Clinical trial results:
A phase IIIb, open-label, local, multicenter study of the molecular features of postmenopausal women with hormone receptor-positive (HR+) HER2-negative advanced breast cancer on first-line treatment with ribociclib plus letrozole and, in patients with a PIK3CA mutation, on second-line treatment with alpelisib plus fulvestrant (BioItaLEE)

Summary

EudraCT number	2017-004176-62
Trial protocol	IT
Global end of trial date	11 December 2023

Results information

Result version number	v1
This version publication date	22 December 2024
First version publication date	22 December 2024

Trial information

Trial identification

Sponsor protocol code	CLEE011AIT01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03439046
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	Novartis Campus, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@Novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@Novartis.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	11 December 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 December 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to identify circulating tumor DNA (ctDNA) alterations, how they evolve, and evaluate their possible association with clinical outcome in both first-line treatment with ribociclib and letrozole and second-line treatment with alpelisib and fulvestrant. Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 February 2018
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	Italy: 287
Worldwide total number of subjects	287
EEA total number of subjects	287

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)	125
From 65 to 84 years	161

85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

All inclusion and exclusion criteria were checked at screening.

Period 1

Period 1 title	Core Phase
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Ribociclib+letrozole (Core Phase)

Arm description:

Ribociclib oral (3 weeks on/1 week off) in combination with oral once daily letrozole: 600 mg tablets ribociclib QD + 2.5 mg tablets letrozole QD

Arm type	Experimental
Investigational medicinal product name	Letrozole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Ribociclib oral (3 weeks on/1 week off) in combination with oral once daily letrozole: 600 mg tablets ribociclib QD + 2.5 mg tablets letrozole QD

Investigational medicinal product name	Ribociclib
Investigational medicinal product code	
Other name	LEE011
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Ribociclib oral (3 weeks on/1 week off) in combination with oral once daily letrozole: 600 mg tablets ribociclib QD + 2.5 mg tablets letrozole QD

Number of subjects in period 1	Ribociclib+letrozole (Core Phase)
Started	287
Completed	184
Not completed	103
Adverse event, serious fatal	27
Other	2
Study terminated by sponsor	45
Lost to follow-up	14
Subject/guardian decision	15

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

Arms	
Arm title	Alpelisib+fulvestrant (Extension Phase)

Arm description:

Alpelisib 300 mg oral daily on a continuous dosing schedule in combination with fulvestrant 500 mg intramuscular on Days 1 and 15 of Cycle 1, and on Day 1 of each cycle thereafter in a 28-day cycle

Arm type	Experimental
Investigational medicinal product name	Fulvestrant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Alpelisib 300 mg oral daily on a continuous dosing schedule in combination with fulvestrant 500 mg intramuscular on Days 1 and 15 of Cycle 1, and on Day 1 of each cycle thereafter in a 28-day cycle

Investigational medicinal product name	Alpelisib
Investigational medicinal product code	
Other name	BYL719
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Alpelisib 300 mg oral daily on a continuous dosing schedule in combination with fulvestrant 500 mg intramuscular on Days 1 and 15 of Cycle 1, and on Day 1 of each cycle thereafter in a 28-day cycle

Number of subjects in period 2[1]	Alpelisib+fulvestrant (Extension Phase)
Started	21
Completed	16
Not completed	5
Adverse event, serious fatal	3
Lost to follow-up	1
Subject/guardian decision	1

Notes:

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

Justification: This arm included patients with PIK3CA mutations who entered the extension phase after treatment discontinuation.

Baseline characteristics

Reporting groups	
Reporting group title	Ribociclib+letrozole (Core Phase)
Reporting group description:	
Ribociclib oral (3 weeks on/1 week off) in combination with oral once daily letrozole: 600 mg tablets ribociclib QD + 2.5 mg tablets letrozole QD	

Reporting group values	Ribociclib+letrozole (Core Phase)	Total	
Number of subjects	287	287	
Age Categorical Units: participants			
in utero	0	0	
Preterm newborns infants	0	0	
0 - <28 days	0	0	
28 days - <2 years	0	0	
2 years - <12 years	0	0	
12 years - <18 years	0	0	
18 years - <65 years	125	125	
65 years - <85 years	161	161	
>=85 years	1	1	
Age Continuous Units: years			
arithmetic mean	65.5		
standard deviation	± 8.39	-	
Sex: Female, Male Units: participants			
Female	287	287	
Male	0	0	
Race/Ethnicity, Customized Units: Subjects			
Caucasian	280	280	
Asian	1	1	
Unknown Race	5	5	
Other Race	1	1	

End points

End points reporting groups

Reporting group title	Ribociclib+letrozole (Core Phase)
Reporting group description:	
Ribociclib oral (3 weeks on/1 week off) in combination with oral once daily letrozole: 600 mg tablets ribociclib QD + 2.5 mg tablets letrozole QD	
Reporting group title	Alpelisib+fulvestrant (Extension Phase)
Reporting group description:	
Alpelisib 300 mg oral daily on a continuous dosing schedule in combination with fulvestrant 500 mg intramuscular on Days 1 and 15 of Cycle 1, and on Day 1 of each cycle thereafter in a 28-day cycle	

Primary: Number of Participants With Hotspot Mutated Genes by Scheduled Timepoint

End point title	Number of Participants With Hotspot Mutated Genes by Scheduled Timepoint[1]
End point description:	
Hotspot mutational analysis on liquid biopsy was performed on the 39 genes belonging to the BioItaLEE custom panel. The data row labels below refer to the number of hotspot-mutated genes at each timepoint. Each cycle was 28 days. PD = progressive disease. EOT = end of treatment.	
End point type	Primary
End point timeframe:	
Up to approximately 5.7 years	

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: Not applicable.

End point values	Ribociclib+letrozole (Core Phase)			
Subject group type	Reporting group			
Number of subjects analysed	263			
Units: participants				
None at Screening n=263	145			
None at Cycle 1 Day 15 n=238	152			
None at Cycle 2 Day 1 n=242	160			
None at First Imaging Evaluation n=206	147			
None at EOT due to PD n=118	50			
None at EOT due to Other n=39	27			
1 at Screening n=263	70			
1 at Cycle 1 Day 15 n=238	51			
1 at Cycle 2 Day 1 n=242	53			
1 at First Imaging Evaluation n=206	40			
1 at EOT due to PD n=118	26			
1 at EOT due to Other n=39	10			
2 at Screening n=263	32			
2 at Cycle 1 Day 15 n=238	28			
2 at Cycle 2 Day 1 n=242	21			
2 at First Imaging Evaluation n=206	11			
2 at EOT due to PD n=118	21			

2 at EOT due to Other n=39	2			
3 or More at Screening n=263	16			
3 or More at Cycle 1 Day 15 n=238	7			
3 or More at Cycle 2 Day 1 n=242	8			
3 or More at First Imaging Evaluation n=206	8			
3 or More at EOT due to PD n=118	21			
3 or More at EOT due to Other n=39	0			

Statistical analyses

No statistical analyses for this end point

Primary: Percent Change From Screening in Target Mutation Variant Allele Frequency (VAF)

End point title	Percent Change From Screening in Target Mutation Variant Allele Frequency (VAF)[2]

End point description:

The target mutation was defined as the hotspot mutation with the highest molecular frequency observed at screening excluding single nucleotide polymorphisms (SNPs, i.e., hotspot mutations observed at all timepoints with a minimum molecular frequency value of 30% and a variation coefficient greater than 0.15). The molecular frequency of target mutation at performed assessments during which the target mutation was not detected was assumed to be equal to 0%.

End point type	Primary

End point timeframe:

Up to approximately 5.7 years

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: Not applicable.

End point values	Ribociclib+letrozole (Core Phase)			
Subject group type	Reporting group			
Number of subjects analysed	263			
Units: percent change				
median (full range (min-max))				
Cycle 1, Day 15 n=104	-94.33 (-100.0 to 134.5)			
Cycle 2, Day 1 n=106	-100.00 (-100.0 to 167.8)			
First Imaging Evaluation n=90	-100.00 (-100.0 to 1110.9)			
End of Treatment due to PD n=66	-47.48 (-100.0 to 1133.9)			
End of treatment due to other n=16	-100.00 (-100.0 to 29.8)			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Partial Response (PR) in the Extension Phase

End point title	Number of Participants With Partial Response (PR) in the Extension Phase[3]

End point description:

PR was assessed per Response Evaluation Criteria in Solid Tumors (RECIST) v. 1.1, criteria and was defined as at least a 30% decrease in the sum of diameter of all target lesions, taking as reference the screening sum of diameters.

End point type	Primary

End point timeframe:

Up to approximately 1.6 years

Notes:

[3] - 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: Not applicable.

End point values	Alpelisib+fulvestrant (Extension Phase)			
Subject group type	Reporting group			
Number of subjects analysed	0[4]			
Units: participants				

Notes:

[4] - This endpoint was not assessed.

Statistical analyses

No statistical analyses for this end point

Primary: Progression-Free Survival (PFS) by Cycle 1 Day 15 Complete Mutational Dynamic Change

End point title	Progression-Free Survival (PFS) by Cycle 1 Day 15 Complete Mutational Dynamic Change[5]

End point description:

PFS: Time (months) from start of the study treatment to first documented progression or death due to any cause, whichever came first. Kaplan-Meier estimates. Persistent Wild Type: Wild Type (or single nucleotide polymorphisms [SNPs] only) at screening without hotspot mutations at any later assessment. Confirmed cleared: Mutated, with 100% decrease in target mutation variant allele frequency (VAF) at C1D15 or at C2D1 also observed at FI. Unconfirmed cleared: Mutated that cleared or at C1D15 or at C2D1 that were not cleared at FI. Late cleared: Mutated without 100% decrease in target mutation VAF at C1D15 and at C2D1 with 100% decrease in target mutation VAF at FI. New mutated: Wild Type ([SNPs] only) at screening with hotspot mutations at C1D15 or C2D1. Late mutated: Wild Type patients (or SNPs only) at screening without hotspot mutations at C1D15 and C2D1 with hotspot mutations at FI. Confirmed mutated: Mutated without 100% decrease in target mutation VAF at any later assessment.

End point type	Primary

End point timeframe:

Up to approximately 5.7 years

Notes:

[5] - 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: Not applicable.

End point values	Ribociclib+letrozole (Core Phase)			
Subject group type	Reporting group			
Number of subjects analysed	187			
Units: months				
median (confidence interval 95%)				
Persistent Wild Type n=76	55.82 (39.06 to 999)			
New Mutated n=19	16.53 (9.03 to 45.90)			
Late Mutated n=8	15.67 (2.00 to 21.42)			
Confirmed Cleared n=46	22.44 (15.93 to 32.23)			
Unconfirmed Cleared n=8	10.22 (2.69 to 999)			
Late Cleared n=12	11.07 (3.29 to 19.09)			
Confirmed Mutated n=18	14.32 (2.89 to 44.22)			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Progression-Free Survival (PFS) Events by Cycle 1 Day 15 Complete Mutational Dynamic Change

End point title	Number of Participants With Progression-Free Survival (PFS) Events by Cycle 1 Day 15 Complete Mutational Dynamic Change[6]

End point description:

Kaplan-Meier estimates. Persistent Wild Type: Wild Type (or single nucleotide polymorphisms [SNPs] only) at screening without hotspot mutations at any later assessment. Confirmed cleared: Mutated, with 100% decrease in target mutation variant allele frequency (VAF) at C1D15 or at C2D1 also observed at FI. Unconfirmed cleared: Mutated that cleared or at C1D15 or at C2D1 that were not cleared at FI. Late cleared: Mutated without 100% decrease in target mutation VAF at C1D15 and at C2D1 with 100% decrease in target mutation VAF at FI. New mutated: Wild Type ([SNPs] only) at screening with hotspot mutations at C1D15 or C2D1. Late mutated: Wild Type patients (or SNPs only) at screening without hotspot mutations at C1D15 and C2D1 with hotspot mutations at FI. Confirmed mutated: Mutated without 100% decrease in target mutation VAF at any later assessment.

End point type	Primary

End point timeframe:

Up to approximately 5.7 years

Notes:

[6] - 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: Not applicable.

End point values	Ribociclib+letrozole (Core Phase)			
Subject group type	Reporting group			
Number of subjects analysed	187			
Units: participants				
Persistent Wild Type n=76	31			

New Mutated n=19	13			
Late Mutated n=8	6			
Confirmed Cleared n=46	28			
Unconfirmed Cleared n=8	6			
Late Cleared n=12	10			
Confirmed Mutated n=18	12			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Screening in Thymidine Kinase 1 (TK1) Serum Level

End point title	Percent Change From Screening in Thymidine Kinase 1 (TK1) Serum Level

End point description:

End point type	Secondary

End point timeframe:

Up to approximately 5.7 years

End point values	Ribociclib+letrozole (Core Phase)			
Subject group type	Reporting group			
Number of subjects analysed	263			
Units: percent change				
median (full range (min-max))				
Cycle 1, Day 15 n=245	-73.2 (-99 to 2370)			
Cycle 2, Day 1 n=241	-39.3 (-96 to 1378)			
First Imaging Evaluation n=208	-46.9 (-99 to 1604)			
End of Treatment due to PD n=89	56.5 (-98 to 10033)			
End of treatment due to other n=35	28.5 (-92 to 109213)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Long Responder Participants With Hotspot Mutated Genes by Scheduled Timepoint

End point title	Number of Long Responder Participants With Hotspot Mutated Genes by Scheduled Timepoint

End point description:

Hotspot mutational analysis on liquid biopsy was performed on the 39 genes belonging to the BioItaLEE custom panel. Data row labels refer to the number of hotspot-mutated genes at each timepoint. Each cycle was 28 days. PD = progressive disease.

End point type	Secondary

End point timeframe:

Up to approximately 5.7 years

End point values	Ribociclib+letrozole (Core Phase)			
Subject group type	Reporting group			
Number of subjects analysed	116			
Units: participants				
None at Screening n=95	64			
None at Cycle 1 Day 15 n=84	60			
None at Cycle 2, Day 1 n=91	67			
None at First Imaging Evaluation n=82	66			
None at EOT due to PD n=27	14			
None at EOT due to Other n=4	1			
1 at Screening n=95	23			
1 at Cycle 1 Day 15 n=84	18			
1 at Cycle 2, Day 1 n=91	22			
1 at First Imaging Evaluation n=82	14			
1 at EOT due to PD n=27	7			
1 at EOT due to Other n=4	3			
2 at Screening n=95	4			
2 at Cycle 1 Day 15 n=84	4			
2 at Cycle 2, Day 1 n=91	2			
2 at First Imaging Evaluation n=82	2			
2 at EOT due to PD n=27	2			
2 at EOT due to Other n=4	0			
3 or More at Screening n=95	4			
3 or More at Cycle 1 Day 15 n=84	2			
3 or More at Cycle 2, Day 1 n=91	0			
3 or More at First Imaging Evaluation n=82	0			
3 or More at EOT due to PD n=27	4			
3 or More at EOT due to Other n=4	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Early Progressor Participants With Hotspot Mutated Genes by Scheduled Timepoint

End point title	Number of Early Progressor Participants With Hotspot Mutated Genes by Scheduled Timepoint

End point description:

Hotspot mutational analysis on liquid biopsy was performed on the 39 genes belonging to the BioItaLEE custom panel. Data row labels refer to the number of hotspot-mutated genes at each timepoint. Each cycle was 28 days. PD = progressive disease.

End point type	Secondary

End point timeframe:

Up to approximately 5.7 years

End point values	Ribociclib+letrozole (Core Phase)			
Subject group type	Reporting group			
Number of subjects analysed	116			
Units: participants				
None at Screening n=21	8			
None at Cycle 1 Day 15 n=19	7			
None at Cycle 2, Day 1 n=21	9			
None at First Imaging Evaluation n=19	9			
None at EOT due to PD n=20	7			
None at EOT due to Other n=0	999			
1 at Screening n=21	5			
1 at Cycle 1 Day 15 n=19	3			
1 at Cycle 2, Day 1 n=21	3			
1 at First Imaging Evaluation n=19	3			
1 at EOT due to PD n=20	4			
1 at EOT due to Other n=0	999			
2 at Screening n=21	5			
2 at Cycle 1 Day 15 n=19	8			
2 at Cycle 2, Day 1 n=21	5			
2 at First Imaging Evaluation n=19	5			
2 at EOT due to PD n=20	5			
2 at EOT due to Other n=0	999			
3 or More at Screening n=21	3			
3 or More at Cycle 1 Day 15 n=19	1			
3 or More at Cycle 2, Day 1 n=21	4			
3 or More at First Imaging Evaluation n=19	2			
3 or More at EOT due to PD n=20	4			
3 or More at EOT due to Other n=0	999			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Screening in Target Mutation Molecular Frequency (VAF) for Long Responders

End point title	Percent Change From Screening in Target Mutation Molecular Frequency (VAF) for Long Responders

End point description:

The target mutation was defined as the hotspot mutation with the highest molecular frequency observed at screening excluding single nucleotide polymorphisms (SNPs, i.e., hotspot mutations observed at all timepoints with a minimum molecular frequency value of 30% and a variation coefficient greater than 0.15). The molecular frequency of target mutation at performed assessments during which the target mutation was not detected was assumed to be equal to 0%.

End point type	Secondary

End point timeframe:

Up to approximately 5.7 years

End point values	Ribociclib+letrozole (Core Phase)			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: percent change				
median (full range (min-max))				
Cycle 1, Day 15 n=26	-98.82 (-100.0 to 101.6)			
Cycle 2, Day 1 n=27	-100.00 (-100.0 to 88.8)			
First Imaging Evaluation n=23	-100.00 (-100.0 to 40.5)			
End of Treatment due to PD n=12	-52.93 (-100.0 to 319.7)			
End of treatment due to other n=2	-35.12 (-100.0 to 29.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Screening in Target Mutation Molecular Frequency (VAF) for Early Progressors

End point title	Percent Change From Screening in Target Mutation Molecular Frequency (VAF) for Early Progressors

End point description:

The target mutation was defined as the hotspot mutation with the highest molecular frequency observed at screening excluding single nucleotide polymorphisms (SNPs, i.e., hotspot mutations observed at all timepoints with a minimum molecular frequency value of 30% and a variation coefficient greater than 0.15). The molecular frequency of target mutation at performed assessments during which the target mutation was not detected was assumed to be equal to 0%.

End point type	Secondary

End point timeframe:

Up to approximately 5.7 years

End point values	Ribociclib+letrozole (Core Phase)			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: percent change				
median (full range (min-max))				
Cycle 1, Day 15 n=12	-42.45 (-100.0 to 77.5)			
Cycle 2, Day 1 n=13	-70.05 (-100.0 to 37.9)			
First Imaging Evaluation n=11	-56.76 (-100.0 to 1110.9)			
End of Treatment due to PD n=12	-24.31 (-100.0 to 707.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Screening Hotspot Mutations per De Novo Patient in Liquid Biopsy Samples and Tissue Samples

End point title	Number of Screening Hotspot Mutations per De Novo Patient in Liquid Biopsy Samples and Tissue Samples

End point description:

Hotspot mutational analysis on liquid biopsy was performed on the 39 genes belonging to the BioItaLEE custom panel. Data row labels refer to the number of hotspot-mutated genes at each timepoint. Each cycle was 28 days. PD = progressive disease.

End point type	Secondary

End point timeframe:

Up to approximately 5.7 years

End point values	Ribociclib+letrozole (Core Phase)			
Subject group type	Reporting group			
Number of subjects analysed	105			
Units: participants				
None (Valid Liquid Biopsy Sample) n=105	59			
One (Valid Liquid Biopsy Sample) n=105	31			
Two (Valid Liquid Biopsy Sample) n=105	11			
Three or More (Valid Liquid Biopsy Sample) n=105	4			
None (Valid Tissue Sample) n=72	23			
One (Valid Tissue Sample) n=72	26			
Two (Valid Tissue Sample) n=72	17			
Three or More (Valid Tissue Sample) n=72	6			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Number of Evaluations of Hotspot Mutations and Non-hotspot Mutations Present in Both Liquid Biopsies and Tissue Samples at Screening

End point title	Overall Number of Evaluations of Hotspot Mutations and Non-hotspot Mutations Present in Both Liquid Biopsies and Tissue Samples at Screening

End point description:

Results data refer to the total number of evaluations (i.e. the number of participants in the biomarker analysis set with both valid baseline liquid biopsy and tissue sample multiplied by 39 considered genes). HM = hotspot-mutated.

End point type	Secondary

End point timeframe:

Up to approximately 5.7 years

End point values	Ribociclib+letrozole (Core Phase)			
Subject group type	Reporting group			
Number of subjects analysed	263			
Units: evaluations				
Liquid Biopsy HM, Tissue Sample HM	68			
Liquid Biopsy HM, Tissue Sample Not HM	27			
Liquid Biopsy Not HM, Tissue Sample HM	99			
Liquid Biopsy Not HM, Tissue Sample Not HM	5227			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Screening Hotspot Mutations per Recurrent Patient in Liquid Biopsy Samples and Tissue Samples

End point title	Number of Screening Hotspot Mutations per Recurrent Patient in Liquid Biopsy Samples and Tissue Samples

End point description:

Hotspot mutational analysis on liquid biopsy was performed on the 39 genes belonging to the BioItaLEE custom panel. Data row labels refer to the number of hotspot-mutated genes at each timepoint. Each cycle was 28 days. PD = progressive disease.

End point type	Secondary

End point timeframe:

Up to approximately 5.7 years

End point values	Ribociclib+letrozole (Core Phase)			
Subject group type	Reporting group			
Number of subjects analysed	158			
Units: participants				
None (Valid Liquid Biopsy Sample) n=158	86			
One (Valid Liquid Biopsy Sample) n=158	39			
Two (Valid Liquid Biopsy Sample) n=158	21			
Three or More (Valid Liquid Biopsy Sample) n=158	12			
None (Valid Tissue Sample) n=67	15			
One (Valid Tissue Sample) n=67	25			
Two (Valid Tissue Sample) n=67	13			
Three or More (Valid Tissue Sample) n=67	14			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Progression (TTP)

End point title	Time to Progression (TTP)

End point description:

Time to progression (TTP) was defined as time from date of start of treatment to the date of event defined as the first documented progression or death due to underlying cancer.

End point type	Secondary

End point timeframe:

Core phase: up to approximately 5.7 years. Extension phase: up to approximately 1.6 years

End point values	Ribociclib+letrozole (Core Phase)			
Subject group type	Reporting group			
Number of subjects analysed	263			
Units: months				
median (confidence interval 95%)	30.42 (21.42 to 40.41)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Best Overall Response Rate of Complete Response (CR) or Partial Response (PR)

End point title	Percentage of Participants With Best Overall Response Rate of Complete Response (CR) or Partial Response (PR)

End point description:

ORR was defined as the percentage of participants with a best overall response defined as complete response (CR) or partial response (PR): (CR+PR) per Response Evaluation Criteria in Solid Tumors (RECIST), v. 1.1. CR=Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm; PR= At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters.

End point type	Secondary

End point timeframe:

Core phase: up to approximately 5.7 years. Extension phase: up to approximately 1.6 years

End point values	Ribociclib+letrozole (Core Phase)			
Subject group type	Reporting group			
Number of subjects analysed	236			
Units: percentage of participants				
median (confidence interval 95%)	38.56 (32.32 to 45.09)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Number of Evaluations of Hotspot Mutations and Non-hotspot Mutations Present in Both Liquid Biopsies and Tissue Samples at End of Treatment

End point title	Overall Number of Evaluations of Hotspot Mutations and Non-hotspot Mutations Present in Both Liquid Biopsies and Tissue Samples at End of Treatment

End point description:

Results data refer to the total number of evaluations (i.e. the number of participants in the biomarker analysis set with both valid baseline liquid biopsy and tissue sample multiplied by 39 considered genes). HM = hotspot-mutated.

End point type	Secondary

End point timeframe:

Up to approximately 5.7 years

End point values	Ribociclib+letrozole (Core Phase)			
Subject group type	Reporting group			
Number of subjects analysed	263			
Units: evaluations				
Liquid Biopsy HM, Tissue Sample HM	5			
Liquid Biopsy HM, Tissue Sample Not HM	1			
Liquid Biopsy Not HM, Tissue Sample HM	0			
Liquid Biopsy Not HM, Tissue Sample Not HM	150			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline Tumor Mutational Burden (TMB) to Progression of Disease During the Core and Extension Phases

End point title	Change From Baseline Tumor Mutational Burden (TMB) to Progression of Disease During the Core and Extension Phases

End point description:

End point type	Secondary

End point timeframe:

Up to approximately 5.7 years

End point values	Ribociclib+letrozole (Core Phase)			
Subject group type	Reporting group			
Number of subjects analysed	0[7]			
Units: Not applicable				
number (not applicable)				

Notes:

[7] - This endpoint was not assessed.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Clinical Benefit Rate

End point title	Percentage of Participants With Clinical Benefit Rate

End point description:

Clinical benefit rate (CBR) was defined as the percentage of participants with a best overall response of complete response (CR), or partial response (PR) or an overall lesion response of stable disease (SD), lasting as per local review, for a duration of at least 24 weeks. Per RECIST v. 1.1, CR was defined as disappearance of all target lesions. PR was defined as at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter. SD was defined as

neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease (PD), taking as reference the smallest sum longest diameter since the treatment started.

End point type	Secondary

End point timeframe:

Core phase: up to approximately 5.7 years. Extension phase: up to approximately 1.6 years

End point values	Ribociclib+letrozole (Core Phase)			
Subject group type	Reporting group			
Number of subjects analysed	236			
Units: percentage of participants				
number (confidence interval 95%)	73.31 (67.18 to 78.84)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline Tumor Microenvironment Parameters to Progression of Disease During the Core and Extension Phases

End point title	Change From Baseline Tumor Microenvironment Parameters to Progression of Disease During the Core and Extension Phases

End point description:

End point type	Secondary

End point timeframe:

Up to approximately 5.7 years

End point values	Ribociclib+letrozole (Core Phase)			
Subject group type	Reporting group			
Number of subjects analysed	0[8]			
Units: Not applicable				
number (not applicable)				

Notes:

[8] - This endpoint was not assessed.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Timeframe for AE	
Adverse event reporting additional description:	
AE additional description	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups	
Reporting group title	Extension Phase
Reporting group description:	
Extension Phase	
Reporting group title	Core Phase
Reporting group description:	
Core Phase	

Serious adverse events	Extension Phase	Core Phase	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 21 (28.57%)	79 / 287 (27.53%)	
number of deaths (all causes)	3	27	
number of deaths resulting from adverse events	0	3	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Endometrial cancer			
subjects affected / exposed	0 / 21 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma			
subjects affected / exposed	0 / 21 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to central nervous system			
subjects affected / exposed	1 / 21 (4.76%)	0 / 287 (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			

subjects affected / exposed	0 / 21 (0.00%)	1 / 287 (0.35%)	
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			
subjects affected / exposed	0 / 21 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Endocrine hypertension			
subjects affected / exposed	0 / 21 (0.00%)	1 / 287 (0.35%)	
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			
Death			
subjects affected / exposed	0 / 21 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pyrexia			
subjects affected / exposed	0 / 21 (0.00%)	3 / 287 (1.05%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 21 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperpyrexia			
subjects affected / exposed	0 / 21 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	0 / 21 (0.00%)	3 / 287 (1.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 2	

Sudden death			
subjects affected / exposed	0 / 21 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Immune system disorders			
Anaphylactic shock			
subjects affected / exposed	0 / 21 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 21 (0.00%)	4 / 287 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary artery thrombosis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 21 (0.00%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pleural effusion			
subjects affected / exposed	1 / 21 (4.76%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 21 (0.00%)	7 / 287 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 21 (0.00%)	3 / 287 (1.05%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	1 / 1	

Respiratory distress			
subjects affected / exposed	0 / 21 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 21 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety disorder			
subjects affected / exposed	0 / 21 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device dislocation			
subjects affected / exposed	0 / 21 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 21 (0.00%)	3 / 287 (1.05%)	
occurrences causally related to treatment / all	0 / 0	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 21 (0.00%)	3 / 287 (1.05%)	
occurrences causally related to treatment / all	0 / 0	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	0 / 21 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram QT prolonged			

subjects affected / exposed	0 / 21 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin decreased			
subjects affected / exposed	0 / 21 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	0 / 21 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Injury			
subjects affected / exposed	0 / 21 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	0 / 21 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 21 (0.00%)	3 / 287 (1.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	0 / 21 (0.00%)	3 / 287 (1.05%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product dispensing error			
subjects affected / exposed	0 / 21 (0.00%)	4 / 287 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			

subjects affected / exposed	0 / 21 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	0 / 21 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrioventricular block second degree			
subjects affected / exposed	0 / 21 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	0 / 21 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 21 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve stenosis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	0 / 21 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocarditis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			

