.

End point values	FAS (Phase II)			
Subject group type	Subject analysis set			
Number of subjects analysed	55			
Units: OR (%) incl. 90% CI (Clopper-Pearson)				
number (confidence interval 90%)	81.8 (71.1 to 89.8)			

Statistical analyses

No statistical analyses for this end point

Primary: Phase II | Primary endpoint (OR during combination therapy) - 2/2

End point title	Phase II | Primary endpoint (OR during combination therapy) - 2/2[2]

End point description:

ORR defined as the proportion of patients whose best overall response, is either complete response (CR), complete response unconfirmed (CRu) or partial response (PR) according to the International Working group criteria for NHL.
The primary endpoint of phase II is OR observed during the combination therapy. Tumor assessments until 21 days after the end of the last treatment cycle started with both trial drugs, were considered.

[CR: 16.4%; CRu: 5.5%; PR: 60.0%; SD: 9.1%; PD: 7.3%; not assessed: 1.8%]

End point type	Primary

End point timeframe:

Start of trial treatment up to 14 days (tolerance +7 days) after end of last cycle.

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: This was a single arm study.

End point values	FAS (Phase II)			
Subject group type	Subject analysis set			
Number of subjects analysed	55			
Units: OR (%) incl. 95% CI (Clopper-Pearson)				
number (confidence interval 95%)	81.8 (69.1 to 90.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase II | Secondary endpoint (OR during trial treatment) - 1/2

End point title	Phase II | Secondary endpoint (OR during trial treatment) - 1/2

End point description:

OR, as defined for the primary endpoint, but based on the best response observed during trial treatment (including both combination and maintenance therapy).

[CR: 34.5%; CRu: 7.3%; PR: 45.5%; SD: 5.5%; PD: 7.3%]

End point type	Secondary

End point timeframe:

Start of trial treatment up to 14 days (tolerance +7 days) after end of last cycle.

End point values	FAS (Phase II)			
Subject group type	Subject analysis set			
Number of subjects analysed	55			
Units: OR (%) incl. 90% CI (Clopper-Pearson)				
number (confidence interval 90%)	87.3 (77.4 to 93.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase II | Secondary endpoint (OR during trial treatment) - 2/2

End point title	Phase II | Secondary endpoint (OR during trial treatment) - 2/2

End point description:

OR, as defined for the primary endpoint, but based on the best response observed during trial treatment (including both combination and maintenance therapy).

[CR: 34.5%; CRu: 7.3%; PR: 45.5%; SD: 5.5%; PD: 7.3%]

End point type	Secondary

End point timeframe:

Start of trial treatment up to 14 days (tolerance +7 days) after end of last cycle.

End point values	FAS (Phase II)			
Subject group type	Subject analysis set			
Number of subjects analysed	55			
Units: OR (%) incl. 95% CI (Clopper-Pearson)				
number (confidence interval 95%)	87.3 (75.5 to 94.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase II | Secondary endpoint (PFS)

End point title	Phase II | Secondary endpoint (PFS)

End point description:

Progression free survival (PFS) was calculated from registration until progression of disease or death as a result of any cause. Patients not experiencing an event, including patients receiving a subsequent anti-MCL therapy without documented progressive disease (or relapse after CR), were censored at the last time they were known to be without progression (i.e. last date of tumor assessment without progression) and before the start of a new anti-MCL therapy, if any.

NOTE: UPPER LIMIT FOR PFS NOT REACHED. DUMMY DATA "999" FOR UPPER LIMIT ENTERED DUE TO DATABASE RESTRICTIONS.

End point type	Secondary

End point timeframe:

From start until end of study.

End point values	FAS (Phase II)			
Subject group type	Subject analysis set			
Number of subjects analysed	55			
Units: PFS (months)				
median (confidence interval 95%)	18.6 (12.5 to 999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase II | Secondary endpoint (TTF)

End point title	Phase II | Secondary endpoint (TTF)

End point description:

Time to treatment failure (TTF) was calculated from registration until treatment failure (due to unacceptable toxicity, progression, patient refusal, death, start of subsequent anti-MCL therapy or any other event that determines the termination of the trial treatment was considered as treatment failure). Patients not experiencing an event were censored at the last time they were known to be under trial treatment.

