



Clinical trial results:

A Prospective, Open-Label, Single-Arm, Phase 2, Multicenter Study Evaluating the Efficacy of Venetoclax Plus Ibrutinib in Subjects with T-Cell Prolymphocytic Leukemia

Summary

EudraCT number	2018-002179-17
Trial protocol	AT NL FR FI GB IT
Global end of trial date	04 November 2021

Results information

Result version number	v2 (current)
This version publication date	26 January 2023
First version publication date	06 December 2022
Version creation reason	<ul style="list-style-type: none">• Correction of full data set Update to Pre-assignment Screening details in the Subject Disposition section.

Trial information

Trial identification

Sponsor protocol code	M18-803
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03873493
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AbbVie Deutschland GmbH & Co. KG
Sponsor organisation address	AbbVie House, Vanwall Business Park, Vanwall Road, Maidenhead, Berkshire, United Kingdom, SL6 4UB
Public contact	Global Medical Services, AbbVie, 001 8006339110, abbvieclinicaltrials@abbvie.com
Scientific contact	Global Medical Services, AbbVie, 001 8006339110, abbvieclinicaltrials@abbvie.com

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	04 November 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 November 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study is to evaluate the efficacy of the combination of venetoclax plus ibrutinib for treating adults with T-cell prolymphocytic leukemia (T-PLL).

Protection of trial subjects:

Subject read and understood the information provided about the study and gave written permission.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 January 2020
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	France: 1
Country: Number of subjects enrolled	Australia: 1
Country: Number of subjects enrolled	United States: 2
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Italy: 3
Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	United Kingdom: 3
Worldwide total number of subjects	14
EEA total number of subjects	8

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)	5
From 65 to 84 years	9
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was planned as an adaptive 2-stage design with Stage 1 to enroll 14 participants and Stage 2 to enroll up to an additional 23 participants based on the number of responders in Stage 1. Stage 2 was not conducted.

Pre-assignment

Screening details:

In total, 16 adults with relapsed or refractory T-cell prolymphocytic leukemia (R/R T-PLL) were screened and 14 subjects were enrolled at 10 sites in 7 countries (Australia, France, Germany, Italy, Netherlands, United Kingdom, and United States).

For one subject "study terminated by sponsor" was entered as study discontinuation reason by mistake.

Period 1

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

Arms

Arm title	Venetoclax + Ibrutinib
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Arm description:

Participants received 400 mg venetoclax orally once a day after a 5-day ramp-up and 420 mg ibrutinib orally once a day for up to 2 years or until progressive disease, intolerance, or they became eligible for stem cell transplantation after achieving complete remission.

Arm type	Experimental
Investigational medicinal product name	Venetoclax
Investigational medicinal product code	ABT-199
Other name	Venclexta®, Venclyxto®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Venetoclax tablets taken orally once a day (QD). Initially, venetoclax was administered utilizing a 5-step dose ramp-up over 5 days. Subjects were hospitalized and closely monitored for 7 days. The venetoclax ramp-up was administered in a daily manner: 20 mg on Week 1 Day 1, 50 mg on Week 1 Day 2, 100 mg on Week 1 Day 3, 200 mg on Week 1 Day 4, and 400 mg on Week 1 Day 5 and thereafter, once daily, until the end-of-treatment. The dose of venetoclax may have been increased to 600 mg QD at Week 8 or thereafter.

Investigational medicinal product name	Ibrutinib
Investigational medicinal product code	PCI-32765
Other name	Imbruvica®
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Ibrutinib capsules taken orally once a day, 420 mg/day until the end-of-treatment.

Number of subjects in period 1	Venetoclax + Ibrutinib
Started	14
Completed	0
Not completed	14
Consent withdrawn by subject	1
Death	9
Other	2
Study Terminated by Sponsor	1
Lost to follow-up	1

Baseline characteristics

Reporting groups

Reporting group title	Overall Study
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Reporting group description:

Participants received 400 mg venetoclax orally once a day after a 5-day ramp-up and 420 mg ibrutinib orally once a day for up to 2 years or until progressive disease, intolerance, or they became eligible for stem cell transplantation after achieving complete remission.

Reporting group values	Overall Study	Total	
Number of subjects	14	14	
Age categorical			
Units: Subjects			
< 40 years	0	0	
40 - < 65 years	5	5	
≥ 65 years	9	9	
Age continuous			
Units: years			
arithmetic mean	66.8	-	
standard deviation	± 9.74	-	
Gender categorical			
Units: Subjects			
Female	8	8	
Male	6	6	
Race			
Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	0	0	
White	14	14	
Eastern Cooperative Oncology Group (ECOG) Performance Status			
ECOG performance status was assessed as follows: 0: Fully active, able to carry on all predisease performance without restriction. 1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. 2: Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours. 3: Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. 4: Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.			
Units: Subjects			
0 (Fully active)	7	7	
1 (Restricted but ambulatory and able to work)	6	6	
2 (Ambulatory but unable to work)	1	1	
Disease Duration			
Units: years			
arithmetic mean	3.229	-	
standard deviation	± 3.2134	-	

End points

End points reporting groups

Reporting group title	Venetoclax + Ibrutinib
Reporting group description: Participants received 400 mg venetoclax orally once a day after a 5-day ramp-up and 420 mg ibrutinib orally once a day for up to 2 years or until progressive disease, intolerance, or they became eligible for stem cell transplantation after achieving complete remission.	

Primary: Overall Response Rate (ORR)

End point title	Overall Response Rate (ORR) ^[1]
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End point description:

ORR is defined as the percentage of participants achieving complete remission (CR), CR with incomplete bone marrow recovery (CRi), or partial remission (PR) as their best response per investigator assessment based on the T-PLL consensus criteria 2019.

CR: All of the following response criteria must be met:

Group A:

- all lymph nodes < 1 cm;
- spleen < 13 cm;
- no constitutional symptoms;
- circulating lymphocyte count < $4 \times 10^9/L$;
- bone marrow T-PLL cells < 5% of mononuclear cells;
- no other specific site involvement.

Group B:

- platelets $\geq 100 \times 10^9 /L$;
- hemoglobin ≥ 11.0 g/dL;
- neutrophils $\geq 1.5 \times 10^9 /L$.

CRi: All of the CR response criteria in Group A met; at least 1 parameter in Group B not achieved unrelated to T-PLL.

PR: At least 2 of the parameters in Group A and 1 parameter in Group B need to improve if previously abnormal. If only 1 parameter of both Groups A and B is abnormal prior to therapy, only 1 parameter needs to improve.

End point type	Primary
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End point timeframe:

Clinical response was assessed at Weeks 4, 8, 12, 16 and 24 for ORR assessment

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: No statistical analyses were conducted.

End point values	Venetoclax + Ibrutinib			
Subject group type	Reporting group			
Number of subjects analysed	14 ^[2]			
Units: percentage of participants				
number (confidence interval 95%)	7.1 (0.2 to 33.9)			

Notes:

[2] - The full analysis set includes all participants who received at least 1 dose of study drug

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS)

End point title	Progression-Free Survival (PFS)
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End point description:

Progression-free survival is defined as the time from the date of first dose of any study drug to the date of earliest disease progression or death. PFS was calculated using Kaplan-Meier methods. Response was assessed by the investigator based on the T-PLL consensus criteria 2019.

Progressive disease (PD) is defined as meeting at least one of the Group A or Group B criteria below:

Group A:

- lymph nodes increase in > 20% in sum of long-axis diameters of up to 3 target lesions (SLD) from nadir;

- spleen increase \geq 50% in vertical length beyond normal from baseline;

- circulating lymphocyte count increase \geq 50% from baseline;

- appearance of a new lesion;

Group B:

- platelet count decrease of \geq 50% from baseline due to T-PLL (not due to drug toxicity);

- hemoglobin decrease of \geq 2 g/dL from baseline due to T-PLL;

- neutrophils decrease of \geq 50% from baseline due to T-PLL.

End point type	Secondary
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End point timeframe:

From first dose of study drug to end of study; median time on study was 30.1 weeks.

End point values	Venetoclax + Ibrutinib			
Subject group type	Reporting group			
Number of subjects analysed	14 ^[3]			
Units: months				
median (confidence interval 95%)	2.7 (1.2 to 5.3)			

Notes:

[3] - Full analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)
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End point description:

Duration of response is defined for participants who achieved a best overall response of CR, CRi, or PR as the time from the date of first response (CR, CRi, or PR) to the earliest date of disease progression or death. DOR was calculated using Kaplan-Meier methods.