subjects affected / exposed	0 / 21 (0.00%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Tremor			
subjects affected / exposed	0 / 21 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 21 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 21 (0.00%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somnolence			
subjects affected / exposed	0 / 21 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hemiparesis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	0 / 21 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coma			
subjects affected / exposed	0 / 21 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cognitive disorder			

subjects affected / exposed	0 / 21 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 21 (0.00%)	4 / 287 (1.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Aphasia			
subjects affected / exposed	0 / 21 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	0 / 21 (0.00%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	0 / 21 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	0 / 21 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	0 / 21 (0.00%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Lens dislocation			
subjects affected / exposed	0 / 21 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Rectal haemorrhage			
subjects affected / exposed	0 / 21 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	0 / 21 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 21 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric perforation			
subjects affected / exposed	0 / 21 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 21 (0.00%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 21 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	0 / 21 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hypertransaminasaemia			
subjects affected / exposed	1 / 21 (4.76%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			

subjects affected / exposed	1 / 21 (4.76%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatotoxicity			
subjects affected / exposed	0 / 21 (0.00%)	1 / 287 (0.35%)	
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			
Rash			
subjects affected / exposed	1 / 21 (4.76%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 21 (0.00%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	0 / 21 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 21 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Pathological fracture			
subjects affected / exposed	0 / 21 (0.00%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
COVID-19			

subjects affected / exposed	0 / 21 (0.00%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Campylobacter infection			
subjects affected / exposed	1 / 21 (4.76%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis A			
subjects affected / exposed	0 / 21 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 21 (0.00%)	3 / 287 (1.05%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	0 / 21 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Urinary tract infection			
subjects affected / exposed	1 / 21 (4.76%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sepsis			
subjects affected / exposed	0 / 21 (0.00%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	1 / 1	
Metabolism and nutrition disorders			
Hyperglycaemia			

subjects affected / exposed	2 / 21 (9.52%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	2 / 2	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	0 / 21 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 21 (4.76%)	3 / 287 (1.05%)	
occurrences causally related to treatment / all	0 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 21 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Extension Phase	Core Phase	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 21 (95.24%)	275 / 287 (95.82%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 21 (14.29%)	58 / 287 (20.21%)	
occurrences (all)	3	144	
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 21 (14.29%)	53 / 287 (18.47%)	
occurrences (all)	4	115	
Blood creatinine increased			
subjects affected / exposed	3 / 21 (14.29%)	28 / 287 (9.76%)	
occurrences (all)	4	83	
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 21 (9.52%)	13 / 287 (4.53%)	
occurrences (all)	2	22	

Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 21 (0.00%)	18 / 287 (6.27%)	
occurrences (all)	0	21	
Lymphocyte count decreased			
subjects affected / exposed	0 / 21 (0.00%)	16 / 287 (5.57%)	
occurrences (all)	0	28	
Neutrophil count decreased			
subjects affected / exposed	0 / 21 (0.00%)	56 / 287 (19.51%)	
occurrences (all)	0	435	
Platelet count decreased			
subjects affected / exposed	0 / 21 (0.00%)	30 / 287 (10.45%)	
occurrences (all)	0	68	
Weight decreased			
subjects affected / exposed	5 / 21 (23.81%)	6 / 287 (2.09%)	
occurrences (all)	5	6	
White blood cell count decreased			
subjects affected / exposed	0 / 21 (0.00%)	61 / 287 (21.25%)	
occurrences (all)	0	222	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 21 (4.76%)	16 / 287 (5.57%)	
occurrences (all)	1	28	
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	2 / 21 (9.52%)	11 / 287 (3.83%)	
occurrences (all)	2	14	
Headache			
subjects affected / exposed	1 / 21 (4.76%)	21 / 287 (7.32%)	
occurrences (all)	1	33	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	0 / 21 (0.00%)	32 / 287 (11.15%)	
occurrences (all)	0	109	
Neutropenia			
subjects affected / exposed	0 / 21 (0.00%)	198 / 287 (68.99%)	
occurrences (all)	0	1914	
Anaemia			

subjects affected / exposed	2 / 21 (9.52%)	105 / 287 (36.59%)	
occurrences (all)	2	327	
Leukopenia			
subjects affected / exposed	0 / 21 (0.00%)	93 / 287 (32.40%)	
occurrences (all)	0	830	
General disorders and administration site conditions			
Pain			
subjects affected / exposed	2 / 21 (9.52%)	4 / 287 (1.39%)	
occurrences (all)	2	4	
Pyrexia			
subjects affected / exposed	4 / 21 (19.05%)	56 / 287 (19.51%)	
occurrences (all)	4	78	
Oedema peripheral			
subjects affected / exposed	2 / 21 (9.52%)	14 / 287 (4.88%)	
occurrences (all)	2	17	
Mucosal inflammation			
subjects affected / exposed	5 / 21 (23.81%)	16 / 287 (5.57%)	
occurrences (all)	8	24	
Fatigue			
subjects affected / exposed	0 / 21 (0.00%)	28 / 287 (9.76%)	
occurrences (all)	0	51	
Chest pain			
subjects affected / exposed	2 / 21 (9.52%)	8 / 287 (2.79%)	
occurrences (all)	2	9	
Asthenia			
subjects affected / exposed	8 / 21 (38.10%)	89 / 287 (31.01%)	
occurrences (all)	11	174	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	12 / 21 (57.14%)	56 / 287 (19.51%)	
occurrences (all)	23	99	
Constipation			
subjects affected / exposed	1 / 21 (4.76%)	27 / 287 (9.41%)	
occurrences (all)	1	30	
Abdominal pain upper			