End point type	Secondary

End point timeframe:

From start until end of study.

End point values	FAS (Phase II)			
Subject group type	Subject analysis set			
Number of subjects analysed	55			
Units: TTFS (months)				
median (confidence interval 95%)	10.1 (7.0 to 14.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase II | Secondary endpoint (DOR)

End point title	Phase II | Secondary endpoint (DOR)

End point description:

Duration of objective response (DOR) was calculated from first observation of CR, CRu or PR until documentation of progression, or relapse thereafter. Only patients with CR, CRu or PR were included in this analysis. Patients without any documentation of progression, or relapse thereafter were censored at the last time they were known to be without progression (i.e. last date of tumor assessment without progression) and before the start of a new anti-MCL therapy, if any.

Only patients with CR, CRu or a PR were included in this analysis.

NOTE: UPPER LIMIT FOR PFS NOT REACHED. DUMMY DATA "999" FOR UPPER LIMIT ENTERED DUE TO DATABASE RESTRICTIONS.

End point type	Secondary

End point timeframe:

From start until end of study.

End point values	FAS (Phase II)			
Subject group type	Subject analysis set			
Number of subjects analysed	48[3]			
Units: DOR (months)				
median (confidence interval 95%)	22.7 (12.3 to 999)			

Notes:

[3] - Number of patients with response = 48.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Between registration and up to 30 days after end of trial treatment.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups	
Reporting group title	Safety Analysis Set
Reporting group description:	
The phase II safety analysis set was defined as all patients who received any dose of trial treatment in phase II and patients from phase I treated with the RP2D.	

Serious adverse events	Safety Analysis Set		
Total subjects affected by serious adverse events			
subjects affected / exposed	39 / 55 (70.91%)		
number of deaths (all causes)	17		
number of deaths resulting from adverse events	2		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Transitional cell carcinoma			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Squamous cell carcinoma			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	0 / 0		
Tumour pain			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Surgical and medical procedures			
Aortic aneurysm repair	Additional description: Endovascular aneurysm repair and splenic artery embolization		
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Breast tumour excision			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Inguinal hernia repair			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Knee arthroplasty			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
General physical health deterioration			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Disease progression			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Reproductive system and breast disorders			
Epididymitis			

subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Platelet count decreased			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Fracture			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Splenic rupture			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Patella fracture			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial fibrillation			

subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pericardial effusion			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peripheral motor neuropathy			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Gastritis			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gallbladder obstruction			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haematuria			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Nephrolithiasis			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Back pain			

subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Endocarditis	Additional description: Bacteremia with gonarthritis and endocarditis			
subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cystitis				
subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Bronchitis				
subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cranial nerve infection				
subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Herpes zoster				
subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	2 / 55 (3.64%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Lung infection				
subjects affected / exposed	6 / 55 (10.91%)			
occurrences causally related to treatment / all	9 / 9			
deaths causally related to treatment / all	0 / 0			
Prostate infection				

subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Sepsis	Additional description: Sepsis grade 5 due to agranulocytosis in context of lymphoma progression		
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Soft tissue infection			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Upper respiratory tract infection			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Tumour lysis syndrome			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Safety Analysis Set		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	55 / 55 (100.00%)		
Investigations			
Neutrophil count decreased			
subjects affected / exposed	7 / 55 (12.73%)		
occurrences (all)	17		

Platelet count decreased subjects affected / exposed occurrences (all)	22 / 55 (40.00%) 38		
Vascular disorders Haematoma subjects affected / exposed occurrences (all) Hot flush subjects affected / exposed occurrences (all) Hypertension subjects affected / exposed occurrences (all)	 11 / 55 (20.00%) 17 4 / 55 (7.27%) 4 7 / 55 (12.73%) 9		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Dysgeusia subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Paraesthesia subjects affected / exposed occurrences (all) Peripheral motor neuropathy subjects affected / exposed occurrences (all) Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	 6 / 55 (10.91%) 8 4 / 55 (7.27%) 4 5 / 55 (9.09%) 6 9 / 55 (16.36%) 10 4 / 55 (7.27%) 4 14 / 55 (25.45%) 19		
General disorders and administration site conditions Oedema peripheral subjects affected / exposed occurrences (all)	 7 / 55 (12.73%) 11		