Response was assessed by the investigator based on the T-PLL consensus criteria 2019.

Progressive disease is defined as meeting at least one of the Group A or Group B criteria below:

Group A:

- lymph nodes increase in > 20% in SLD from nadir;

- spleen increase \geq 50% in vertical length beyond normal from baseline;

- circulating lymphocyte count increase \geq 50% from baseline;

- appearance of a new lesion;

Group B:

- platelet count decrease of \geq 50% from baseline due to T-PLL (not due to drug toxicity);

- hemoglobin decrease of \geq 2 g/dL from baseline due to T-PLL;

- neutrophils decrease of \geq 50% from baseline due to T-PLL.

End point type	Secondary
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End point timeframe:

From first dose of study drug to end of study; median time on study was 30.1 weeks.

End point values	Venetoclax + Ibrutinib			
Subject group type	Reporting group			
Number of subjects analysed	1 ^[4]			
Units: months				
median (full range (min-max))	4.6 (4.6 to 4.6)			

Notes:

[4] - Full analysis set participants with a best overall response of CR, CRi, or PR

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Progression (TTP)

End point title	Time to Progression (TTP)
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End point description:

TTP is defined as the time from the date of the participant's first dose of any study drug to the date of earliest disease progression. TTP was calculated using Kaplan-Meier methods.

Clinical response (laboratory and physical examination assessments) was assessed by the investigator according to the T-PLL consensus criteria 2019.

Progressive disease is defined as meeting at least one of the criteria of Group A or Group B below:

Group A:

- lymph nodes increase in > 20% in SLD from nadir;
- spleen increase \geq 50% in vertical length beyond normal from baseline;
- circulating lymphocyte count increase \geq 50% from baseline;
- appearance of a new lesion;

Group B:

- platelet count decrease of \geq 50% from baseline due to T-PLL (not due to drug toxicity);
- hemoglobin decrease of \geq 2 g/dL from baseline due to T-PLL;
- neutrophils decrease of \geq 50% from baseline due to T-PLL.

End point type	Secondary
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End point timeframe:

From first dose of study drug to end of study; median time on study was 30.1 weeks.

End point values	Venetoclax + Ibrutinib			
Subject group type	Reporting group			
Number of subjects analysed	14 ^[5]			
Units: months				
median (confidence interval 95%)	2.7 (1.2 to 5.3)			

Notes:

[5] - Full analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Event-free Survival (EFS)

End point title	Event-free Survival (EFS)
End point description:	
Event-free survival is defined as time from participant's first dose of any study drug to the date of earliest disease progression, death, or start of a new anti-T-PLL therapy. EFS was calculated using Kaplan-Meier methods.	
Clinical response (laboratory and physical examination assessments) was assessed by the investigator according to the T-PLL consensus criteria 2019.	
Progressive disease is defined as meeting at least one of the criteria of Group A or Group B below:	
Group A:	
-lymph nodes increase in > 20% in SLD from nadir;	
-spleen increase \geq 50% in vertical length beyond normal from baseline;	
-circulating lymphocyte count increase \geq 50% from baseline;	
-appearance of a new lesion;	
Group B:	
-platelet count decrease of \geq 50% from baseline due to T-PLL (not due to drug toxicity);	
-hemoglobin decrease of \geq 2 g/dL from baseline due to T-PLL;	
-neutrophils decrease of \geq 50% from baseline due to T-PLL.	
End point type	Secondary
End point timeframe:	
From first dose of study drug to end of study; median time on study was 30.1 weeks.	

End point values	Venetoclax + Ibrutinib			
Subject group type	Reporting group			
Number of subjects analysed	14 ^[6]			
Units: months				
median (confidence interval 95%)	2.6 (0.6 to 5.3)			

Notes:

[6] - Full analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR)

End point title	Disease Control Rate (DCR)
End point description:	
DCR is defined as the percentage of participants who achieved CR, CRi, PR, or stable disease (SD) as best overall response per investigator assessment based on the T-PLL consensus criteria 2019.	
Stable disease is defined as meeting all of the following criteria for at least 3 months:	
-lymph nodes change of -29% to +20% in SLD;	
-spleen change of -49% to +49% beyond normal from baseline;	
-circulating lymphocyte count $> 30 \times 10^9$ /L or change of -49% to +49%;	
-platelet count change of -49% to +49%;	
-hemoglobin < 11.0 g/dL or change $< 50\%$ from baseline or change < 2 g/dL;	
-neutrophils change of -49% to +49%.	
End point type	Secondary
End point timeframe:	
Clinical response was assessed at Weeks 4, 8, 12, 16, and 24 for DCR assessment	

End point values	Venetoclax + Ibrutinib			
Subject group type	Reporting group			
Number of subjects analysed	14 ^[7]			
Units: percentage of participants				
number (confidence interval 95%)	28.6 (8.4 to 58.1)			

Notes:

[7] - Full analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)
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End point description:

Overall survival is defined as the time from the date of the participant's first dose of any study drug to death from any cause. OS was calculated using Kaplan-Meier methods.

End point type	Secondary
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End point timeframe:

From first dose of study drug to end of study; median time on study was 30.1 weeks.

End point values	Venetoclax + Ibrutinib			
Subject group type	Reporting group			
Number of subjects analysed	14 ^[8]			
Units: months				
median (confidence interval 95%)	7.3 (1.6 to 10.9)			

Notes:

[8] - Full analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Eligible Participants Reaching Autologous or Allogeneic Transplantation

End point title	Number of Eligible Participants Reaching Autologous or Allogeneic Transplantation
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End point description:

Participants eligible for autologous or allogeneic transplantation were transplant-naïve participants who achieved complete remission.

End point type	Secondary
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End point timeframe:

From first dose of study drug to end of study; median time on study was 30.1 weeks.

End point values	Venetoclax + Ibrutinib			
Subject group type	Reporting group			
Number of subjects analysed	0 ^[9]			
Units: participants				

Notes:

[9] - Transplant-naive participants who achieved CR. No participants were eligible for transplant.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Treatment-emergent Adverse Events (TEAE)

End point title	Number of Participants With Treatment-emergent Adverse Events (TEAE)
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End point description:

An adverse event (AE) is any untoward medical occurrence in a clinical investigation participant administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. Treatment-emergent AEs are any event with onset after the first dose of study drug and no more than 30 days after the last dose of study drug.

A serious AE (SAE) was an event that resulted in death, was life-threatening, resulted in hospitalization or prolongation of hospitalization, persistent or significant disability/incapacity, or an important medical event requiring medical or surgical intervention to prevent a serious outcome.

The Investigator rated the severity of each AE according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 5.0, where grade 1 = mild, grade 2 = moderate, grade 3 = severe, grade 4 = life-threatening and grade 5 = death.

The Investigator assessed the relationship of the AE to the use of study drug.

End point type	Secondary
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End point timeframe:

From first dose of study drug up to 30 days after last dose; median time on treatment was 13.86 weeks (range 1.0 to 44.4 weeks)

End point values	Venetoclax + Ibrutinib			
Subject group type	Reporting group			
Number of subjects analysed	14 ^[10]			
Units: participants				
Any treatment-emergent adverse event	14			
TEAE with NCI-CTCAE toxicity Grade 3, 4, or 5	11			
Serious adverse event	8			
TEAE leading to venetoclax discontinuation incl PD	11			
TEAE leading to venetoclax interruption	9			
TEAE leading to venetoclax reduction	2			
TEAE possibly related to venetoclax	10			
TEAE leading to ibrutinib discontinuation incl PD	11			
TEAE leading to ibrutinib interruption	10			

TEAE leading to ibrutinib reduction	1			
TEAE possibly related to ibrutinib	13			
SAE possibly related to venetoclax	3			
SAE possibly related to ibrutinib	4			
TEAE leading to death	5			
All deaths	10			

Notes:

[10] - All participants who received at least 1 dose of study drug (either venetoclax or ibrutinib)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All-cause mortality is reported from enrollment through end of study; median time on study was 30.1 weeks.

AEs are reported from first dose of study drug up to 30 days after last dose; median time on treatment was 13.86 weeks (range 1.0 to 44.4 weeks).

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	24.0
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Reporting groups

Reporting group title	Venetoclax + Ibrutinib
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Reporting group description:

Participants received 400 mg venetoclax orally once a day after a 5-day ramp-up and 420 mg ibrutinib orally once a day for up to 2 years or until progressive disease, intolerance, or they became eligible for stem cell transplantation after achieving complete remission.

Serious adverse events	Venetoclax + Ibrutinib		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 14 (57.14%)		
number of deaths (all causes)	10		
number of deaths resulting from adverse events	5		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
MALIGNANT NEOPLASM PROGRESSION			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
MALIGNANT PLEURAL EFFUSION			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
PHLEBITIS			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			

ANAEMIA			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
NEUTROPENIA			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
DISEASE PROGRESSION			
subjects affected / exposed	4 / 14 (28.57%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 3		
EUTHANASIA			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Gastrointestinal disorders			
NAUSEA			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
RENAL TUBULAR DISORDER			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
URINARY RETENTION			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
FACET JOINT SYNDROME			

subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
ASPERGILLUS INFECTION			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
INFECTION			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
OROPHARYNGEAL CANDIDIASIS			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Venetoclax + Ibrutinib		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 14 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
LIPOMA			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Vascular disorders			
ARTERIOSCLEROSIS			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
HYPOTENSION			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
General disorders and administration site conditions			

ASTHENIA			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
CATHETER SITE PAIN			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
COMPLICATION ASSOCIATED WITH DEVICE			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
DISEASE PROGRESSION			
subjects affected / exposed	5 / 14 (35.71%)		
occurrences (all)	5		
FATIGUE			
subjects affected / exposed	3 / 14 (21.43%)		
occurrences (all)	3		
OEDEMA PERIPHERAL			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
DYSPNOEA			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
EPISTAXIS			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
NASAL ULCER			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
OROPHARYNGEAL PAIN			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
PULMONARY OEDEMA			

subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Psychiatric disorders INSOMNIA subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 2		
Product issues DEVICE FAILURE subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Investigations BLOOD BILIRUBIN INCREASED subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 2		
BLOOD CREATININE INCREASED subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
LYMPHOCYTE COUNT INCREASED subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
MAGNETIC RESONANCE IMAGING HEAD ABNORMAL subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
NEUTROPHIL COUNT DECREASED subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
PLATELET COUNT DECREASED subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
WEIGHT DECREASED subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
WHITE BLOOD CELL COUNT DECREASED subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Injury, poisoning and procedural			

<p>complications</p> <p>CONTUSION</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>FALL</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>WOUND</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>2 / 14 (14.29%)</p> <p>2</p> <p>1 / 14 (7.14%)</p> <p>2</p> <p>1 / 14 (7.14%)</p> <p>1</p>		
<p>Cardiac disorders</p> <p>ATRIAL FIBRILLATION</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>TACHYCARDIA</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 14 (7.14%)</p> <p>1</p> <p>1 / 14 (7.14%)</p> <p>1</p>		
<p>Nervous system disorders</p> <p>CEREBRAL ATROPHY</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>CEREBRAL INFARCTION</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>DIZZINESS</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>HEADACHE</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>MEMORY IMPAIRMENT</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 14 (7.14%)</p> <p>1</p> <p>1 / 14 (7.14%)</p> <p>1</p> <p>3 / 14 (21.43%)</p> <p>3</p> <p>1 / 14 (7.14%)</p> <p>1</p> <p>1 / 14 (7.14%)</p> <p>1</p>		
<p>Blood and lymphatic system disorders</p> <p>ANAEMIA</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>3 / 14 (21.43%)</p> <p>4</p>		

FEBRILE NEUTROPENIA subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
NEUTROPENIA subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Ear and labyrinth disorders MIDDLE EAR EFFUSION subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
HYPOACUSIS subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Eye disorders EYE SWELLING subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
LACRIMATION INCREASED subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Gastrointestinal disorders ABDOMINAL PAIN UPPER subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
CONSTIPATION subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 2		
DIARRHOEA subjects affected / exposed occurrences (all)	8 / 14 (57.14%) 11		
DYSPEPSIA subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
DYSPHAGIA subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 3		
GLOSSODYNIA			

subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
MELAENA			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
NAUSEA			
subjects affected / exposed	6 / 14 (42.86%)		
occurrences (all)	7		
PANCREATIC STEATOSIS			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
STOMATITIS			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	2		
TONGUE ERUPTION			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
VOMITING			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
Hepatobiliary disorders			
HYPERPLASTIC CHOLECYSTOPATHY			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
ERYTHEMA			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
PETECHIAE			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
PRURITUS			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
RASH			

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>RASH MACULO-PAPULAR</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>SKIN LESION</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>3 / 14 (21.43%)</p> <p>3</p> <p>1 / 14 (7.14%)</p> <p>1</p> <p>1 / 14 (7.14%)</p> <p>2</p>		
<p>Renal and urinary disorders</p> <p>BLADDER DIVERTICULUM</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>URINARY INCONTINENCE</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 14 (7.14%)</p> <p>1</p> <p>1 / 14 (7.14%)</p> <p>1</p>		
<p>Endocrine disorders</p> <p>ANDROGEN DEFICIENCY</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 14 (7.14%)</p> <p>1</p>		
<p>Musculoskeletal and connective tissue disorders</p> <p>ARTHRALGIA</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>BACK PAIN</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>MUSCLE SPASMS</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>2 / 14 (14.29%)</p> <p>2</p> <p>1 / 14 (7.14%)</p> <p>1</p> <p>1 / 14 (7.14%)</p> <p>1</p>		
<p>Infections and infestations</p> <p>CELLULITIS</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>ESCHERICHIA URINARY TRACT INFECTION</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 14 (7.14%)</p> <p>1</p> <p>1 / 14 (7.14%)</p> <p>1</p>		

FOLLICULITIS			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
GASTROENTERITIS			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
INFECTION			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
NASOPHARYNGITIS			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
ORAL CANDIDIASIS			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
PARVOVIRUS B19 INFECTION			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
RHINITIS			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
RHINOVIRUS INFECTION			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
TONSILLITIS			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
URINARY TRACT INFECTION			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	3		
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
FOLATE DEFICIENCY			

subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
HYPERGLYCAEMIA			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
HYPERKALAEMIA			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
HYPERPHOSPHATAEMIA			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
HYPOALBUMINAEMIA			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
HYPOCALCAEMIA			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
HYPOKALAEMIA			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
HYPOMAGNESAEMIA			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
HYPONATRAEMIA			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
HYPOPHOSPHATAEMIA			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
TUMOUR LYSIS SYNDROME			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 May 2019	Removed nodular partial response (nPR) from the definition of ORR because nPR is not applicable for T-PLL. Added computed tomography (CT) scan for confirmation of response and updated the protocol so that CT scans for disease assessment were performed using a T-PLL-adapted version of the response evaluation criteria in lymphoma (RECIL) 2017 instead of using standard response evaluation criteria in solid tumors (RECIST). Updated the eligibility criteria to reduce the risk of dose interruptions or modifications, added safety guidelines for AEs associated with the underlying disease under investigation, and revised the toxicity management of ibrutinib to align with the company core data sheets dose modification guidelines.
11 November 2020	Reference to the (RECIL-based) T-PLL consensus criteria 2019 was added into the primary endpoint. Revisions were made to align the secondary objectives and endpoints. Clarified that the potential continuation of therapy is subject to local regulations and to extend the post-treatment follow-up visits period in the protocol. Updated the eligibility criteria for creatinine clearance, revised the washout period for live or attenuated vaccines, clarified that seasonal flu vaccines are allowed, and revised the contraception recommendations for male subjects. Updated the eligibility criteria to exclude subjects positive for SARS-CoV-2. Added laboratory monitoring for TLS for any increase in venetoclax dose. Updated the disease assessment criteria using the (RECIL-based) T-PLL consensus criteria and clarified that disease assessment will continue after last dose of study drug.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
01 April 2020	An enrollment hold occurred from 01 April 2020 until 15 June 2020 upon recommendation from the Steering Committee in response to the coronavirus disease 2019 (COVID-19) pandemic.	15 June 2020

Notes:

Limitations and caveats

None reported