Clinical trial results:
A phase II randomized trial comparing alpelisib and fulvestrant versus chemotherapy as maintenance therapy in patients with PIK3CA mutated advanced breast cancer

Summary

EudraCT number	2017-000154-19
Trial protocol	FR
Global end of trial date	18 November 2022

Results information

Result version number	v1 (current)
This version publication date	23 October 2025
First version publication date	23 October 2025

Trial information

Trial identification

Sponsor protocol code	UC-0105/1701

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03386162
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	UNICANCER
Sponsor organisation address	101 rue de Tolbiac, Paris, France, 75015
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Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	25 October 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 July 2022
Global end of trial reached?	Yes
Global end of trial date	18 November 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Determine whether treatment with alpelisib plus fulvestrant prolongs progression-free survival (PFS) compared to maintenance chemotherapy in patients PIK3CA mutated with hormone receptor positive (HR+), HER2-negative advanced breast cancer, who do not present a progressive disease after 6-8 cycles of chemotherapy.

Protection of trial subjects:

This study was conducted in compliance with the protocol, in accordance with the French national regulatory requirements and the Declaration of Helsinki (1964) and subsequent amendments, ICH Good Clinical Practice (GCP) Guidelines (CPMP/ICH/135/95), the European Directive (2001/20/CE) and the applicable local regulatory requirements and laws.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 April 2018
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	24 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 31
Worldwide total number of subjects	31
EEA total number of subjects	31

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)	15
From 65 to 84 years	16
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

From 05-Apr-2018 to 03-Aug-2020, 31 patients were included and randomized in a 2:1 ratio across 14 centers. Thus, 20 and 11 patients were allocated to the experimental Arm A3 (alpelisib) and control Arm B3 (standard chemotherapy), respectively.

Pre-assignment

Screening details:

The main Inclusion criteria:
- Women (or men) with histologically confirmed metastatic breast cancer
- Hormone receptor positive (HR+) and no Her2 over-expression, according to local assessment.
- Presence of PIK3CA mutation on exon 9 or 20, determined on metastatic tissue specimen (frozen or FFPE) or plasma (ctDNA).

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A3: alpelisib + fulvestrant +/- LH-RH analogs

Arm description:

In the experimental Arm A3, patients were receiving:
- Alpelisib 300 mg administered orally once daily on a continuous dosing schedule starting on Cycle 1 Day 1 in a 21-day cycle, in combination with
- fulvestrant 2x250 mg intra muscular every 28 days (+/- 3 days) starting on Cycle 1 Day 1 with an additional injection on Day 15 according to Summary of Product Characteristics (SmPC) conditions.
- LH-RH agonists for premenopausal women only was administered every 28 days (+/- 3 days) according to SmPC conditions, starting on Cycle 1 Day 1.

In Arm A3, a cycle was defined as a 21-day (± 2 days) period for alpelisib.

Fulvestrant and/or LH-RH analogs were administered every 28 days independently from the 21-day cycles of alpelisib.
The last day of a complete treatment cycle was Day 21. Day 1 of the next cycle started on Day 22.

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

Dosage and administration details:

Patients received 300 mg once daily every day, starting at Day 1.

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:

As per usual practice : 2x250 mg, every 28 days, starting at Day 1, with 1 additional injection of 2x250mg at D15 after the first injection.

Investigational medicinal product name	LH-RH agonits on the market: Goserelin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Implant
Routes of administration	Subcutaneous use

Dosage and administration details:

As per usual practice : 3.6 mg every 28 days, starting at Day 1.

Investigational medicinal product name	LH-RH agonits on the market : Leuprorelin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

As per usual practice: 3.75 mg every 28 days, starting at Day 1.

Arm title	Arm B3: standard chemotherapy

Arm description:

In the control Arm B3, patients were receiving:
- Standard chemotherapy (at the investigator’s choice) continued as maintenance chemotherapy, or no antineoplastic treatment in case of toxicity.
Maintenance chemotherapy agents had to be administered and dose reduced according to SmPC recommendations and local standard practice.

Arm type	Control arm

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Arm A3: alpelisib + fulvestrant +/- LH-RH analogs	Arm B3: standard chemotherapy
Started	20	11
Completed	1	0
Not completed	19	11
Physician decision	-	2
Adverse event	5	-
RECIST progression	13	7
Study drug not administred	1	2

Baseline characteristics

Reporting groups

Reporting group title	Arm A3: alpelisib + fulvestrant +/- LH-RH analogs

Reporting group description:

In the experimental Arm A3, patients were receiving:
- Alpelisib 300 mg administered orally once daily on a continuous dosing schedule starting on Cycle 1 Day 1 in a 21-day cycle, in combination with
- fulvestrant 2x250 mg intra muscular every 28 days (+/- 3 days) starting on Cycle 1 Day 1 with an additional injection on Day 15 according to Summary of Product Characteristics (SmPC) conditions.
- LH-RH agonists for premenopausal women only was administered every 28 days (+/- 3 days) according to SmPC conditions, starting on Cycle 1 Day 1.

In Arm A3, a cycle was defined as a 21-day (± 2 days) period for alpelisib.

Fulvestrant and/or LH-RH analogs were administered every 28 days independently from the 21-day cycles of alpelisib.
The last day of a complete treatment cycle was Day 21. Day 1 of the next cycle started on Day 22.

Reporting group title	Arm B3: standard chemotherapy

Reporting group description:

In the control Arm B3, patients were receiving:
- Standard chemotherapy (at the investigator's choice) continued as maintenance chemotherapy, or no antineoplastic treatment in case of toxicity.
Maintenance chemotherapy agents had to be administered and dose reduced according to SmPC recommendations and local standard practice.

Reporting group values	Arm A3: alpelisib + fulvestrant +/- LH-RH analogs	Arm B3: standard chemotherapy	Total
Number of subjects	20	11	31
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	8	6	14
From 65-84 years	12	5	17
85 years and over	0	0	0
Age continuous Units: years			
median	66.5	58	
full range (min-max)	34 to 75	41 to 74	-
Gender categorical Units: Subjects			
Female	18	11	29
Male	2	0	2
Menopausal status Units: Subjects			
Non-menopausal	3	1	4
Post-menopausal	15	10	25

Na	2	0	2
ECOG performance status Units: Subjects			
ECOG 0	11	5	16
ECOG 1	8	5	13
Missing	1	1	2

End points

End points reporting groups

Reporting group title	Arm A3: alpelisib + fulvestrant +/- LH-RH analogs

Reporting group description:

In the experimental Arm A3, patients were receiving:
- Alpelisib 300 mg administered orally once daily on a continuous dosing schedule starting on Cycle 1 Day 1 in a 21-day cycle, in combination with
- fulvestrant 2x250 mg intra muscular every 28 days (+/- 3 days) starting on Cycle 1 Day 1 with an additional injection on Day 15 according to Summary of Product Characteristics (SmPC) conditions.
- LH-RH agonists for premenopausal women only was administered every 28 days (+/- 3 days) according to SmPC conditions, starting on Cycle 1 Day 1.

In Arm A3, a cycle was defined as a 21-day (± 2 days) period for alpelisib.

Fulvestrant and/or LH-RH analogs were administered every 28 days independently from the 21-day cycles of alpelisib.
The last day of a complete treatment cycle was Day 21. Day 1 of the next cycle started on Day 22.

Reporting group title	Arm B3: standard chemotherapy

Reporting group description:

In the control Arm B3, patients were receiving:
- Standard chemotherapy (at the investigator's choice) continued as maintenance chemotherapy, or no antineoplastic treatment in case of toxicity.
Maintenance chemotherapy agents had to be administered and dose reduced according to SmPC recommendations and local standard practice.

Primary: Progression-free survival (PFS)

End point title	Progression-free survival (PFS)

End point description:

The primary endpoint of the study was the PFS and was defined as the time from randomization to the first documented progression of disease or death, whatever the cause. The tumor assessments were made by the investigators based on RECIST 1.1 criteria. Patients still alive at the time of analysis without documented progression (including lost to follow-up) were censored at the last known alive date.

End point type	Primary

End point timeframe:

Time from randomization to the first documented progression of disease or death, whatever the cause.

End point values	Arm A3: alpelisib + fulvestrant +/- LH-RH analogs	Arm B3: standard chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	11		
Units: Months				
median (confidence interval 95%)	9.5 (3.5 to 13.3)	8.0 (1.3 to 15.5)		

Statistical analyses

Statistical analysis title	PFS analysis
Comparison groups	Arm A3: alpelisib + fulvestrant +/- LH-RH analogs v Arm B3: standard chemotherapy
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9769
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.41
upper limit	2.4

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

The Overall Survival (OS) was the time from randomization to death due to any cause. Patients still alive at the time of analysis (including lost to follow-up) were censored at the last known alive date.

End point type	Secondary

End point timeframe:

Time from randomization to death due to any cause.

End point values	Arm A3: alpelisib + fulvestrant +/- LH-RH analogs	Arm B3: standard chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	11		
Units: Patients				
Died	12	3		
Alive	8	8		

Statistical analyses

No statistical analyses for this end point

Secondary: Objective response rate (ORR)

End point title	Objective response rate (ORR)

End point description:

The objective response rate (ORR) was the percentage of patients with at least one tumor assessment demonstrating a complete response (CR) or partial response (PR) using RECIST v1.1 criteria.
The tumor assessments after first progression or treatment switching was ignored.

End point type	Secondary

End point timeframe:

Tumor response is assessed every 21 days from treatment initiation until first progression or death from any cause,

End point values	Arm A3: alpelisib + fulvestrant +/- LH-RH analogs	Arm B3: standard chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	11		
Units: percent				
number (not applicable)	22.2	25		

Statistical analyses

No statistical analyses for this end point

Secondary: PFS sensitivity analysis

End point title	PFS sensitivity analysis

End point description:

End point type	Secondary

End point timeframe:

Time from randomization to the first documented progression of disease or death, whatever the cause.

End point values	Arm A3: alpelisib + fulvestrant +/- LH-RH analogs	Arm B3: standard chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	11		
Units: Months				
median (confidence interval 95%)	7.8 (4 to 13.3)	8 (1.3 to 15.5)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from the date of the patient's signing of the informed consent, during treatment, and during follow up.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	Arm A3: alpelisib + fulvestrant +/- LH-RH analogs

Reporting group description:

In the experimental Arm A3, patients were receiving: - Alpelisib 300 mg administered orally once daily on a continuous dosing schedule starting on Cycle 1 Day 1 in a 21-day cycle, in combination with - fulvestrant 2x250 mg intra muscular every 28 days (+/- 3 days) starting on Cycle 1 Day 1 with an additional injection on Day 15 according to Summary of Product Characteristics (SmPC) conditions. - LH-RH agonists for premenopausal women only was administered every 28 days (+/- 3 days) according to SmPC conditions, starting on Cycle 1 Day 1. In Arm A3, a cycle was defined as a 21-day (± 2 days) period for alpelisib. Fulvestrant and/or LH-RH analogs were administered every 28 days independently from the 21-day cycles of alpelisib. The last day of a complete treatment cycle was Day 21. Day 1 of the next cycle started on Day 22.

Reporting group title	Arm B3: standard chemotherapy

Reporting group description:

In the control Arm B3, patients were receiving:
- Standard chemotherapy (at the investigator's choice) continued as maintenance chemotherapy, or no antineoplastic treatment in case of toxicity.
Maintenance chemotherapy agents had to be administered and dose reduced according to SmPC recommendations and local standard practice.

Serious adverse events	Arm A3: alpelisib + fulvestrant +/- LH-RH analogs	Arm B3: standard chemotherapy	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 19 (26.32%)	0 / 9 (0.00%)	
number of deaths (all causes)	12	2	
number of deaths resulting from adverse events	0	0	
Investigations			
Electrocardiogram QT corrected interval prolonged			
subjects affected / exposed	1 / 19 (5.26%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Epileptic seizure			

subjects affected / exposed	1 / 19 (5.26%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 19 (5.26%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disease progression			
subjects affected / exposed	1 / 19 (5.26%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 19 (5.26%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypoglycemia			
subjects affected / exposed	1 / 19 (5.26%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Arm A3: alpelisib + fulvestrant +/- LH-RH analogs	Arm B3: standard chemotherapy	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 19 (100.00%)	8 / 9 (88.89%)	
Vascular disorders			
Flushing			
subjects affected / exposed	1 / 19 (5.26%)	0 / 9 (0.00%)	
occurrences (all)	13	0	
Hot Flush			
subjects affected / exposed	2 / 19 (10.53%)	1 / 9 (11.11%)	
occurrences (all)	4	1	

Hypertension			
subjects affected / exposed	4 / 19 (21.05%)	0 / 9 (0.00%)	
occurrences (all)	13	0	
Lymphedema			
subjects affected / exposed	4 / 19 (21.05%)	0 / 9 (0.00%)	
occurrences (all)	18	0	
Vein disorder			
subjects affected / exposed	1 / 19 (5.26%)	0 / 9 (0.00%)	
occurrences (all)	6	0	
Venous thrombosis			
subjects affected / exposed	1 / 19 (5.26%)	0 / 9 (0.00%)	
occurrences (all)	15	0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	10 / 19 (52.63%)	5 / 9 (55.56%)	
occurrences (all)	38	31	
Fatigue			
subjects affected / exposed	6 / 19 (31.58%)	1 / 9 (11.11%)	
occurrences (all)	54	8	
Mucosal Inflammation			
subjects affected / exposed	3 / 19 (15.79%)	0 / 9 (0.00%)	
occurrences (all)	8	0	
General physical health deterioration			
subjects affected / exposed	2 / 19 (10.53%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Edema			
subjects affected / exposed	2 / 19 (10.53%)	0 / 9 (0.00%)	
occurrences (all)	3	0	
Reproductive system and breast disorders			
Breast Pain			
subjects affected / exposed	1 / 19 (5.26%)	0 / 9 (0.00%)	
occurrences (all)	5	0	
Nipple Exudate Bloody			
subjects affected / exposed	1 / 19 (5.26%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Vaginal Hemorrhage			

subjects affected / exposed	1 / 19 (5.26%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Vulvovaginal Dryness			
subjects affected / exposed	1 / 19 (5.26%)	0 / 9 (0.00%)	
occurrences (all)	6	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 19 (10.53%)	0 / 9 (0.00%)	
occurrences (all)	3	0	
Dyspnea			
subjects affected / exposed	1 / 19 (5.26%)	1 / 9 (11.11%)	
occurrences (all)	1	2	
Epistaxis			
subjects affected / exposed	1 / 19 (5.26%)	0 / 9 (0.00%)	
occurrences (all)	3	0	
Rhinorrhea			
subjects affected / exposed	0 / 19 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	2	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 19 (5.26%)	1 / 9 (11.11%)	
occurrences (all)	4	7	
Confusional State			
subjects affected / exposed	1 / 19 (5.26%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Depression			
subjects affected / exposed	1 / 19 (5.26%)	0 / 9 (0.00%)	
occurrences (all)	7	0	
Insomnia			
subjects affected / exposed	2 / 19 (10.53%)	0 / 9 (0.00%)	
occurrences (all)	7	0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 19 (5.26%)	1 / 9 (11.11%)	
occurrences (all)	1	3	
Aspartate Aminotransferase Increased			

subjects affected / exposed	1 / 19 (5.26%)	1 / 9 (11.11%)	
occurrences (all)	2	3	
Blood Alkaline Phosphatase Increased			
subjects affected / exposed	0 / 19 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	3	
Blood Bilirubin Increased			
subjects affected / exposed	1 / 19 (5.26%)	0 / 9 (0.00%)	
occurrences (all)	3	0	
Blood Creatine Phosphokinase Increased			
subjects affected / exposed	1 / 19 (5.26%)	0 / 9 (0.00%)	
occurrences (all)	3	0	
Blood Creatinine Increased			
subjects affected / exposed	2 / 19 (10.53%)	0 / 9 (0.00%)	
occurrences (all)	9	0	
Creatinine Renal Clearance Decreased			
subjects affected / exposed	1 / 19 (5.26%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Electrocardiogram Qt Prolonged			
subjects affected / exposed	1 / 19 (5.26%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Insulin C-Peptide Increased			
subjects affected / exposed	1 / 19 (5.26%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Lipase Increased			
subjects affected / exposed	1 / 19 (5.26%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Weight Decreased			
subjects affected / exposed	3 / 19 (15.79%)	0 / 9 (0.00%)	
occurrences (all)	11	0	
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 19 (5.26%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Pericarditis			

subjects affected / exposed	1 / 19 (5.26%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Tachycardia			
subjects affected / exposed	1 / 19 (5.26%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Amnesia			
subjects affected / exposed	0 / 19 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	2	
Balance disorder			
subjects affected / exposed	0 / 19 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	2	
Dysgeusia			
subjects affected / exposed	4 / 19 (21.05%)	0 / 9 (0.00%)	
occurrences (all)	17	0	
Epilepsy			
subjects affected / exposed	1 / 19 (5.26%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Headache			
subjects affected / exposed	3 / 19 (15.79%)	1 / 9 (11.11%)	
occurrences (all)	9	1	
Hepatic Encephalopathy			
subjects affected / exposed	1 / 19 (5.26%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Memory impairment			
subjects affected / exposed	1 / 19 (5.26%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Neuropathy peripheral			
subjects affected / exposed	2 / 19 (10.53%)	2 / 9 (22.22%)	
occurrences (all)	13	4	
Paresthesia			
subjects affected / exposed	2 / 19 (10.53%)	1 / 9 (11.11%)	
occurrences (all)	3	5	
Peripheral Motor Neuropathy			
subjects affected / exposed	1 / 19 (5.26%)	0 / 9 (0.00%)	
occurrences (all)	2	0	

Peripheral Sensory Neuropathy			
subjects affected / exposed	1 / 19 (5.26%)	0 / 9 (0.00%)	
occurrences (all)	6	0	
Sciatica			
subjects affected / exposed	0 / 19 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	2	
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	4 / 19 (21.05%)	0 / 9 (0.00%)	
occurrences (all)	9	0	
Lymphopenia			
subjects affected / exposed	1 / 19 (5.26%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Neutropenia			
subjects affected / exposed	1 / 19 (5.26%)	2 / 9 (22.22%)	
occurrences (all)	1	2	
Thrombocytopenia			
subjects affected / exposed	2 / 19 (10.53%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Eye disorders			
Dry eye			
subjects affected / exposed	2 / 19 (10.53%)	1 / 9 (11.11%)	
occurrences (all)	5	1	
Eczema eyelids			
subjects affected / exposed	1 / 19 (5.26%)	0 / 9 (0.00%)	
occurrences (all)	3	0	
Lacrimation Increased			
subjects affected / exposed	0 / 19 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	2	
Retinal disorder			
subjects affected / exposed	1 / 19 (5.26%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Visual Impairment			
subjects affected / exposed	1 / 19 (5.26%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			

Abdominal Distension			
subjects affected / exposed	1 / 19 (5.26%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Abdominal Pain			
subjects affected / exposed	2 / 19 (10.53%)	1 / 9 (11.11%)	
occurrences (all)	7	3	
Abdominal Pain Upper			
subjects affected / exposed	2 / 19 (10.53%)	1 / 9 (11.11%)	
occurrences (all)	4	2	
Aphthous Ulcer			
subjects affected / exposed	3 / 19 (15.79%)	0 / 9 (0.00%)	
occurrences (all)	9	0	
Constipation			
subjects affected / exposed	5 / 19 (26.32%)	1 / 9 (11.11%)	
occurrences (all)	6	3	
Diarrhoea			
subjects affected / exposed	14 / 19 (73.68%)	5 / 9 (55.56%)	
occurrences (all)	107	25	
Dry mouth			
subjects affected / exposed	2 / 19 (10.53%)	0 / 9 (0.00%)	
occurrences (all)	5	0	
Dyspepsia			
subjects affected / exposed	0 / 19 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Gastroesophageal Reflux Disease			
subjects affected / exposed	1 / 19 (5.26%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Hemorrhoids			
subjects affected / exposed	0 / 19 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	2	
Mouth Ulceration			
subjects affected / exposed	3 / 19 (15.79%)	0 / 9 (0.00%)	
occurrences (all)	6	0	
Nausea			
subjects affected / exposed	9 / 19 (47.37%)	4 / 9 (44.44%)	
occurrences (all)	32	11	

Esophagitis			
subjects affected / exposed	1 / 19 (5.26%)	1 / 9 (11.11%)	
occurrences (all)	2	1	
Stomatitis			
subjects affected / exposed	4 / 19 (21.05%)	0 / 9 (0.00%)	
occurrences (all)	7	0	
Vomiting			
subjects affected / exposed	5 / 19 (26.32%)	0 / 9 (0.00%)	
occurrences (all)	7	0	
Hepatobiliary disorders			
Cholestasis			
subjects affected / exposed	2 / 19 (10.53%)	0 / 9 (0.00%)	
occurrences (all)	4	0	
Hepatic Cytolysis			
subjects affected / exposed	2 / 19 (10.53%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	4 / 19 (21.05%)	1 / 9 (11.11%)	
occurrences (all)	30	2	
Dermatitis Acneiform			
subjects affected / exposed	1 / 19 (5.26%)	0 / 9 (0.00%)	
occurrences (all)	5	0	
Digital Pulpitis			
subjects affected / exposed	1 / 19 (5.26%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Dry skin			
subjects affected / exposed	3 / 19 (15.79%)	0 / 9 (0.00%)	
occurrences (all)	27	0	
Eczema			
subjects affected / exposed	1 / 19 (5.26%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Erythema			
subjects affected / exposed	2 / 19 (10.53%)	1 / 9 (11.11%)	
occurrences (all)	2	1	
Livedo Reticularis			

subjects affected / exposed	1 / 19 (5.26%)	0 / 9 (0.00%)	
occurrences (all)	3	0	
Mucocutaneous Rash			
subjects affected / exposed	1 / 19 (5.26%)	0 / 9 (0.00%)	
occurrences (all)	3	0	
Nail Disorder			
subjects affected / exposed	2 / 19 (10.53%)	3 / 9 (33.33%)	
occurrences (all)	8	31	
Palmar-Plantar Erythrodysaesthesia Syndrome			
subjects affected / exposed	3 / 19 (15.79%)	3 / 9 (33.33%)	
occurrences (all)	14	49	
Panniculitis			
subjects affected / exposed	1 / 19 (5.26%)	0 / 9 (0.00%)	
occurrences (all)	5	0	
Photosensitivity Reaction			
subjects affected / exposed	1 / 19 (5.26%)	0 / 9 (0.00%)	
occurrences (all)	3	0	
Plantar Erythema			
subjects affected / exposed	0 / 19 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Pruritus			
subjects affected / exposed	2 / 19 (10.53%)	0 / 9 (0.00%)	
occurrences (all)	4	0	
Rash			
subjects affected / exposed	5 / 19 (26.32%)	1 / 9 (11.11%)	
occurrences (all)	8	1	
Skin Hemorrhage			
subjects affected / exposed	1 / 19 (5.26%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Skin lesion			
subjects affected / exposed	1 / 19 (5.26%)	0 / 9 (0.00%)	
occurrences (all)	4	0	
Subcutaneous Abscess			
subjects affected / exposed	1 / 19 (5.26%)	0 / 9 (0.00%)	
occurrences (all)	1	0	

Urticaria			
subjects affected / exposed	1 / 19 (5.26%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Xeroderma			
subjects affected / exposed	1 / 19 (5.26%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 19 (5.26%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Renal Failure			
subjects affected / exposed	4 / 19 (21.05%)	0 / 9 (0.00%)	
occurrences (all)	14	0	
Endocrine disorders			
Adrenal Hemorrhage			
subjects affected / exposed	1 / 19 (5.26%)	0 / 9 (0.00%)	
occurrences (all)	10	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 19 (26.32%)	2 / 9 (22.22%)	
occurrences (all)	22	4	
Back Pain			
subjects affected / exposed	2 / 19 (10.53%)	2 / 9 (22.22%)	
occurrences (all)	8	3	
Muscle Spasms			
subjects affected / exposed	6 / 19 (31.58%)	0 / 9 (0.00%)	
occurrences (all)	25	0	
Muscular weakness			
subjects affected / exposed	1 / 19 (5.26%)	0 / 9 (0.00%)	
occurrences (all)	3	0	
Musculoskeletal Chest Pain			
subjects affected / exposed	0 / 19 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Myalgia			
subjects affected / exposed	1 / 19 (5.26%)	1 / 9 (11.11%)	
occurrences (all)	2	2	

Neck Pain			
subjects affected / exposed	2 / 19 (10.53%)	0 / 9 (0.00%)	
occurrences (all)	3	0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 19 (5.26%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Conjunctivitis			
subjects affected / exposed	0 / 19 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	2	
Cystitis			
subjects affected / exposed	1 / 19 (5.26%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Dermo-Hypodermitis			
subjects affected / exposed	1 / 19 (5.26%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Ear infection			
subjects affected / exposed	1 / 19 (5.26%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Fungal infection			
subjects affected / exposed	1 / 19 (5.26%)	1 / 9 (11.11%)	
occurrences (all)	1	1	
Localized Infection			
subjects affected / exposed	0 / 19 (0.00%)	2 / 9 (22.22%)	
occurrences (all)	0	3	
Nail Infection			
subjects affected / exposed	0 / 19 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Paronychia			
subjects affected / exposed	1 / 19 (5.26%)	0 / 9 (0.00%)	
occurrences (all)	4	0	
Pneumonia			
subjects affected / exposed	1 / 19 (5.26%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Rash pustular			

subjects affected / exposed	1 / 19 (5.26%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Respiratory Tract Infection			
subjects affected / exposed	0 / 19 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Rhinitis			
subjects affected / exposed	0 / 19 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Tooth abscess			
subjects affected / exposed	1 / 19 (5.26%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Urinary Tract Infection			
subjects affected / exposed	2 / 19 (10.53%)	0 / 9 (0.00%)	
occurrences (all)	6	0	
Metabolism and nutrition disorders			
Cell Death			
subjects affected / exposed	2 / 19 (10.53%)	1 / 9 (11.11%)	
occurrences (all)	2	1	
Decreased Appetite			
subjects affected / exposed	10 / 19 (52.63%)	0 / 9 (0.00%)	
occurrences (all)	52	0	
Diabetes Mellitus			
subjects affected / exposed	1 / 19 (5.26%)	0 / 9 (0.00%)	
occurrences (all)	4	0	
Hyperglycemia			
subjects affected / exposed	12 / 19 (63.16%)	0 / 9 (0.00%)	
occurrences (all)	94	0	
Hyperkalemia			
subjects affected / exposed	1 / 19 (5.26%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Hyperuricemia			
subjects affected / exposed	1 / 19 (5.26%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Hypoglycemia			
subjects affected / exposed	3 / 19 (15.79%)	0 / 9 (0.00%)	
occurrences (all)	4	0	

Hypokalemia subjects affected / exposed occurrences (all)	3 / 19 (15.79%) 12	0 / 9 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 December 2017	- Modification of the investigators list
09 February 2018	- Modification of the investigators list
05 April 2018	- Modification of the investigators list
20 June 2019	- Modification of the study protocol: 1- Following national recommendations update, inclusion criteria N°27 (uracilemia < 16 ng/ml) was added to prevent severe or fatal toxicities in patients having a partial or total enzyme deficiency in dihydropyrimidine dehydrogenase (DPD) 2- Addition of a blood sample collection for the ancillary study on ctDNA - Updated version of the alpelisib (BYL719) investigator brochure (Version 10, 12-Jul-2017 and Version 11, 05-Jul-2018) with impact on the safety patients and/or protocol: 1- A second Stevenson Johnson Syndrome case and 2 new cases of erythema multiform had been reported. 2- Several adverse reactions already described had a frequency changed (dry mouth, vertigo, and nail loss). The informed consent form had been updated. Patient care and follow-up remained appropriate and unchanged in protocol 3- Two cases of anaphylactic shock were reported as probably related to alpelisib treatment in combination studies (one with ribociclib and one with cetuximab). The risk of anaphylactic shock was classified as uncommon and had been added to the informed consent form. Patient care and follow-up remained appropriate and unchanged in protocol 4- Three cases of increased lipase levels were added as likely related to alpelisib treatment in combination studies with cetuximab, AUY922 (Novartis) or fulvestrant. 5-The section on severe skin reactions had been updated to reinforce the management of these toxicities and the protocol was updated with these new instructions 6- Addition of contraceptive methods, preclinical studies in rats and rabbits, and hepatic disturbances were added to the IB. Protocol was not updated - Modification of the of the informed consent form: compliance with the new data protection regulation - Modification of the investigators list

11 March 2020	- Modification of the study protocol to extend the inclusion period by 15 months (from 30 months to 45 months) - Updated version of the alpelisib (BYL719) investigator brochure (Version 12, 26-Jul-2019 and Version 13, 10-Oct-2019) with impact on the safety patients and/or protocol: 1- In the version 12, a single table reporting the expected severe adverse reactions with alpelisib and fulvestrant was added: - One severe adverse reaction, osteonecrosis of the jaw, was added - Some severe adverse reactions described in previous version were not mentioned anymore - Some severe expected adverse reactions changed in frequency (i.e. acute renal failure changed from uncommon to common) - New adverse events were described 2- In the version 13, a new potential reaction was added; drug hypersensitivity syndrome (DRESS). - Modification of the study protocol: - Addition of osteonecrosis of the jaw in the safety section and non-inclusion criteria N°28. Patient care and follow-up remained appropriate and unchanged in protocol - Addition of DRESS in the safety section. Patient care and follow-up remained appropriate and unchanged in protocol - Modification of the informed consent form consistent with the BI updates - Modification of the investigators list
27 June 2022	- On the 03-Aug-2020, the sponsor and the co-investigator conjointly decided to an early and permanently stop of patients inclusions in the study. The decision was based on the low recruitment noticed on Aug-2020, with only 31 patients mutated in the PI3K gene included out of the 90 patients expected in 30 months. The end of the SAFIR02 Breast molecular screening study (2013-001652-36), which until then had made it possible to identify anomalies of the PI3KCA gene, had make it more difficult to reach the objective of 90 patients included. Two patients in the Arm A3 (alpelisib) were still under treatment and completed the study as planned in the protocol. The IEC and the AC were notified by letter on the 10-Aug-2020 and 13-Sep-2021, respectively. - On the 21-Jul-2022, no patients were currently taken alpelisib treatment and nine patients were in post-treatment follow-up. It was no longer necessary to collect long-term follow-up data as the study could not be analyzed based on its endpoints. The early and definitive termination of all patients monitoring in the SAFIR-PI3K study was notified by letter on the 27-Jun-2022 to the IEC and the ANSM.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date

03 August 2020	The sponsor and the co-investigator conjointly decided to an early and permanently stop of patients inclusions in the study. The decision was based on the low recruitment noticed on Aug-2020, with only 31 patients mutated in the PI3K gene included out of the 90 patients expected in 30 months. The end of the SAFIR02 Breast molecular screening study (2013-001652-36), which until then had made it possible to identify anomalies of the PI3KCA gene, had make it more difficult to reach the objective of 90 patients included. Two patients in the Arm A3 (alpelisib) were still under treatment and completed the study as planned in the protocol. The IEC and the AC were notified by letter on the 10-Aug-2020 and 13-Sep-2021, respectively.	-

Notes:

Limitations and caveats

None reported