Fatigue			
subjects affected / exposed	22 / 55 (40.00%)		
occurrences (all)	42		
Pyrexia			
subjects affected / exposed	16 / 55 (29.09%)		
occurrences (all)	27		
Influenza like illness			
subjects affected / exposed	7 / 55 (12.73%)		
occurrences (all)	8		
Injection site reaction			
subjects affected / exposed	12 / 55 (21.82%)		
occurrences (all)	18		
Localised oedema			
subjects affected / exposed	4 / 55 (7.27%)		
occurrences (all)	4		
Pain			
subjects affected / exposed	4 / 55 (7.27%)		
occurrences (all)	5		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	11 / 55 (20.00%)		
occurrences (all)	14		
Diarrhoea			
subjects affected / exposed	26 / 55 (47.27%)		
occurrences (all)	47		
Gastritis			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	3		
Stomatitis			
subjects affected / exposed	10 / 55 (18.18%)		
occurrences (all)	20		
Nausea			
subjects affected / exposed	12 / 55 (21.82%)		
occurrences (all)	16		
Vomiting			

subjects affected / exposed	9 / 55 (16.36%)		
occurrences (all)	11		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	8 / 55 (14.55%)		
occurrences (all)	17		
Dyspnoea			
subjects affected / exposed	6 / 55 (10.91%)		
occurrences (all)	8		
Epistaxis			
subjects affected / exposed	4 / 55 (7.27%)		
occurrences (all)	23		
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	7 / 55 (12.73%)		
occurrences (all)	10		
Hyperhidrosis			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	3		
Pruritus			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	3		
Rash maculo-papular			
subjects affected / exposed	6 / 55 (10.91%)		
occurrences (all)	6		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	3		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 55 (7.27%)		
occurrences (all)	7		
Back pain			
subjects affected / exposed	6 / 55 (10.91%)		
occurrences (all)	10		

Myalgia subjects affected / exposed occurrences (all)	4 / 55 (7.27%) 4		
Infections and infestations Conjunctivitis subjects affected / exposed occurrences (all) Bronchitis subjects affected / exposed occurrences (all) Lung infection subjects affected / exposed occurrences (all) Skin infection subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all)	 8 / 55 (14.55%) 10 7 / 55 (12.73%) 8 8 / 55 (14.55%) 13 7 / 55 (12.73%) 8 6 / 55 (10.91%) 11 4 / 55 (7.27%) 5		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	 7 / 55 (12.73%) 12		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 December 2015	Substantial protocol amendment in order to remove the PET measurements for bone marrow assessment. Due to new discussions with experts for PET imaging it was clarified that the bone marrow involvement for patients with MCL can only be analyzed via PET/CT for a certain subgroup of patients (focal FDG uptake in the bone marrow) and not for the whole patient population of the trial. The PET measurements for bone marrow assessment were therefore deleted in the amended protocol.
23 December 2016	Substantial protocol amendment in order to update the risk section of the protocol due to the update of the investigator brochure of ibrutinib. In addition, the inclusion criterion 6.1.3 was changed from maximum 2 previous treatment lines to any treatment line. The duration of combination treatment was also updated allowing patients who received at least 4 cycles of ibrutinib and bortezomib (instead of 6 cycles) to proceed with maintenance therapy.
22 June 2018	Substantial protocol amendment in order to update the adverse event reporting, the implementation of the adapted serious adverse event reporting form and the adaptation of the uncommon side effects section in the protocol due to the release of the new investigator brochure of ibrutinib.
11 March 2019	Due to low accrual, a substantial amendment has been issued in order to allow an interim efficacy analysis once the first 31 patients of phase II have completed the combination therapy. The continuation of the trial should have depended on the outcome of this analysis.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Primary and final analysis was performed after all patients in the Phase II FAS completed combination therapy. Originally, final analysis was planned after trial termination (LPLV). However, the trial was terminated after primary analysis.

Notes: