Sponsor

Novartis.

Generic Drug Name

Ribociclib/buparlisib

Trial Indication(s)

Locally advanced or metastatic breast cancer

Protocol Number

CLEE011A2112C

Protocol Title

A Phase I dose escalation study of LEE011 in combination with buparlisib and letrozole for the treatment of HR+, HER2-negative post-menopausal women with locally advanced or metastatic breast cancer

Clinical Trial Phase

Phase I

Phase of Drug Development

Phase IV (LEE011)/Phase III (BKM120)

Study Start/End Dates

First patient enrolled: 27-Jun-2014 (first patient first visit)

Last patient completed: 30-Oct-2016 (last patient last visit).

Reason for Termination (If applicable)

The study was terminated early, because the study treatment combination was not tolerated at low doses. Based on the review of the emerging safety data from the trial, it was unanimously agreed to by the Principal Investigators at the second Dose Escalation Meeting, to stop enrollment in the study. The decision was made after careful review of the clinical safety and the pharmacokinetics (PK) profile data from the first two cohorts showing that even at low doses of ribociclib and buparlisib with standard dose of letrozole, the combination was not tolerable. The decision was made to not enroll any new patients on the study. However, patients from the first two cohorts could remain in the study if the Investigator believed that the patient could be benefitting from the ongoing treatment.

Due to the aforementioned reason, the expansion phase of the study was not initiated.

Study Design/Methodology

This was an open label, multi-center Phase I dose-escalation and dose-expansion study investigating the safety and tolerability, PK, pharmacodynamics, and preliminary efficacy of the triple combination of letrozole + ribociclib + buparlisib in postmenopausal women with HR+/HER2-negative locally advanced or metastatic breast cancer.

Centers

Five centers in two participating countries: US (4) and Spain (1)

Objectives:

Primary objectives

Dose escalation

To estimate the maximum tolerated dose (MTD) and/or recommended phase two dose (RP2D) of the triple combination, letrozole, ribociclib + buparlisib in patients with HR+/HER2-negative advanced breast cancer by evaluating the incidence of dose-limiting toxicity (DLTs) in the first cycle of treatment.

Dose expansion

To further characterize the safety and tolerability of the triple combination at the RP2D.

Secondary objectives

Dose escalation

To characterize the safety and tolerability of the triple combination,

To characterize the PK profiles of ribociclib, buparlisib, and letrozole when given in combination; as well as to evaluate any other clinically significant metabolites that could be identified.

Dose expansion

To further characterize the PK profiles of ribociclib, buparlisib, and letrozole when given in combination; as well as to evaluate any other clinically significant metabolites that could be identified,

To assess preliminary anti-cancer activity of letrozole + ribociclib + buparlisib.

Test Product (s), Dose(s), and Mode(s) of Administration

Capsule for oral use of ribociclib 50 mg or 200 mg (daily dose: 200 mg; days 1-21);

Capsule for oral use of buparlisib 10 mg or 50 mg (daily dose: 40 mg; days 1-28);

Oral tablets of letrozole 2.5 mg (daily dose: 2.5 mg; days 1-28).

Statistical Methods

An adaptive Bayesian logistic regression model (BLRM) guided by the escalation with overdose control principle was used to make dose recommendations and estimate the MTD during the dose-escalation phase of the study. This analysis was carried out in dose determining set.

PK parameters were summarized based on each individual plasma concentration-time profile of patients.

Preliminary tumor activity was planned to be assessed using overall response rate and progression free survival (PFS) time. PFS times were planned to be summarized in each cohort (ribociclib 200 mg+ buparlisib 40 mg + letrozole 2.5 mg or ribociclib 200 mg+ buparlisib 30 mg + letrozole 2.5 mg) according to Kaplan-Meier methodology.

Safety analyses were carried out using the Safety set. BLRM analysis for dose escalation and MTD decisions were based on dose determining set. PK analysis was carried out based on PK analysis set. All other analyses were carried out in Full Analysis set.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria

Female patients aged 18 years or older with histologically and/or cytologically confirmed diagnosis of breast cancer (radiologic evidence of inoperable locally advanced or metastatic breast cancer). Patients had HER2-negative, estrogen-receptor positive and/or progesterone receptor positive breast cancer.

Exclusion criteria

Patient had received prior treatment with CDK4/6 or PI3K pathway inhibitor;

Patient with known hypersensitivity to any of the excipients of letrozole, ribociclib, or buparlisib;

Patients with inflammatory breast cancer;

Patient had a concurrent malignancy or malignancy within 3 years of study enrollment with the exception of adequately treated in situ carcinoma of any type, basal cell carcinoma, squamous cell carcinoma, non-melanomatous skin cancer, or curatively resected cervical cancer;

Patients who were receiving treatment with agents that are known to cause QTc prolongation in humans;

Patient had symptomatic central nervous system (CNS) metastases;

Patient had active cardiac disease or a history of cardiac dysfunction;

Patient was currently receiving any of the following medications:

That are known strong inducers or inhibitors of CYP3A4,

That have a known risk to prolong the QT interval or induce Torsades de Pointes,

That have a narrow therapeutic window and are predominantly metabolized through CYP3A4.

Certain scores on an anxiety and depression mood questionnaires;

Patient had a medically documented history of or active major depressive episode, bipolar disorder (I or II), obsessive-compulsive disorder, schizophrenia, a history of suicidal attempt or ideation, or homicidal ideation (e.g., risk of doing harm to self or others), or with active severe personality disorders (defined according to DSM-IV);

Diabetes as defined by fasting plasma glucose >120 mg/dL or HbA1C >8%.

Participant Flow Table

Patient disposition by treatment (Full analysis set)

Disposition Reason	200 mg LEE011 + 40 mg BKM120 + 2.5 mg LET N=7 n (%)	200 mg LEE011 + 30 mg BKM120 + 2.5 mg LET N=6 n (%)	All patients N=13 n (%)
Patients Treated	**7 (100.0)**	**6 (100.0)**	**13 (100.0)**
Treatment ongoing*	0	0	0
End of treatment	7 (100.0)	6 (100.0)	13 (100.0)
Primary reason for end of treatment			
Adverse event	3 (42.9)	2 (33.3)	5 (38.5)
Physician decision	0	1 (16.7)	1 (7.7)
Progressive disease	3 (42.9)	3 (50.0)	6 (46.2)
Subject/guardian decision	1 (14.3)	0	1 (7.7)

* Patients ongoing at the time of the cut-off 29-Dec-2016.

- Percentage is based on N.

- End of treatment reasons were reported on last visit within [last day of treatment and (last day of treatment +30)] days period.

Baseline Characteristics

Demographics by treatment group (Full analysis set)

Demographic variable	200 mg LEE011 + 40 mg BKM120 + 2.5 mg LET N=7	200 mg LEE011 + 30 mg BKM120+ 2.5 mg LET N=6	All patients N=13
Age (years)			
n	7	6	13
Mean	60.3	52.8	56.8
SD	5.99	11.27	9.26
Median	61.0	51.5	57.0
Minimum	53.0	37.0	37.0
Maximum	69.0	68.0	69.0
Age category (years) -n (%)			
<65 Years	5 (71.4)	5 (83.3)	10 (76.9)
>=65 Years	2 (28.6)	1 (16.7)	3 (23.1)
Sex -n (%)			
Female	7 (100)	6 (100)	13 (100)
Race -n (%)			
Caucasian	7 (100)	6 (100)	13 (100)
Ethnicity -n (%)			
Hispanic/Latino	1 (14.3)	2 (33.3)	3 (23.1)
Not Reported	2 (28.6)	1 (16.7)	3 (23.1)
Other	3 (42.9)	1 (16.7)	4 (30.8)
Unknown	1 (14.3)	2 (33.3)	3 (23.1)

Demographic variable	200 mg LEE011 + 40 mg BKM120 + 2.5 mg LET N=7	200 mg LEE011 + 30 mg BKM120+ 2.5 mg LET N=6	All patients N=13
Weight (kg)			
n	7	6	13
Mean	75.3	61.1	68.8
SD	15.97	8.48	14.55
Median	71.0	60.8	68.0
Minimum	56.0	50.2	50.2
Maximum	105.2	72.6	105.2
Height (cm)			
n	7	6	13
Mean	164.3	155.6	160.3
SD	5.34	5.52	6.85
Median	165.1	157.5	160.0
Minimum	157.5	147.0	147.0
Maximum	170.2	160.6	170.2
Body mass index (kg/m^2)			
n	7	6	13
Mean	27.8	25.2	26.6
SD	4.63	2.58	3.91
Median	26.0	24.1	25.6
Minimum	22.6	22.8	22.6
Maximum	36.3	28.8	36.3
ECOG performance status -n (%)			
0	2 (28.6)	4 (66.7)	6 (46.2)
1	5 (71.4)	2 (33.3)	7 (53.8)

Primary Outcome Result(s)

Dose limiting toxicities by primary system organ class, preferred term and treatment (Dose determining set)

	200 mg LEE011 + 40 mg BKM120 + 2.5 mg LET N=6 n (%)	200 mg LEE011 + 30 mg BKM120 + 2.5 mg LET N=4 n (%)	All patients N=10 n (%)
Any primary system organ class			
Total	1 (16.7)	0	1 (10.0)
Investigations			
Total	1 (16.7)	0	1 (10.0)
Gamma-glutamyltransferase increased	1 (16.7)	0	1 (10.0)

The study was terminated without declaring MTD and RP2D.

Secondary Outcome Result(s)

Summary of Efficacy

	200 mg LEE011 + 40 mg BKM120 + 2.5 mg LET N=7 n (%)	200 mg LEE011 + 30 mg BKM120 + 2.5 mg LET N=6 n (%)	All patients N=13 n (%)
Best overall response			
Complete response	0	0	0
Stable disease	2 (28.6)	4 (66.7)	6 (46.2)
Non-complete response non-progressive disease	3 (42.9)	0	3 (23.1)
Progressive disease	1 (14.3)	2 (33.3)	3 (23.1)
Unknown	1 (14.3)	0	1 (7.7)

Summary of pharmacokinetics

Pharmacokinetics for LEE011 (Cmax)

End point values	200 + 40 + 2.5 mg	200 + 30 + 2.5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3[2]	6[3]		
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
C1D1 - Cmax	147.8 (± 10.6)	202.8 (± 37.7)		
C1D15 - Cmax	290.1 (± 7.1)	353.2 (± 44.8)		
C2D15 - Cmax	300.0 (± 0.0)	300.0 (± 0.5)		

Notes:

[2] - For C1D1 n =3, For C1D15 n = 2, For C2D15 n = 1

[3] - For C1D1 n = 6, For C1D15 n = 2, For C2D15 n = 2

Pharmacokinetics for LEE011 (Tmax)

End point values	200 + 40 + 2.5 mg	200 + 30 + 2.5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3[4]	6[5]		
Units: hours				
median (full range (min-max))				
C1D1 - Tmax	3.9 (2 to 4.3)	4.1 (2 to 5.8)		
C1D15 - Tmax	5.7 (3.9 to 7.6)	3 (2.1 to 3.9)		
C2D15 - Tmax	1.9 (1.9 to 1.9)	4.1 (2 to 6.3)		

Notes:

[4] - For C1D1 n =3, For C1D15 n = 2, For C2D15 n = 1

[5] - For C1D1 n =6, For C1D15 n = 2, For C2D15 n = 2

Pharmacokinetics for LEE011 (AUC0-24h)

End point values	200 + 40 + 2.5 mg	200 + 30 + 2.5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3[6]	6[7]		
Units: hr*ng/mL				
geometric mean (geometric coefficient of variation)				
C1D1	1772.7 (± 33.2)	2093.4 (± 71.8)		
C1D15	4777.4 (± 16.2)	4343.5 (± 97.1)		
C2D15	3168.9 (± 0)	3487.0 (± 29.3)		

Notes:

[6] - For C1D1 n =3, For C1D15 n = 2, For C2D15 n = 1

[7] - For C1D1 n =6, For C1D15 n = 2, For C2D15 n = 2

Pharmacokinetics for BKM120 (Cmax)

End point values	200 + 40 + 2.5 mg	200 + 30 + 2.5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4[8]	6[9]		
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
C1D1 - Cmax	292.4 (± 47.7)	233.1 (± 38.2)		
C1D15 - Cmax	836.1 (± 18.4)	501.2 (± 4.7)		
C2D15 - Cmax	832.0 (± 0)	353.5 (± 34.4)		

Notes:

[8] - For C1D1 n = 4, For C1D15 n = 2, For C2D15 n = 1

[9] - For C1D1 n = 6, For C1D15 n = 2, For C2D15 n = 2

Pharmacokinetics for BKM120 (Tmax)

End point values	200 + 40 + 2.5 mg	200 + 30 + 2.5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4[10]	6[11]		
Units: hours				
median (full range (min-max))				
C1D1 - Tmax	1.5 (1 to 2.2)	1.7 (1 to 4.1)		
C1D15 - Tmax	2.9 (1.9 to 4)	1.5 (1.1 to 1.9)		
C2D15 - Tmax	1 (1 to 1)	3.1 (2 to 4.3)		

Notes:

[10] - For C1D1 n = 4, For C1D15 n = 2, For C2D15 n = 1

[11] - For C1D1 n = 6, For C1D15 n = 2, For C2D15 n = 2

Pharmacokinetics for BKM120 (AUC0-24h)

End point values	200 + 40 + 2.5 mg	200 + 30 + 2.5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4[12]	6[13]		
Units: hr*ng/mL				
geometric mean (geometric coefficient of variation)				
C1D1	2533.1 (± 26.0)	2037.7 (± 28.3)		
C1D15	13927.9 (± 5.5)	7108.0 (± 51.1)		
C2D15	11148.0 (± 0)	5686.5 (± 16.5)		

Notes:

[12] - For C1D1 n = 4, For C1D15 n = 2, For C2D15 n = 1

[13] - For C1D1 n = 6, For C1D15 n = 2, For C2D15 n = 2

Pharmacokinetics for Letrozole (Cmax)

End point values	200 + 40 + 2.5 mg	200 + 30 + 2.5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4[14]	6[15]		
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
C1D1 - Cmax	23.0 (± 60.8)	34.5 (± 47.3)		
C1D15 - Cmax	145.0 (± 0)	102.0 (± 6.8)		
C2D15 - Cmax	67.6 (± 51.3)	134.5 (± 17.9)		

Notes:

[14] - For C1D1 n = 4, For C1D15 n = 1, For C2D15 n = 3

[15] - For C1D1 n = 6, For C1D15 n = 2, For C2D15 n = 3

Pharmacokinetics for Letrozole (Tmax)

End point values	200 + 40 + 2.5 mg	200 + 30 + 2.5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4[16]	6[17]		
Units: hours				
median (full range (min-max))				
C1D1 - Tmax	2 (1 to 2.2)	2.1 (1 to 4.1)		
C1D15 - Tmax	4 (4 to 4)	4 (2.1 to 6)		
C2D15 - Tmax	1.9 (0.9 to 2.1)	4.2 (4 to 4.3)		

Notes:

[16] - For C1D1 n = 4, For C1D15 n = 1, For C2D15 n = 3

[17] - For C1D1 n = 6, For C1D15 n = 2, For C2D15 n = 3

Pharmacokinetics for Letrozole (AUC0-24h)

End point values	200 + 40 + 2.5 mg	200 + 30 + 2.5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4[18]	6[19]		
Units: hr*ng/mL				
geometric mean (geometric coefficient of variation)				
C1D1	337.1 (± 36.4)	489.2 (± 59.3)		
C1D15	2722.7 (± 0)	2156.9 (± 1.3)		
C2D15	1225.0 (± 67.9)	2652.1 (± 21.9)		

Notes:

[18] - For C1D1 n = 4, For C1D15 n = 1, For C2D15 n = 3

[19] - For C1D1 n = 6, For C1D15 n = 2, For C2D15 n = 3

Pharmacokinetics for LEQ803, a metabolite of LEE011 (Cmax)

End point values	200 + 40 + 2.5 mg	200 + 30 + 2.5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3[20]	6[21]		
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
C1D1 - Cmax	18.2 (± 63.7)	27.9 (± 24.9)		
C1D15 - Cmax	76.1 (± 55.9)	82.4 (± 33.8)		
C2D15 - Cmax	48.6 (± 0)	63.5 (± 3.5)		

Notes:

[20] - For C1D1 n = 3, For C1D15 n = 2, For C2D15 n = 1

[21] - For C1D1 n = 6, For C1D15 n = 2, For C2D15 n = 2

Pharmacokinetics for LEQ803, a metabolite of LEE011 (Tmax)

End point values	200 + 40 + 2.5 mg	200 + 30 + 2.5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3[22]	6[23]		
Units: hours				
median (full range (min-max))				
C1D1 - Tmax	3.9 (2 to 7.5)	4.2 (2 to 5.8)		
C1D15 - Tmax	6.6 (5.5 to 7.6)	4.9 (2.1 to 7.7)		
C2D15 - Tmax	1.9 (1.9 to 1.9)	5.1 (4 to 6.3)		

Notes:

[22] - For C1D1 n = 3, For C1D15 n = 2, For C2D15 n = 1

[23] - For C1D1 n = 6, For C1D15 n = 2, For C2D15 n = 2

Pharmacokinetics for LEQ803, a metabolite of LEE011 (AUC0-24h)

End point values	200 + 40 + 2.5 mg	200 + 30 + 2.5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3[24]	6[25]		
Units: hr*ng/mL				
geometric mean (geometric coefficient of variation)				
C1D1	301.7 (± 62.7)	373.3 (± 27.0)		
C1D15	1437.4 (± 57.0)	1421.6 (± 47.3)		
C2D15	887.0 (± 0)	1043.5 (± 1.7)		

Notes:

[24] - For C1D1 n = 3, For C1D15 n = 2, For C2D15 n = 1

[25] - For C1D1 n = 6, For C1D15 n = 2, For C2D15 n = 1

Summary of Safety

Safety Results

Overview of adverse events (Safety set)

Category	200 mg LEE011 + 40 mg BKM120 + 2.5 mg LET N=7		200 mg LEE011 + 30 mg BKM120 + 2.5 mg LET N=6		All patients N=13	
	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Adverse events (AEs)	7 (100)	6 (85.7)	6 (100)	4 (66.7)	13 (100)	10 (76.9)
Treatment-related	7 (100)	6 (85.7)	6 (100)	3 (50.0)	13 (100)	9 (69.2)
Serious AEs	0	0	1 (16.7)	1 (16.7)	1 (7.7)	1 (7.7)
Treatment-related	0	0	1 (16.7)	1 (16.7)	1 (16.7)	1 (16.7)
Deaths	0	0	0	0	0	0
AEs leading to discontinuation	3 (42.9)	0	2 (33.3)	1 (16.7)	5 (38.5)	1 (7.7)
Treatment-related	3 (42.9)	0	2 (33.3)	1 (16.7)	5 (38.5)	1 (7.7)
AEs leading to dose adjustment or interruption	7 (100)	5 (71.4)	5 (83.3)	3 (50.0)	12 (92.3)	8 (61.5)

Adverse events, regardless of study drug relationship by system organ class, maximum grade and treatment (Safety set)

Primary system organ class	200 mg LEE011 + 40 mg BKM120 + 2.5 mg LET N=7		200 mg LEE011 + 30 mg BKM120 + 2.5 mg LET N=6		All patients N=13	
	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
-Total	**7 (100)**	**6 (85.7)**	**6 (100)**	**4 (66.7)**	**13 (100)**	**10 (76.9)**
Investigations	7 (100)	5 (71.4)	5 (83.3)	2 (33.3)	12 (92.3)	7 (53.8)

Primary system organ class	200 mg LEE011 + 40 mg BKM120 + 2.5 mg LET N=7		200 mg LEE011 + 30 mg BKM120 + 2.5 mg LET N=6		All patients N=13	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Gastrointestinal disorders	6 (85.7)	1 (14.3)	4 (66.7)	1 (16.7)	10 (76.9)	2 (15.4)
General disorders and administration site conditions	5 (71.4)	0	3 (50.0)	0	8 (61.5)	0
Metabolism and nutrition disorders	3 (42.9)	1 (14.3)	5 (83.3)	3 (50.0)	8 (61.5)	4 (30.8)
Musculoskeletal and connective tissue disorders	4 (57.1)	0	4 (66.7)	0	8 (61.5)	0
Skin and subcutaneous tissue disorders	2 (28.6)	0	5 (83.3)	0	7 (53.8)	0
Infections and infestations	2 (28.6)	0	4 (66.7)	1 (16.7)	6 (46.2)	1 (7.7)
Nervous system disorders	4 (57.1)	0	2 (33.3)	0	6 (46.2)	0
Respiratory, thoracic and mediastinal disorders	3 (42.9)	0	2 (33.3)	0	5 (38.5)	0
Vascular disorders	3 (42.9)	1 (14.3)	2 (33.3)	0	5 (38.5)	1 (7.7)
Blood and lymphatic system disorders	1 (14.3)	0	2 (33.3)	1 (16.7)	3 (23.1)	1 (7.7)
Psychiatric disorders	1 (14.3)	0	2 (33.3)	0	3 (23.1)	0
Injury, poisoning and procedural complications	2 (28.6)	0	0	0	2 (15.4)	0
Renal and urinary disorders	1 (14.3)	0	1 (16.7)	0	2 (15.4)	0
Reproductive system and breast disorders	1 (14.3)	0	1 (16.7)	0	2 (15.4)	0
Eye disorders	0	0	1 (16.7)	0	1 (7.7)	0
Immune system disorders	0	0	1 (16.7)	0	1 (7.7)	0

- Primary system organ classes are sorted in descending frequency in the “All patients” “All grades” column.
- A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment with maximum grade.
- A patient with multiple adverse events is counted only once in the total row.
- AEs up to 30 days after the last study treatment were included.
- MedDRA Version 19.1 has been used for the reporting of adverse events.

Adverse events, regardless of study drug relationship by preferred term, maximum grade and treatment (in at least 10%; all patients, all grades) (Safety set)

Preferred Term	200 mg LEE011 + 40 mg BKM120 + 2.5 mg LET N=7		200 mg LEE011 + 30 mg BKM120 + 2.5 mg LET N=6		All patients N=13	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
-Total	**7 (100)**	**6 (85.7)**	**6 (100)**	**4 (66.7)**	**13 (100)**	**10 (76.9)**
Alanine aminotransferase increased	5 (71.4)	3 (42.9)	4 (66.7)	2 (33.3)	9 (69.2)	5 (38.5)

Preferred Term	200 mg LEE011 + 40 mg BKM120 + 2.5 mg LET N=7		200 mg LEE011 + 30 mg BKM120 + 2.5 mg LET N=6		All patients N=13	
	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Aspartate aminotransferase increased	5 (71.4)	3 (42.9)	4 (66.7)	1 (16.7)	9 (69.2)	4 (30.8)
Fatigue	4 (57.1)	0	2 (33.3)	0	6 (46.2)	0
Diarrhoea	2 (28.6)	1 (14.3)	3 (50.0)	1 (16.7)	5 (38.5)	2 (15.4)
Decreased appetite	0	0	4 (66.7)	0	4 (30.8)	0
Arthralgia	2 (28.6)	0	1 (16.7)	0	3 (23.1)	0
Back pain	2 (28.6)	0	1 (16.7)	0	3 (23.1)	0
Cough	1 (14.3)	0	2 (33.3)	0	3 (23.1)	0
Dizziness	2 (28.6)	0	1 (16.7)	0	3 (23.1)	0
Nausea	2 (28.6)	0	1 (16.7)	0	3 (23.1)	0
Neutropenia	1 (14.3)	0	2 (33.3)	1 (16.7)	3 (23.1)	1 (7.7)
Rash maculo-papular	0	0	3 (50.0)	0	3 (23.1)	0
Abdominal pain	0	0	2 (33.3)	0	2 (15.4)	0
Anxiety	1 (14.3)	0	1 (16.7)	0	2 (15.4)	0
Blood alkaline phosphatase increased	2 (28.6)	1 (14.3)	0	0	2 (15.4)	1 (7.7)
Blood creatinine increased	2 (28.6)	0	0	0	2 (15.4)	0
Gamma-glutamyltransferase increased	2 (28.6)	1 (14.3)	0	0	2 (15.4)	1 (7.7)
Headache	1 (14.3)	0	1 (16.7)	0	2 (15.4)	0
Hyperglycaemia	1 (14.3)	0	1 (16.7)	1 (16.7)	2 (15.4)	1 (7.7)
Hypokalaemia	1 (14.3)	0	1 (16.7)	1 (16.7)	2 (15.4)	1 (7.7)
Hypophosphataemia	0	0	2 (33.3)	2 (33.3)	2 (15.4)	2 (15.4)
Hypotension	2 (28.6)	0	0	0	2 (15.4)	0
Leukopenia	1 (14.3)	0	1 (16.7)	0	2 (15.4)	0
Nasal congestion	1 (14.3)	0	1 (16.7)	0	2 (15.4)	0
Neutrophil count decreased	0	0	2 (33.3)	0	2 (15.4)	0
Non-cardiac chest pain	0	0	2 (33.3)	0	2 (15.4)	0
Pollakiuria	1 (14.3)	0	1 (16.7)	0	2 (15.4)	0
Somnolence	1 (14.3)	0	1 (16.7)	0	2 (15.4)	0
Upper respiratory tract infection	1 (14.3)	0	1 (16.7)	0	2 (15.4)	0
Vomiting	2 (28.6)	0	0	0	2 (15.4)	0
White blood cell count decreased	0	0	2 (33.3)	0	2 (15.4)	0

- A subject with multiple adverse events is counted only once in the total row.
- A subject with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment with maximum grade.
- Preferred terms are sorted in descending frequency in the “All patients” “All grades” column.
- AEs up to 30 days after the last study treatment were included.
- MedDRA Version 19.1 has been used for the reporting of adverse events.

Other Relevant Findings

None.

Conclusion

The study was terminated early due to an unfavorable safety profile with the study drug combination (ribociclib, buparlisib, and letrozole). Both ribociclib and letrozole exposure did not appear to be affected by the dosing level of buparlisib. Additionally both drugs did not influence buparlisib pharmacokinetics suggesting the lack of potential drug-drug interactions.

The maximum tolerated dose and the recommended phase II dose were not declared. As limited data were collected, antitumor activity could not be adequately assessed.

Date of Clinical Trial Report

21-Jul-2017