subjects affected / exposed	1 / 21 (4.76%)	16 / 287 (5.57%)	
occurrences (all)	1	24	
Abdominal pain			
subjects affected / exposed	1 / 21 (4.76%)	20 / 287 (6.97%)	
occurrences (all)	1	23	
Stomatitis			
subjects affected / exposed	3 / 21 (14.29%)	9 / 287 (3.14%)	
occurrences (all)	3	10	
Nausea			
subjects affected / exposed	7 / 21 (33.33%)	95 / 287 (33.10%)	
occurrences (all)	8	162	
Vomiting			
subjects affected / exposed	3 / 21 (14.29%)	47 / 287 (16.38%)	
occurrences (all)	4	68	
Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	2 / 21 (9.52%)	2 / 287 (0.70%)	
occurrences (all)	2	2	
Cough			
subjects affected / exposed	1 / 21 (4.76%)	42 / 287 (14.63%)	
occurrences (all)	1	57	
Dyspnoea			
subjects affected / exposed	2 / 21 (9.52%)	23 / 287 (8.01%)	
occurrences (all)	2	30	
Pleural effusion			
subjects affected / exposed	2 / 21 (9.52%)	1 / 287 (0.35%)	
occurrences (all)	2	1	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 21 (4.76%)	27 / 287 (9.41%)	
occurrences (all)	1	31	
Rash			
subjects affected / exposed	8 / 21 (38.10%)	32 / 287 (11.15%)	
occurrences (all)	10	55	
Pruritus			

subjects affected / exposed	3 / 21 (14.29%)	47 / 287 (16.38%)	
occurrences (all)	3	72	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 21 (4.76%)	56 / 287 (19.51%)	
occurrences (all)	1	87	
Back pain			
subjects affected / exposed	2 / 21 (9.52%)	27 / 287 (9.41%)	
occurrences (all)	2	34	
Bone pain			
subjects affected / exposed	1 / 21 (4.76%)	28 / 287 (9.76%)	
occurrences (all)	1	34	
Groin pain			
subjects affected / exposed	2 / 21 (9.52%)	1 / 287 (0.35%)	
occurrences (all)	2	2	
Musculoskeletal pain			
subjects affected / exposed	2 / 21 (9.52%)	11 / 287 (3.83%)	
occurrences (all)	2	14	
Pain in extremity			
subjects affected / exposed	0 / 21 (0.00%)	15 / 287 (5.23%)	
occurrences (all)	0	21	
Infections and infestations			
COVID-19			
subjects affected / exposed	1 / 21 (4.76%)	16 / 287 (5.57%)	
occurrences (all)	1	18	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 21 (14.29%)	23 / 287 (8.01%)	
occurrences (all)	4	31	
Hyperglycaemia			
subjects affected / exposed	14 / 21 (66.67%)	11 / 287 (3.83%)	
occurrences (all)	22	16	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 July 2018	This amendment: updated number of patients, timing of interim analysis, definition of end of study (EOS); clarified the inclusion and exclusion criteria and updated the definition of patient population; updated the management of treatment cycles in case of drug interruption and timelines or frequency of some trial assessments; updated and clarified biological sample collection timelines and assessments; updated definition of biomarker analysis set (BAS) and timing of interim analysis; added the updated references.
28 May 2019	This amendment: updated the background and rationale; updated study design, treatment, visit schedule, and safety information with alpelisib for the Extension Phase; added the statistical methods and data analysis for the Extension Phase; added the updated references; added the guidelines for alpelisib treatment.
11 December 2019	This amendment: updated clinical experience and approval information of alpelisib; added SOLAR-1 pharmacokinetic analyses and data on food effect; updated the inclusion /exclusion criteria based on alpelisib IB edition 13; updated additional guidance on missed dose instructions and follow-up on potential drug-induced liver injury (DILI); updated guidance on dose interruption/modifications, management of adverse events (AEs) associated with the use of alpelisib, and guidance for follow-up on toxicities; added general information on managing concomitant medications; updated permitted concomitant medications to be used with caution, prohibited medications, and the use of bisphosphonates/ denosumab based on updated information in relation to alpelisib; updated the list of medications according to amendment.
19 April 2023	This amendment: defined the procedure for study exit and established the possible post-trial access for alpelisib; changed detail in study procedure related to the final study visit and introduced the mechanism to ensure therapeutic continuity.

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.

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results.

Notes: