Novartis Clinical Trial Results

Sponsor

Novartis

Generic Drug Name

Alpelisib

Trial Indication(s)

Advanced solid tumors

Protocol Number

CBYL719Z2102

Protocol Title

A phase Ib dose-finding study of BYL719 plus everolimus and BYL719 plus everolimus plus exemestane in patients with advanced solid tumors, with dose-expansion cohorts in renal cell cancer (RCC), pancreatic neuroendocrine tumors (pNETs), and advanced breast cancer (BC) patients.

Clinical Trial Phase

Phase Ib

Phase of Drug Development

Phase Ib

Study Start/End Dates

14-May-2014 to 12-Apr-2019

Reason for Termination (If applicable)

NA

Study Design/Methodology

This was a Phase Ib, open-label, multi-center, dose-finding study of alpelisib and everolimus in subjects with advanced solid tumors, and of alpelisib, everolimus and exemestane in advanced breast cancer subjects. The initial dose level of alpelisib was 300 milligram (mg) every day (qd) and everolimus was initially administered at 2.5 mg qd. The dose-finding study (escalation phase) was followed by an expansion phase where safety and preliminary efficacy of the doublet (alpelisib and everolimus) as well as of the triplet (alpelisib, everolimus and exemestane) were assessed in selected subject populations.

Centers

21 centers in 9 countries: France (3), Germany (4), Hong Kong (1), Hungary (1), Italy (4), Netherlands (2), Spain (3), United Kingdom (1), United States (2).

Objectives:

Primary objective(s)

Dose escalation phase:

The primary objectives of the study was:

- To determine the maximum tolerated dose/ recommended dose for expansion (MTD/RDE) of alpelisib in combination with everolimus, and the MTD/RDE of alpelisib in combination with everolimus and exemestane.

Secondary objective(s)

The Secondary objectives of the study were:

- To describe safety and tolerability of the doublet and triplet combination.
- To evaluate whether alpelisib affects the pharmacokinetics of everolimus and determine the magnitude of the drug-drug-interaction.
- To characterize the pharmacokinetics (PK) of alpelisib, BZG791 and everolimus; and of alpelisib, BZG791, everolimus and exemestane when administered together.

Dose expansion phase:

The primary objectives of the study was:

- To describe safety and tolerability of the doublet by cohort and then pooled for the doublet, and by treatment (alpelisib and exemestane and triplet combination based on the overall population of PIK3C [a gene which encodes the p110alpha catalytic subunit] mutant and non-mutant) for the breast cancer (BC) expansion.

Secondary objective(s)

The Secondary objectives of the study were:

- To explore preliminary signs of efficacy of alpelisib and everolimus in selected subject populations by cohort.
- To evaluate other antitumor activity parameters such as response rate, clinical benefit rate, and duration of response by cohort for the doublet and by treatment (alpelisib and exemestane, and triplet combination based on the overall population of PIK3CA mutant and non-mutant) for the BC expansion.

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

Each subject received the combination of alpelisib and everolimus. They were administered orally once daily starting on Day 1 in a 28-day cycle. In the doublet escalation phase, alpelisib was administered at 300 mg or 250 mg in combination with 2.5 mg everolimus. In the triplet escalation phase, alpelisib was administered at 200 mg in combination with 2.5 mg everolimus and 25 mg exemestane. In the doublet expansion phase, alpelisib was administered at 250 mg in combination with 2.5 mg everolimus. In the breast cancer expansion phase, alpelisib was administered at 200 mg in combination with 2.5 mg everolimus and 25 mg exemestane or alpelisib was administered at 250 mg in combination with 25 mg exemestane.

Statistical Methods

- Three interim-analysis were performed in this study:
    - To support the declared MTD/RDE of the doublet combination (alpelisib and everolimus)
    - To support the declared MTD/RDE of the triplet combination (alpelisib, everolimus and exemestane) were performed after all subjects enrolled in the respective dose escalation phases have completed Day 35 or have discontinued study treatment
    - To evaluate impact of alpelisib co-administration on the pharmacokinetics of everolimus and determine the magnitude of the drug-drug-interaction

- The primary variable for the dose escalation phase was the incidence of dose limiting toxicities in the first 35 days. Estimation of the MTD/RDE of the combination treatment was based upon the estimation of the probability of dose limiting toxicity (DLT) in the first 35 days for subjects in the dose-determining analysis set (DDS).
- For the final analysis, cumulative safety data was analyzed for all patients randomized in the study up to LPLV (12-Apr-2019).
- Specific groupings of Adverse Events of Special Interest (AESI) were considered and the number of subjects with at least one event in each grouping were reported. Such groups consisted of AEs for which there was a specific clinical interest in connection with alpelisib or everolimus treatment (i.e. where alpelisib / everolimus may influence a common mechanism of action responsible for triggering them) or AEs which were similar in nature (although not identical).

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria

- Patient is an adult ≥ 18 years old who has signed the Informed Consent Form prior to any screening procedures being performed and is able to comply with protocol requirement.
- Patient has tumor tissue available for the analysis of PI3K signaling.
- Patients has an eastern cooperative oncology group performance status less than or equal to (<=) 2
- Patient has adequate bone marrow and organ function
- Patient is able to swallow and retain oral medication
- Patient has either measurable or non-measurable disease as per response evaluation criteria in solid tumor (RECIST 1.1)

Exclusion Criteria

- Patient has received previous treatment with a Phosphatidylinositol 3-kinase (PI3K) and/or Protein Kinase B (AKT) and/or mammalian target of rapamycin (mTOR) inhibitor (e.g. sirolimus, temsirolimus, deforolimus). Prior mTOR inhibitor treatment is allowed only in the mTOR inhibitor-pretreated patients' cohort (expansion cohort 3).
- Known intolerance or hypersensitivity to everolimus or other rapamycin analogs (e.g. sirolimus, temsirolimus).
- Patient with primary central nervous system (CNS) tumor or CNS tumor involvement.
- Patient with diabetes mellitus, or documented steroid-induced diabetes mellitus.
- Patient has a clinically significant cardiac disease or impaired cardiac function, or has any severe and/or uncontrolled medical conditions.
- Pregnant or nursing (lactating) women.

Participant Flow Table

Subject disposition by dose level - Doublet escalation phase (Full analysis set)

	Alpelisib 300mg + Everolimus 2.5mg N=7 n (%)	Alpelisib 250mg + Everolimus 2.5mg N=6 n (%)	All subjects N=13 n (%)
Subjects treated			
Discontinued from treatment	7 (100)	6 (100)	13 (100)
Reason for discontinuation			
Progressive disease	3 (42.9)	4 (66.7)	7 (53.8)
Adverse event	2 (28.6)	2 (33.3)	4 (30.8)
Death	1 (14.3)	0	1 (7.7)
Physician decision	1 (14.3)	0	1 (7.7)
Post-treatment follow-up for subjects who discontinued treatment			
Did not enter post-treatment follow-up	4 (57.1)	4 (66.7)	8 (61.5)
Entered post-treatment follow-up, discontinued	3 (42.9)	2 (33.3)	5 (38.5)
Reason for discontinuation			
Death	2 (28.6)	0	2 (15.4)
Progressive disease	1 (14.3)	1 (16.7)	2 (15.4)
Lost to follow-up	0	1 (16.7)	1 (7.7)

Subject disposition by dose level - Triplet escalation phase (Full analysis set)

	Alpelisib 200mg + Everolimus 2.5mg + Exemestane 25mg N=7 n (%)
Subjects treated	
Discontinued from treatment	7 (100)
Reason for discontinuation	
Subject/guardian decision	4 (57.1)
Progressive disease	2 (28.6)
Adverse event	1 (14.3)
Post-treatment follow-up for subjects who discontinued treatment	
Did not enter post-treatment follow-up	7 (100)

Subject disposition by cohort - Doublet expansion phase (Full analysis set)

	RCC N=21	pNET N=17	Prior mTOR N=10	All subjects N=48
	n (%)	n (%)	n (%)	n (%)
Subjects treated				
Discontinued from treatment	21 (100)	17 (100)	10 (100)	48 (100)
Reason for discontinuation				
Progressive disease	13 (61.9)	12 (70.6)	8 (80.0)	33 (68.8)
Adverse event	2 (9.5)	3 (17.6)	1 (10.0)	6 (12.5)
Subject/guardian decision	4 (19.0)	2 (11.8)	0	6 (12.5)
Physician decision	1 (4.8)	0	1 (10.0)	2 (4.2)
Death	1 (4.8)	0	0	1 (2.1)
Post-treatment follow-up for subjects who discontinued treatment				
Did not enter post-treatment follow-up	18 (85.7)	15 (88.2)	9 (90.0)	42 (87.5)
Entered post-treatment follow-up, discontinued	3 (14.3)	2 (11.8)	1 (10.0)	6 (12.5)
Reason for discontinuation				
Death	0	1 (5.9)	1 (10.0)	2 (4.2)
Progressive disease	2 (9.5)	0	0	2 (4.2)
New therapy for study indication	0	1 (5.9)	0	1 (2.1)
Subject/guardian decision	1 (4.8)	0	0	1 (2.1)

Planned starting doses for the Doublet are BYL719 250 mg + Everolimus 2.5 mg

Subject disposition by treatment - Breast Cancer expansion phase (Full analysis set)

	Alpelisib 200mg + Everolimus 2.5mg + Exemestane 25mg N=8 n (%)	Alpelisib 250mg + Exemestane 25mg N=3 n (%)	All subjects N=11 n (%)
Subjects randomized/treated			
Discontinued from treatment	8 (100)	3 (100)	11 (100)
Treated	8 (100)	3 (100)	11 (100)
Reason for discontinuation			
Adverse event	4 (50.0)	0	4 (36.4)
Progressive disease	3 (37.5)	3 (100)	6 (54.5)
Subject/guardian decision	1 (12.5)	0	1 (9.1)
Post-treatment follow-up for subjects who discontinued treatment			
Did not enter post-treatment follow-up	6 (75.0)	1 (33.3)	7 (63.6)
Entered cross-over phase	0	2 (66.7)	2 (18.2)
Entered post-treatment follow-up, discontinued	2 (25.0)	0	2 (18.2)
Reason for discontinuation			
New therapy for study indication	2 (25.0)	0	2 (18.2)

Baseline Characteristics

Demographics and baseline characteristics by dose level - Doublet escalation phase (Full analysis set)

Demographic Variable	Alpelisib 300mg + Everolimus 2.5mg N=7	Alpelisib 250mg + Everolimus 2.5mg N=6	All subjects N=13
Age (Years)			
n	7	6	13
Mean (SD)	60.1 (13.41)	63.8 (7.99)	61.8 (10.96)
Median	54.0	67.0	65.0
Q1-Q3	49.0 - 76.0	56.0 - 70.0	52.0 - 70.0
Min-Max	46 - 77	52 - 71	46 - 77
Age category -n (%)			
18 - <65	4 (57.1)	2 (33.3)	6 (46.2)
65 - <85	3 (42.9)	4 (66.7)	7 (53.8)
Sex -n (%)			
Female	4 (57.1)	5 (83.3)	9 (69.2)
Male	3 (42.9)	1 (16.7)	4 (30.8)
Race -n (%)			
White	7 (100)	5 (83.3)	12 (92.3)
Unknown	0	1 (16.7)	1 (7.7)
Ethnicity -n (%)			
Other	6 (85.7)	5 (83.3)	11 (84.6)
Unknown	1 (14.3)	1 (16.7)	2 (15.4)
Weight (kg)			
n	7	6	13
Mean (SD)	75.3 (14.81)	77.3 (14.89)	76.2 (14.26)
Median	76.6	71.3	76.2
Q1-Q3	56.2 - 85.8	68.0 - 86.0	68.0 - 85.8
Min-Max	56 - 96	64 - 103	56 - 103

Demographic Variable	Alpelisib 300mg + Everolimus 2.5mg N=7	Alpelisib 250mg + Everolimus 2.5mg N=6	All subjects N=13
Height (cm)			
n	7	6	13
Mean (SD)	166.2 (16.25)	160.5 (6.41)	163.6 (12.56)
Median	162.6	161.5	162.6
Q1-Q3	152.0 - 186.0	154.0 - 167.0	153.0 - 167.0
Min-Max	149 - 187	152 - 167	149 - 187
Body Mass Index (kg/m2)			
n	7	6	13
Mean (SD)	27.6 (6.39)	30.0 (5.38)	28.7 (5.84)
Median	25.2	30.5	26.6
Q1-Q3	22.9 - 36.4	26.6 - 30.8	24.0 - 30.8
Min-Max	22 - 37	23 - 39	22 - 39
ECOG performance status - n (%)			
0	2 (28.6)	2 (33.3)	4 (30.8)
1	4 (57.1)	4 (66.7)	8 (61.5)
2	1 (14.3)	0	1 (7.7)
3	0	0	0
4	0	0	0

Demographics and baseline characteristics by dose level - Triplet escalation phase (Full analysis set)

Demographic Variable	Alpelisib 200mg + Everolimus 2.5mg + Exemestane 25mg N=7
Age (Years)	
n	7
Mean (SD)	61.7 (9.27)
Median	63.0
Q1-Q3	52.0 - 71.0
Min-Max	47 - 72
Age category -n (%)	
18 - <65	4 (57.1)
65 - <85	3 (42.9)
Sex -n (%)	
Female	7 (100)
Race -n (%)	
White	7 (100)
Ethnicity -n (%)	
Other	7 (100)
Weight (kg)	
n	7
Mean (SD)	68.1 (17.04)
Median	63.0
Q1-Q3	53.0 - 90.0
Min-Max	50 - 92

Demographic Variable	Alpelisib 200mg + Everolimus 2.5mg + Exemestane 25mg N=7
Height (cm)	
n	7
Mean (SD)	161.9 (4.30)
Median	163.0
Q1-Q3	160.0 - 164.0
Min-Max	154 - 168
Body Mass Index (kg/m2)	
n	7
Mean (SD)	26.0 (6.14)
Median	26.6
Q1-Q3	20.7 - 31.9
Min-Max	19 - 35
ECOG performance status - n (%)	
0	6 (85.7)
1	1 (14.3)
2	0
3	0
4	0

Demographics and baseline characteristics by cohort - Doublet expansion phase (Full analysis set)

Demographic variable	RCC N=21	pNET N=17	Prior mTOR N=10	All subjects N=48
Age (years)				
Mean (SD)	60.7 (10.19)	62.1 (12.46)	57.7 (9.24)	60.5 (10.77)
Median	62.0	63.0	59.0	60.5
Min-Max	41 - 80	45 - 83	40 - 76	40 - 83
Age category -n (%)				
18 - <65	13 (61.9)	10 (58.8)	9 (90.0)	32 (66.7)
65 - <85	8 (38.1)	7 (41.2)	1 (10.0)	16 (33.3)
Sex -n (%)				
Male	16 (76.2)	11 (64.7)	3 (30.0)	30 (62.5)
Female	5 (23.8)	6 (35.3)	7 (70.0)	18 (37.5)
Race -n (%)				
White	20 (95.2)	15 (88.2)	10 (100)	45 (93.8)
Asian	1 (4.8)	1 (5.9)	0	2 (4.2)
Unknown	0	1 (5.9)	0	1 (2.1)
Weight (kg)				
Mean (SD)	76.8 (15.54)	72.1 (15.60)	67.6 (12.87)	73.2 (15.17)
Median	75.8	72.6	68.0	72.7
Min-Max	52 - 116	44 - 100	49 - 84	44 - 116
ECOG performance status – n (%)				
0	9 (42.9)	12 (70.6)	6 (60.0)	27 (56.3)
1	10 (47.6)	5 (29.4)	3 (30.0)	18 (37.5)
2	2 (9.5)	0	1 (10.0)	3 (6.3)

Planned starting doses for the Doublet are BYL719 250 mg + Everolimus 2.5 mg

Demographics and baseline characteristics by treatment - Breast Cancer expansion phase (Full analysis set)

Demographic Variable	Alpelisib 200mg + Everolimus 2.5mg + Exemestane 25mg N=8	Alpelisib 250mg + Exemestane 25mg N=3	All subjects N=11
Age (Years)			
n	8	3	11
Mean (SD)	60.8 (6.94)	53.7 (19.66)	58.8 (11.04)
Median	59.0	46.0	59.0
Q1-Q3	57.0 - 64.5	39.0 - 76.0	51.0 - 66.0
Min-Max	51 - 74	39 - 76	39 - 76
Age category -n (%)			
18 - <65	6 (75.0)	2 (66.7)	8 (72.7)
65 - <85	2 (25.0)	1 (33.3)	3 (27.3)
Sex -n (%)			
Female	8 (100)	3 (100)	11 (100)
Race -n (%)			
White	7 (87.5)	2 (66.7)	9 (81.8)
Asian	1 (12.5)	1 (33.3)	2 (18.2)
Ethnicity -n (%)			
Other	5 (62.5)	1 (33.3)	6 (54.5)
East Asian	1 (12.5)	0	1 (9.1)
Hispanic or Latino	1 (12.5)	0	1 (9.1)
Not reported	1 (12.5)	2 (66.7)	3 (27.3)
Weight (kg)			
n	8	3	11
Mean (SD)	63.1 (7.29)	60.1 (8.28)	62.3 (7.27)
Median	62.0	62.3	62.3
Q1-Q3	56.8 - 69.9	50.9 - 67.0	55.1 - 68.7
Min-Max	55 - 73	51 - 67	51 - 73

Demographic Variable	Alpelisib 200mg + Everolimus 2.5mg + Exemestane 25mg N=8	Alpelisib 250mg + Exemestane 25mg N=3	All subjects N=11
Height (cm)			
n	8	3	11
Mean (SD)	160.6 (9.80)	157.0 (4.58)	159.6 (8.61)
Median	157.3	156.0	156.0
Q1-Q3	154.0 - 171.0	153.0 - 162.0	153.0 - 170.0
Min-Max	147 - 173	153 - 162	147 - 173
Body Mass Index (kg/m2)			
n	8	3	11
Mean (SD)	24.5 (2.22)	24.4 (3.02)	24.5 (2.30)
Median	24.7	25.5	25.0
Q1-Q3	23.3 - 26.1	20.9 - 26.6	22.7 - 26.6
Min-Max	20 - 27	21 - 27	20 - 27
ECOG performance status - n (%)			
0	7 (87.5)	3 (100)	10 (90.9)
1	1 (12.5)	0	1 (9.1)
2	0	0	0
3	0	0	0
4	0	0	0

Primary Outcome Result(s)

Dose limiting toxicities occurring during the first 35 days of treatment by preferred term by dose level - Doublet escalation phase (Dose determining set).

Primary system organ class Preferred term	Alpelisib 300mg + Everolimus 2.5mg N=3 n (%)	Alpelisib 250mg + Everolimus 2.5mg N=6 n (%)	Alpelisib 200mg + Everolimus 2.5mg N=1 n (%)
Number of subjects with at least one event	2 (66.7)	2 (33.3)	1 (100)
Gastrointestinal disorders	1 (33.3)	0	1 (100)
Diarrhoea	1 (33.3)	0	1 (100)
Stomatitis	0	0	1 (100)
Metabolism and nutrition disorders	1 (33.3)	2 (33.3)	0
Hyperglycaemia	1 (33.3)	1 (16.7)	0
Hypocalcaemia	0	1 (16.7)	0

Dose Limiting Toxicities occurring during the first 35 days of treatment by system organ class and preferred term, by dose level - Triplet escalation phase (Dose determining set)

Primary system organ class Preferred term	Alpelisib 200mg + Everolimus 2.5mg + Exemestane 25mg N=7 n (%)
Number of subjects with at least one event	1 (14.3)
Renal and urinary disorders	1 (14.3)
Acute kidney injury	1 (14.3)

Adverse events by system organ class by cohort - Doublet expansion phase (Safety set)

Primary system organ class	RCC N=21		pNET N=17		Prior mTOR N=10		All subjects N=48	
	All Grades n (%)	Grade >=3 n (%)	All Grades n (%)	Grade >=3 n (%)	All Grades n (%)	Grade >=3 n (%)	All Grades n (%)	Grade >=3 n (%)
Number of subjects with at least one event	21 (100)	19 (90.5)	17 (100)	14 (82.4)	10 (100)	5 (50.0)	48 (100)	38 (79.2)
Metabolism and nutrition disorders	19 (90.5)	10 (47.6)	15 (88.2)	7 (41.2)	8 (80.0)	4 (40.0)	42 (87.5)	21 (43.8)
Gastrointestinal disorders	18 (85.7)	3 (14.3)	13 (76.5)	6 (35.3)	8 (80.0)	0	39 (81.3)	9 (18.8)
General disorders and administration site conditions	17 (81.0)	3 (14.3)	10 (58.8)	2 (11.8)	5 (50.0)	1 (10.0)	32 (66.7)	6 (12.5)
Investigations	13 (61.9)	4 (19.0)	7 (41.2)	2 (11.8)	4 (40.0)	1 (10.0)	24 (50.0)	7 (14.6)
Infections and infestations	11 (52.4)	2 (9.5)	7 (41.2)	4 (23.5)	4 (40.0)	1 (10.0)	22 (45.8)	7 (14.6)
Skin and subcutaneous tissue disorders	12 (57.1)	2 (9.5)	9 (52.9)	0	1 (10.0)	0	22 (45.8)	2 (4.2)
Musculoskeletal and connective tissue disorders	10 (47.6)	2 (9.5)	6 (35.3)	1 (5.9)	4 (40.0)	1 (10.0)	20 (41.7)	4 (8.3)
Respiratory, thoracic and mediastinal disorders	12 (57.1)	4 (19.0)	7 (41.2)	2 (11.8)	1 (10.0)	0	20 (41.7)	6 (12.5)
Blood and lymphatic system disorders	9 (42.9)	3 (14.3)	7 (41.2)	0	3 (30.0)	2 (20.0)	19 (39.6)	5 (10.4)
Nervous system disorders	10 (47.6)	1 (4.8)	6 (35.3)	0	2 (20.0)	1 (10.0)	18 (37.5)	2 (4.2)
Psychiatric disorders	8 (38.1)	0	4 (23.5)	1 (5.9)	1 (10.0)	0	13 (27.1)	1 (2.1)
Renal and urinary disorders	5 (23.8)	1 (4.8)	4 (23.5)	0	3 (30.0)	1 (10.0)	12 (25.0)	2 (4.2)
Eye disorders	4 (19.0)	0	3 (17.6)	0	1 (10.0)	0	8 (16.7)	0
Vascular disorders	2 (9.5)	1 (4.8)	4 (23.5)	1 (5.9)	1 (10.0)	0	7 (14.6)	2 (4.2)
Cardiac disorders	3 (14.3)	0	2 (11.8)	1 (5.9)	0	0	5 (10.4)	1 (2.1)

Primary system organ class	RCC N=21		pNET N=17		Prior mTOR N=10		All subjects N=48	
	All Grades n (%)	Grade >=3 n (%)	All Grades n (%)	Grade >=3 n (%)	All Grades n (%)	Grade >=3 n (%)	All Grades n (%)	Grade >=3 n (%)
Injury, poisoning and procedural complications	3 (14.3)	1 (4.8)	2 (11.8)	0	0	0	5 (10.4)	1 (2.1)
Reproductive system and breast disorders	3 (14.3)	1 (4.8)	1 (5.9)	0	1 (10.0)	0	5 (10.4)	1 (2.1)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	4 (19.0)	2 (9.5)	0	0	0	0	4 (8.3)	2 (4.2)
Hepatobiliary disorders	1 (4.8)	0	1 (5.9)	0	0	0	2 (4.2)	0
Congenital, familial and genetic disorders	1 (4.8)	0	0	0	0	0	1 (2.1)	0
Ear and labyrinth disorders	0	0	0	0	1 (10.0)	0	1 (2.1)	0
Endocrine disorders	1 (4.8)	0	0	0	0	0	1 (2.1)	0
Social circumstances	1 (4.8)	0	0	0	0	0	1 (2.1)	0

Planned starting doses for the Doublet are BYL719 250 mg + Everolimus 2.5 mg
Numbers (n) represent counts of subjects.
A subject with multiple severity grades for a SOC is only counted under the maximum grade.
MedDRA version 22.0, CTCAE version 4.03.

Adverse events by preferred term regardless of study drug relationship by cohort (at least 5% in All subjects) - Doublet expansion phase (Safety set)

Preferred term	RCC N=21		pNET N=17		Prior mTOR N=10		All subjects N=48	
	All Grades n (%)	Grade >=3 n (%)	All Grades n (%)	Grade >=3 n (%)	All Grades n (%)	Grade >=3 n (%)	All Grades n (%)	Grade >=3 n (%)
Number of subjects with at least one event	21 (100)	19 (90.5)	17 (100)	14 (82.4)	10 (100)	5 (50.0)	48 (100)	38 (79.2)
Hyperglycaemia	13 (61.9)	7 (33.3)	9 (52.9)	6 (35.3)	6 (60.0)	3 (30.0)	28 (58.3)	16 (33.3)
Diarrhoea	12 (57.1)	2 (9.5)	10 (58.8)	2 (11.8)	4 (40.0)	0	26 (54.2)	4 (8.3)
Decreased appetite	11 (52.4)	2 (9.5)	9 (52.9)	0	5 (50.0)	0	25 (52.1)	2 (4.2)
Stomatitis	9 (42.9)	0	7 (41.2)	2 (11.8)	3 (30.0)	0	19 (39.6)	2 (4.2)
Fatigue	12 (57.1)	2 (9.5)	5 (29.4)	0	0	0	17 (35.4)	2 (4.2)
Nausea	7 (33.3)	0	4 (23.5)	0	3 (30.0)	0	14 (29.2)	0
Anaemia	7 (33.3)	2 (9.5)	4 (23.5)	0	2 (20.0)	2 (20.0)	13 (27.1)	4 (8.3)
Rash	8 (38.1)	0	5 (29.4)	0	0	0	13 (27.1)	0
Vomiting	3 (14.3)	0	4 (23.5)	2 (11.8)	4 (40.0)	0	11 (22.9)	2 (4.2)
Asthenia	2 (9.5)	1 (4.8)	3 (17.6)	1 (5.9)	4 (40.0)	0	9 (18.8)	2 (4.2)
Oedema peripheral	7 (33.3)	0	1 (5.9)	0	1 (10.0)	0	9 (18.8)	0
Weight decreased	5 (23.8)	0	3 (17.6)	0	1 (10.0)	0	9 (18.8)	0
Abdominal pain	4 (19.0)	0	3 (17.6)	0	1 (10.0)	0	8 (16.7)	0
Cough	6 (28.6)	0	2 (11.8)	0	0	0	8 (16.7)	0
Dysgeusia	3 (14.3)	0	4 (23.5)	0	1 (10.0)	0	8 (16.7)	0
Pruritus	8 (38.1)	1 (4.8)	0	0	0	0	8 (16.7)	1 (2.1)
Pyrexia	3 (14.3)	0	4 (23.5)	0	1 (10.0)	0	8 (16.7)	0
Headache	4 (19.0)	0	3 (17.6)	0	0	0	7 (14.6)	0
Hypertriglyceridaemia	4 (19.0)	1 (4.8)	1 (5.9)	1 (5.9)	2 (20.0)	1 (10.0)	7 (14.6)	3 (6.3)
Blood creatinine increased	5 (23.8)	0	1 (5.9)	0	0	0	6 (12.5)	0

Preferred term	RCC N=21		pNET N=17		Prior mTOR N=10		All subjects N=48	
	All Grades n (%)	Grade >=3 n (%)	All Grades n (%)	Grade >=3 n (%)	All Grades n (%)	Grade >=3 n (%)	All Grades n (%)	Grade >=3 n (%)
Number of subjects with at least one event	21 (100)	19 (90.5)	17 (100)	14 (82.4)	10 (100)	5 (50.0)	48 (100)	38 (79.2)
Hyperglycaemia	13 (61.9)	7 (33.3)	9 (52.9)	6 (35.3)	6 (60.0)	3 (30.0)	28 (58.3)	16 (33.3)
Diarrhoea	12 (57.1)	2 (9.5)	10 (58.8)	2 (11.8)	4 (40.0)	0	26 (54.2)	4 (8.3)
Decreased appetite	11 (52.4)	2 (9.5)	9 (52.9)	0	5 (50.0)	0	25 (52.1)	2 (4.2)
Stomatitis	9 (42.9)	0	7 (41.2)	2 (11.8)	3 (30.0)	0	19 (39.6)	2 (4.2)
Fatigue	12 (57.1)	2 (9.5)	5 (29.4)	0	0	0	17 (35.4)	2 (4.2)
Nausea	7 (33.3)	0	4 (23.5)	0	3 (30.0)	0	14 (29.2)	0
Anaemia	7 (33.3)	2 (9.5)	4 (23.5)	0	2 (20.0)	2 (20.0)	13 (27.1)	4 (8.3)
Rash	8 (38.1)	0	5 (29.4)	0	0	0	13 (27.1)	0
Vomiting	3 (14.3)	0	4 (23.5)	2 (11.8)	4 (40.0)	0	11 (22.9)	2 (4.2)
Asthenia	2 (9.5)	1 (4.8)	3 (17.6)	1 (5.9)	4 (40.0)	0	9 (18.8)	2 (4.2)
Oedema peripheral	7 (33.3)	0	1 (5.9)	0	1 (10.0)	0	9 (18.8)	0
Weight decreased	5 (23.8)	0	3 (17.6)	0	1 (10.0)	0	9 (18.8)	0
Abdominal pain	4 (19.0)	0	3 (17.6)	0	1 (10.0)	0	8 (16.7)	0
Cough	6 (28.6)	0	2 (11.8)	0	0	0	8 (16.7)	0
Dysgeusia	3 (14.3)	0	4 (23.5)	0	1 (10.0)	0	8 (16.7)	0
Pruritus	8 (38.1)	1 (4.8)	0	0	0	0	8 (16.7)	1 (2.1)
Pyrexia	3 (14.3)	0	4 (23.5)	0	1 (10.0)	0	8 (16.7)	0
Headache	4 (19.0)	0	3 (17.6)	0	0	0	7 (14.6)	0
Hypertriglyceridaemia	4 (19.0)	1 (4.8)	1 (5.9)	1 (5.9)	2 (20.0)	1 (10.0)	7 (14.6)	3 (6.3)
Blood creatinine increased	5 (23.8)	0	1 (5.9)	0	0	0	6 (12.5)	0

Preferred term	RCC N=21		pNET N=17		Prior mTOR N=10		All subjects N=48	
	All Grades n (%)	Grade >=3 n (%)	All Grades n (%)	Grade >=3 n (%)	All Grades n (%)	Grade >=3 n (%)	All Grades n (%)	Grade >=3 n (%)
Abdominal pain upper	0	0	3 (17.6)	1 (5.9)	0	0	3 (6.3)	1 (2.1)
Acute kidney injury	2 (9.5)	1 (4.8)	1 (5.9)	0	0	0	3 (6.3)	1 (2.1)
Bone pain	2 (9.5)	1 (4.8)	1 (5.9)	0	0	0	3 (6.3)	1 (2.1)
Flank pain	1 (4.8)	0	2 (11.8)	1 (5.9)	0	0	3 (6.3)	1 (2.1)
Haemorrhoids	2 (9.5)	0	1 (5.9)	0	0	0	3 (6.3)	0
Influenza like illness	2 (9.5)	0	1 (5.9)	0	0	0	3 (6.3)	0
Lipase increased	3 (14.3)	2 (9.5)	0	0	0	0	3 (6.3)	2 (4.2)
Muscle spasms	3 (14.3)	0	0	0	0	0	3 (6.3)	0
Neutropenia	0	0	3 (17.6)	0	0	0	3 (6.3)	0
Pain in extremity	2 (9.5)	1 (4.8)	1 (5.9)	0	0	0	3 (6.3)	1 (2.1)
Pneumonia	1 (4.8)	1 (4.8)	2 (11.8)	2 (11.8)	0	0	3 (6.3)	3 (6.3)
Rash maculo-papular	3 (14.3)	1 (4.8)	0	0	0	0	3 (6.3)	1 (2.1)
Thrombocytopenia	1 (4.8)	0	2 (11.8)	0	0	0	3 (6.3)	0
Vision blurred	2 (9.5)	0	1 (5.9)	0	0	0	3 (6.3)	0

Planned starting doses for the Doublet are BYL719 250 mg + Everolimus 2.5 mg
Numbers (n) represent counts of subjects.
A subject with multiple severity grades for an AE is only counted under the maximum grade.
MedDRA version 22.0, CTCAE version 4.03.

Dose adjustments and discontinuation of study treatment by cohort - Doublet expansion phase (Safety set)

	RCC		pNET	
	Alpelisib N=21 n (%)	Everolimus N=21 n (%)	Alpelisib N=17 n (%)	Everolimus N=17 n (%)
Number of subjects - n(%)				
With no dose reduction and/or interruption	5 (23.8)	4 (19.0)	3 (17.6)	3 (17.6)
With at least one dose reduction and/or interruption	16 (76.2)	17 (81.0)	14 (82.4)	14 (82.4)
Dose reductions				
Number of subjects - n(%)				
With no dose reduction	14 (66.7)	NA	8 (47.1)	NA
With at least one dose reduction	7 (33.3)	NA	9 (52.9)	NA
Only one dose reduction	4 (19.0)	NA	5 (29.4)	NA
Two dose reductions	2 (9.5)	NA	4 (23.5)	NA
More than two dose reductions	1 (4.8)	NA	0	NA
Number of subjects with at least one dose reduction by reason - n(%)				
Adverse Event	5 (23.8)	NA	8 (47.1)	NA
Physician Decision	2 (9.5)	NA	2 (11.8)	NA
Dosing Error	1 (4.8)	NA	0	NA
Dose interruptions				
Number of subjects - n(%)				
With no dose interruption	5 (23.8)	4 (19.0)	3 (17.6)	3 (17.6)
With at least one dose interruption	16 (76.2)	17 (81.0)	14 (82.4)	14 (82.4)
Only one dose interruption	9 (42.9)	10 (47.6)	4 (23.5)	4 (23.5)
Two dose interruptions	3 (14.3)	3 (14.3)	6 (35.3)	9 (52.9)
More than two dose interruptions	4 (19.0)	4 (19.0)	4 (23.5)	1 (5.9)

	Prior mTOR		All subjects	
	Alpelisib N=10 n (%)	Everolimus N=10 n (%)	Alpelisib N=48 n (%)	Everolimus N=48 n (%)
Number of subjects - n(%)				
With no dose reduction and/or interruption	4 (40.0)	4 (40.0)	12 (25.0)	11 (22.9)
With at least one dose reduction and/or interruption	6 (60.0)	6 (60.0)	36 (75.0)	37 (77.1)
Dose reductions				
Number of subjects - n(%)				
With no dose reduction	7 (70.0)	NA	29 (60.4)	NA
With at least one dose reduction	3 (30.0)	NA	19 (39.6)	NA
Only one dose reduction	1 (10.0)	NA	10 (20.8)	NA
Two dose reductions	2 (20.0)	NA	8 (16.7)	NA
More than two dose reductions	0	NA	1 (2.1)	NA
Number of subjects with at least one dose reduction by reason - n(%)				
Adverse Event	3 (30.0)	NA	16 (33.3)	NA
Physician Decision	0	NA	4 (8.3)	NA
Dosing Error	0	NA	1 (2.1)	NA
Dose interruptions				
Number of subjects - n(%)				
With no dose interruption	4 (40.0)	4 (40.0)	12 (25.0)	11 (22.9)
With at least one dose interruption	6 (60.0)	6 (60.0)	36 (75.0)	37 (77.1)
Only one dose interruption	1 (10.0)	1 (10.0)	14 (29.2)	15 (31.3)
Two dose interruptions	1 (10.0)	1 (10.0)	10 (20.8)	13 (27.1)
More than two dose interruptions	4 (40.0)	4 (40.0)	12 (25.0)	9 (18.8)

	RCC		pNET	
	Alpelisib N=21 n (%)	Everolimus N=21 n (%)	Alpelisib N=17 n (%)	Everolimus N=17 n (%)
Number of subjects with at least one dose interruption by reason-n(%)				
Adverse Event	14 (66.7)	15 (71.4)	13 (76.5)	13 (76.5)
Dosing Error	4 (19.0)	3 (14.3)	1 (5.9)	1 (5.9)
Physician Decision	2 (9.5)	2 (9.5)	1 (5.9)	1 (5.9)
Subject/Guardian Decision	0	0	1 (5.9)	0
Permanent discontinuation Number of subjects - n(%)	20 (95.2)	20 (95.2)	16 (94.1)	16 (94.1)
Reason for permanent discontinuation				
Progressive Disease	12 (57.1)	12 (57.1)	11 (64.7)	11 (64.7)
Adverse Event	2 (9.5)	2 (9.5)	3 (17.6)	3 (17.6)
Subject/Guardian Decision	4 (19.0)	4 (19.0)	2 (11.8)	2 (11.8)
Death	1 (4.8)	1 (4.8)	0	0
Physician Decision	1 (4.8)	1 (4.8)	0	0

	Prior mTOR		All subjects	
	Alpelisib N=10 n (%)	Everolimus N=10 n (%)	Alpelisib N=48 n (%)	Everolimus N=48 n (%)
Number of subjects with at least one dose interruption by reason-n(%)				
Adverse Event	5 (50.0)	5 (50.0)	32 (66.7)	33 (68.8)
Dosing Error	1 (10.0)	1 (10.0)	6 (12.5)	5 (10.4)
Physician Decision	2 (20.0)	1 (10.0)	5 (10.4)	4 (8.3)
Subject/Guardian Decision	0	1 (10.0)	1 (2.1)	1 (2.1)
Permanent discontinuation Number of subjects - n(%)	10 (100)	10 (100)	46 (95.8)	46 (95.8)
Reason for permanent discontinuation				
Progressive Disease	8 (80.0)	8 (80.0)	31 (64.6)	31 (64.6)
Adverse Event	2 (20.0)	2 (20.0)	7 (14.6)	7 (14.6)
Subject/Guardian Decision	0	0	6 (12.5)	6 (12.5)
Death	0	0	1 (2.1)	1 (2.1)
Physician Decision	0	0	1 (2.1)	1 (2.1)

Dose of study treatment received by cohort - Doublet expansion phase (Safety set)

	RCC		pNET	
	Alpelisib N=21	Everolimus N=21	Alpelisib N=17	Everolimus N=17
Total number of subjects -n (%)	21 (100)	21 (100)	17 (100)	17 (100)
Average daily dose (mg)				
Mean (SD)	234.2 (26.76)	2.5 (0.00)	222.9 (31.51)	2.5 (0.00)
Median	250.0	2.5	225.0	2.5
Q1-Q3	222.3 - 250.0	2.5 - 2.5	206.8 - 250.0	2.5 - 2.5
Min-Max	154.2 - 250.0	2.5 - 2.5	157.8 - 250.3	2.5 - 2.5
Cumulative dose (mg)				
Mean (SD)	43669.0 (36354.29)	496.1 (438.60)	43182.4 (52928.21)	481.2 (534.77)
Median	27500.0	275.0	21500.0	250.0
Q1-Q3	14000.0 - 71500.0	140.0 - 847.5	9100.0 - 66900.0	112.5 - 697.5
Min-Max	3500.0 - 110500.0	50.0 - 1365.0	1750.0 - 162750.0	17.5 - 1627.5
Dose intensity (mg/day)				
Mean (SD)	222.8 (29.96)	2.4 (0.11)	191.0 (49.02)	2.2 (0.26)
Median	233.3	2.4	188.4	2.2
Q1-Q3	199.3 - 249.1	2.3 - 2.5	165.4 - 245.2	2.1 - 2.5
Min-Max	147.8 - 250.0	2.2 - 2.5	103.6 - 250.0	1.7 - 2.5
Relative dose intensity (%)				
Mean (SD)	89.1 (11.99)	95.1 (4.26)	76.4 (19.61)	88.6 (10.48)
Median	93.3	95.2	75.3	88.5
Q1-Q3	79.7 - 99.7	91.4 - 98.7	66.2 - 98.1	82.4 - 98.2
Min-Max	59.1 - 100.0	86.7 - 100.0	41.4 - 100.0	66.2 - 100.0

	Prior mTOR		All subjects	
	Alpelisib N=10	Everolimus N=10	Alpelisib N=48	Everolimus N=48
Total number of subjects -n (%)	10 (100)	10 (100)	48 (100)	48 (100)
Average daily dose (mg)				
Mean (SD)	237.4 (20.37)	2.5 (0.00)	230.9 (27.56)	2.5 (0.00)
Median	250.0	2.5	250.0	2.5
Q1-Q3	212.9 - 250.0	2.5 - 2.5	210.6 - 250.0	2.5 - 2.5
Min-Max	203.6 - 250.0	2.5 - 2.5	154.2 - 250.3	2.5 - 2.5
Cumulative dose (mg)				
Mean (SD)	27635.0 (25566.20)	301.3 (269.19)	40156.3 (41029.39)	450.2 (446.21)
Median	27000.0	278.8	25075.0	275.0
Q1-Q3	3500.0 - 46500.0	35.0 - 482.5	9275.0 - 67450.0	110.0 - 715.0
Min-Max	1250.0 - 80500.0	30.0 - 822.5	1250.0 - 162750.0	17.5 - 1627.5
Dose intensity (mg/day)				
Mean (SD)	209.5 (61.65)	2.2 (0.53)	208.7 (46.15)	2.3 (0.30)
Median	246.5	2.5	229.7	2.4
Q1-Q3	173.2 - 250.0	2.1 - 2.5	176.8 - 249.6	2.2 - 2.5
Min-Max	71.1 - 250.0	0.9 - 2.5	71.1 - 250.0	0.9 - 2.5
Relative dose intensity (%)				
Mean (SD)	83.8 (24.66)	87.4 (21.05)	83.5 (18.46)	91.2 (11.93)
Median	98.6	98.7	91.9	94.6
Q1-Q3	69.3 - 100.0	85.4 - 100.0	70.7 - 99.8	86.7 - 99.4
Min-Max	28.4 - 100.0	34.2 - 100.0	28.4 - 100.0	34.2 - 100.0

Planned starting doses for the Doublet are BYL719 250 mg + Everolimus 2.5 mg
Average dose does not consider drug free days, whereas dose intensity and relative dose intensity include days of zero dose in the calculation.

Secondary Outcome Result(s)

Overview of adverse events by dose level - Doublet escalation phase (Safety set)

Category	Alpelisib 300 mg + Everolimus 2.5 mg N=6		Alpelisib 250 mg + Everolimus 2.5 mg N=6		Alpelisib 200 mg + Everolimus 2.5 mg N=1		All subjects N=13	
	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)
Adverse events	6 (100.0)	5 (83.3)	6 (100.0)	5 (83.3)	1 (100.0)	1 (100.0)	13 (100.0)	11 (84.6)
Treatment-related	6 (100.0)	5 (83.3)	6 (100.0)	5 (83.3)	1 (100.0)	1 (100.0)	13 (100.0)	11 (84.6)
SAEs	4 (66.7)	1 (16.7)	2 (33.3)	2 (33.3)	0	0	6 (46.2)	3 (23.1)
Treatment-related	3 (50.0)	1 (16.7)	2 (33.3)	2 (33.3)	0	0	5 (38.5)	3 (23.1)
Fatal SAEs	1 (16.7)	1 (16.7)	0	0	0	0	1 (7.7)	1 (7.7)
Treatment-related	0	0	0	0	0	0	0	0
AEs leading to discontinuation	1 (16.7)	0	2 (33.3)	2 (33.3)	1 (100.0)	1 (100.0)	4 (30.8)	3 (23.1)
Treatment-related	0	0	1 (16.7)	1 (16.7)	1 (100.0)	1 (100.0)	2 (15.4)	2 (15.4)
AEs leading to dose adjustment/interruption	6 (100.0)	4 (66.7)	4 (66.7)	3 (50.0)	1 (100.0)	1 (100.0)	11 (84.6)	8 (61.5)

A subject with multiple severity grades for an AE is only counted under the maximum grade.
MedDRA version 20.1, CTCAE version 4.03.

Dose adjustments and discontinuation of study treatment by dose level - Doublet escalation phase (Safety set)

	Alpelisib 300mg + Everolimus 2.5mg		Alpelisib 250mg + Everolimus 2.5mg	
	Alpelisib N=6 n (%)	Everolimus N=6 n (%)	Alpelisib N=6 n (%)	Everolimus N=6 n (%)
Number of subjects - n(%)				
With no dose reduction and/or interruption	3 (50.0)	3 (50.0)	1 (16.7)	1 (16.7)
With at least one dose reduction and/or interruption	3 (50.0)	3 (50.0)	5 (83.3)	5 (83.3)
Dose reductions				
Number of subjects - n(%)				
With no dose reduction	3 (50.0)	NA	4 (66.7)	NA
With at least one dose reduction	3 (50.0)	NA	2 (33.3)	NA
Only one dose reduction	1 (16.7)	NA	2 (33.3)	NA
Two dose reductions	2 (33.3)	NA	0	NA
Number of subjects with at least one dose reduction by reason - n(%)				
Adverse Event	3 (50.0)	NA	2 (33.3)	NA
Missing	0	NA	0	NA
Dose interruptions				
Number of subjects - n(%)				
With no dose interruption	3 (50.0)	3 (50.0)	1 (16.7)	1 (16.7)
With at least one dose interruption	3 (50.0)	3 (50.0)	5 (83.3)	5 (83.3)
Only one dose interruption	0	0	1 (16.7)	1 (16.7)
Two dose interruptions	0	0	1 (16.7)	2 (33.3)
More than two dose interruptions	3 (50.0)	3 (50.0)	3 (50.0)	2 (33.3)
Number of subjects with at least one dose interruption by reason-n(%)				
Adverse Event	3 (50.0)	3 (50.0)	4 (66.7)	4 (66.7)
Dosing Error	0	0	2 (33.3)	2 (33.3)
Physician Decision	0	0	1 (16.7)	1 (16.7)

	Alpelisib 200mg + Everolimus 2.5mg		All subjects	
	Alpelisib N=1 n (%)	Everolimus N=1 n (%)	Alpelisib N=13 n (%)	Everolimus N=13 n (%)
Number of subjects - n(%)				
With no dose reduction and/or interruption	0	0	4 (30.8)	4 (30.8)
With at least one dose reduction and/or interruption	1 (100)	1 (100)	9 (69.2)	9 (69.2)
Dose reductions				
Number of subjects - n(%)				
With no dose reduction	0	NA	7 (53.8)	NA
With at least one dose reduction	1 (100)	NA	6 (46.2)	NA
Only one dose reduction	1 (100)	NA	4 (30.8)	NA
Two dose reductions	0	NA	2 (15.4)	NA
Number of subjects with at least one dose reduction by reason - n(%)				
Adverse Event	0	NA	5 (38.5)	NA
Missing	1 (100)	NA	1 (7.7)	NA
Dose interruptions				
Number of subjects - n(%)				
With no dose interruption	0	0	4 (30.8)	4 (30.8)
With at least one dose interruption	1 (100)	1 (100)	9 (69.2)	9 (69.2)
Only one dose interruption	0	0	1 (7.7)	1 (7.7)
Two dose interruptions	1 (100)	1 (100)	2 (15.4)	3 (23.1)
More than two dose interruptions	0	0	6 (46.2)	5 (38.5)
Number of subjects with at least one dose interruption by reason-n(%)				
Adverse Event	1 (100)	1 (100)	8 (61.5)	8 (61.5)
Dosing Error	0	0	2 (15.4)	2 (15.4)
Physician Decision	0	0	1 (7.7)	1 (7.7)

Dose adjustments and discontinuation of study treatment by dose level - Triplet escalation phase (Safety set)

	Alpelisib 200mg + Everolimus 2.5mg + Exemestane 25mg		
	Alpelisib N=7 n (%)	Everolimus N=7 n (%)	Exemestane N=7 n (%)
Number of subjects - n(%)			
With no dose reduction and/or interruption	2 (28.6)	2 (28.6)	3 (42.9)
With at least one dose reduction and/or interruption	5 (71.4)	5 (71.4)	4 (57.1)
Dose reductions			
Number of subjects - n(%)			
With no dose reduction	5 (71.4)	NA	NA
With at least one dose reduction	2 (28.6)	NA	NA
Only one dose reduction	1 (14.3)	NA	NA
Two dose reductions	1 (14.3)	NA	NA
Number of subjects with at least one dose reduction by reason - n(%)			
Adverse Event	2 (28.6)	NA	NA
Dose interruptions			
Number of subjects - n(%)			
With no dose interruption	2 (28.6)	2 (28.6)	3 (42.9)
With at least one dose interruption	5 (71.4)	5 (71.4)	4 (57.1)
Only one dose interruption	0	0	3 (42.9)
Two dose interruptions	3 (42.9)	3 (42.9)	0
More than two dose interruptions	2 (28.6)	2 (28.6)	1 (14.3)
Number of subjects with at least one dose interruption by reason-n(%)			
Adverse Event	4 (57.1)	4 (57.1)	0
Dosing Error	3 (42.9)	2 (28.6)	3 (42.9)
Physician Decision	1 (14.3)	1 (14.3)	0

	Alpelisib 200mg + Everolimus 2.5mg + Exemestane 25mg		
	Alpelisib N=7 n (%)	Everolimus N=7 n (%)	Exemestane N=7 n (%)
Number of subjects with at least one dose interruption by reason-n(%)			
Subject/Guardian Decision	0	1 (14.3)	1 (14.3)
Permanent discontinuation Number of subjects - n(%)	7 (100)	7 (100)	7 (100)
Reason for permanent discontinuation			
Subject/Guardian Decision	4 (57.1)	4 (57.1)	4 (57.1)
Progressive Disease	2 (28.6)	2 (28.6)	2 (28.6)
Adverse Event	1 (14.3)	1 (14.3)	1 (14.3)

Dose of study treatment received by dose level - Doublet escalation phase (Safety set)

	Alpelisib 300mg + Everolimus 2.5mg		Alpelisib 250mg + Everolimus 2.5mg	
	Alpelisib N=6	Everolimus N=6	Alpelisib N=6	Everolimus N=6
Total number of subjects -n (%)	6 (100)	6 (100)	6 (100)	6 (100)
Average daily dose (mg)				
Mean (SD)	266.8 (38.05)	2.5 (0.00)	244.9 (8.64)	2.5 (0.00)
Median	276.8	2.5	250.0	2.5
Q1-Q3	224.5 - 300.0	2.5 - 2.5	238.9 - 250.0	2.5 - 2.5
Min-Max	222.4 - 300.0	2.5 - 2.5	229.9 - 250.8	2.5 - 2.5
Cumulative dose (mg)				
Mean (SD)	14325.0 (10426.40)	164.6 (113.79)	19633.3 (11842.75)	222.5 (123.56)
Median	16650.0	183.8	20575.0	235.0
Q1-Q3	2400.0 - 24350.0	37.5 - 260.0	12250.0 - 26500.0	140.0 - 310.0
Min-Max	1200.0 - 24700.0	30.0 - 292.5	2150.0 - 35750.0	40.0 - 375.0
Dose intensity (mg/day)				
Mean (SD)	244.2 (70.05)	2.3 (0.39)	194.9 (56.43)	2.1 (0.42)
Median	266.0	2.4	210.0	2.2
Q1-Q3	205.8 - 300.0	2.3 - 2.5	183.6 - 226.3	2.0 - 2.3
Min-Max	127.7 - 300.0	1.5 - 2.5	89.6 - 250.0	1.3 - 2.5
Relative dose intensity (%)				
Mean (SD)	81.4 (23.35)	90.6 (15.78)	78.0 (22.57)	83.7 (16.86)
Median	88.7	96.1	84.0	89.4
Q1-Q3	68.6 - 100.0	92.0 - 100.0	73.4 - 90.5	80.9 - 90.9
Min-Max	42.6 - 100.0	59.4 - 100.0	35.8 - 100.0	51.6 - 100.0

	Alpelisib 200mg + Everolimus 2.5mg		All subjects	
	Alpelisib N=1	Everolimus N=1	Alpelisib N=13	Everolimus N=13
Total number of subjects -n (%)	1 (100)	1 (100)	13 (100)	13 (100)
Average daily dose (mg)				
Mean (SD)	200.0	2.5	251.5 (31.52)	2.5 (0.00)
Median	200.0	2.5	250.0	2.5
Q1-Q3	200.0 - 200.0	2.5 - 2.5	229.9 - 253.6	2.5 - 2.5
Min-Max	200.0 - 200.0	2.5 - 2.5	200.0 - 300.0	2.5 - 2.5
Cumulative dose (mg)				
Mean (SD)	5600.0	87.5	16103.8 (10988.11)	185.4 (116.02)
Median	5600.0	87.5	16550.0	185.0
Q1-Q3	5600.0 - 5600.0	87.5 - 87.5	5600.0 - 24600.0	87.5 - 285.0
Min-Max	5600.0 - 5600.0	87.5 - 87.5	1200.0 - 35750.0	30.0 - 375.0
Dose intensity (mg/day)				
Mean (SD)	101.8	1.4	210.5 (71.04)	2.1 (0.44)
Median	101.8	1.4	220.7	2.3
Q1-Q3	101.8 - 101.8	1.4 - 1.4	183.6 - 250.0	2.0 - 2.5
Min-Max	101.8 - 101.8	1.4 - 1.4	89.6 - 300.0	1.3 - 2.5
Relative dose intensity (%)				
Mean (SD)	33.9	56.5	76.2 (24.57)	84.8 (17.51)
Median	33.9	56.5	79.7	90.9
Q1-Q3	33.9 - 33.9	56.5 - 56.5	68.6 - 100.0	80.9 - 100.0
Min-Max	33.9 - 33.9	56.5 - 56.5	33.9 - 100.0	51.6 - 100.0

Average dose does not consider drug free days, whereas dose intensity and relative dose intensity include days of zero dose in the calculation.

Primary PK parameters for plasma alpelisib by dose level - Doublet escalation and Doublet expansion with full PK (Pharmacokinetic analysis set)

Timepoint: Cycle 1 Day 15

Parameter	Statistics	Alpelisib 250mg + Everolimus 2.5mg N=19	Alpelisib 300mg + Everolimus 2.5mg N=6
AUClast (ng*hr/mL)	n	15	4
	Mean (SD)	21700 (11900)	34800 (9980)
	CV%	54.6	28.7
	Geo-mean	16000	33800
	Geo-CV%	156.7	28.5
	Median	23100	32900
	Min-Max	449-43700	25700-47900
AUCtau (ng*hr/mL)	n	14	3
	Mean (SD)	24500 (10500)	33800 (12200)
	CV%	42.7	36.2
	Geo-mean	21900	32500
	Geo-CV%	56.6	34.8
	Median	27000	27600
	Min-Max	6730-43100	25800-47900
Cmax (ng/mL)	n	14	4
	Mean (SD)	2270 (653)	2640 (482)
	CV%	28.7	18.3
	Geo-mean	2160	2610
	Geo-CV%	38.5	17.3
	Median	2370	2470
	Min-Max	750-3190	2300-3340
Tmax (hr)	n	14	4
	Mean (SD)	NA	NA

Timepoint: Cycle 1 Day 15

Parameter	Statistics	Alpelisib 250mg + Everolimus 2.5mg N=19	Alpelisib 300mg + Everolimus 2.5mg N=6
Tmax (hr)	CV%	NA	NA
	Geo-mean	NA	NA
	Geo-CV%	NA	NA
	Median	3.04	5.00
	Min-Max	1.00-6.00	1.92-6.00

Timepoint: Cycle 2 Day 1

Parameter	Statistics	Alpelisib 250mg + Everolimus 2.5mg N=19	Alpelisib 300mg + Everolimus 2.5mg N=6
AUClast (ng*hr/mL)	n	15	2
	Mean (SD)	22400 (9560)	9470 (1190)
	CV%	42.6	12.5
	Geo-mean	20600	9440
	Geo-CV%	46.5	12.6
	Median	19400	9470
	Min-Max	9540-43100	8630-10300
AUCtau (ng*hr/mL)	n	13	2
	Mean (SD)	24500 (9000)	16000 (10100)
	CV%	36.8	62.8
	Geo-mean	22700	14300
	Geo-CV%	44.2	76.0
	Median	24000	16000
	Min-Max	9510-37200	8890-23100
Cmax (ng/mL)	n	15	2
	Mean (SD)	2500 (809)	1090 (548)
	CV%	32.3	50.2
	Geo-mean	2370	1020
	Geo-CV%	35.3	56.3
	Median	2500	1090
	Min-Max	1350-3940	705-1480
Tmax (hr)	n	15	2
	Mean (SD)	NA	NA

Timepoint: Cycle 2 Day 1

Parameter	Statistics	Alpelisib 250mg + Everolimus 2.5mg N=19	Alpelisib 300mg + Everolimus 2.5mg N=6
Tmax (hr)	CV%	NA	NA
	Geo-mean	NA	NA
	Geo-CV%	NA	NA
	Median	3.00	2.67
	Min-Max	1.00-6.00	2.33-3.00

n = number of subjects with corresponding evaluable PK parameters.
One subject with planned dose level Alpelisib 300mg + Everolimus 2.5mg received Alpelisib 200mg + Everolimus 2.5mg (actual dose level) and is not included in the table.

Primary PK parameters for plasma alpelisib by dose level - Triplet escalation (full PK) (Pharmacokinetic analysis set)

Timepoint: Cycle 1 Day 15

Parameter	Statistics	Alpelisib 200mg + Everolimus 2.5mg + Exemestane 25mg N=7
AUClast (ng*hr/mL)	n	7
	Mean (SD)	23500 (5380)
	CV%	22.8
	Geo-mean	23000
	Geo-CV%	22.7
	Median	20700
	Min-Max	18400-31300
AUCtau (ng*hr/mL)	n	7
	Mean (SD)	23600 (5430)
	CV%	23.0
	Geo-mean	23100
	Geo-CV%	22.9
	Median	20700
	Min-Max	18400-31300
Cmax (ng/mL)	n	7
	Mean (SD)	2150 (520)
	CV%	24.2
	Geo-mean	2110
	Geo-CV%	21.8
	Median	2040
	Min-Max	1590-3260
Tmax (hr)	n	7
	Mean (SD)	NA
	CV%	NA

Timepoint: Cycle 1 Day 15

Parameter	Statistics	Alpelisib 200mg + Everolimus 2.5mg + Exemestane 25mg N=7
Tmax (hr)	Geo-mean	NA
	Geo-CV%	NA
	Median	2.00
	Min-Max	1.50-4.00

Timepoint: Cycle 2 Day 1

Parameter	Statistics	Alpelisib 200mg + Everolimus 2.5mg + Exemestane 25mg N=7
AUClast (ng*hr/mL)	n	6
	Mean (SD)	23100 (5700)
	CV%	24.6
	Geo-mean	22500
	Geo-CV%	25.2
	Median	22600
	Min-Max	17000-30500
AUCtau (ng*hr/mL)	n	6
	Mean (SD)	23300 (5860)
	CV%	25.2
	Geo-mean	22700
	Geo-CV%	25.8
	Median	22600
	Min-Max	17000-30500
Cmax (ng/mL)	n	6
	Mean (SD)	2250 (464)
	CV%	20.6
	Geo-mean	2210
	Geo-CV%	22.6
	Median	2370
	Min-Max	1520-2750
Tmax (hr)	n	6
	Mean (SD)	NA
	CV%	NA

Timepoint: Cycle 2 Day 1

Parameter	Statistics	Alpelisib 200mg + Everolimus 2.5mg + Exemestane 25mg N=7
Tmax (hr)	Geo-mean	NA
	Geo-CV%	NA
	Median	3.00
	Min-Max	2.00-4.00

n = number of subjects with corresponding evaluable PK parameters.

Primary PK parameters for blood everolimus by dose level - Doublet escalation and Doublet expansion with full PK (Pharmacokinetic analysis set)

Timepoint: Cycle 1 Day 7

Parameter	Statistics	Alpelisib 250mg + Everolimus 2.5mg N=19	Alpelisib 300mg + Everolimus 2.5mg N=6
AUClast (ng*hr/mL)	n	17	5
	Mean (SD)	158 (92.2)	135 (56.5)
	CV%	58.2	41.9
	Geo-mean	138	124
	Geo-CV%	57.4	48.6
	Median	132	144
	Min-Max	64.6-376	72.1-196
AUCtau (ng*hr/mL)	n	17	5
	Mean (SD)	164 (90.1)	147 (45.3)
	CV%	55.0	30.8
	Geo-mean	145	141
	Geo-CV%	52.1	35.4
	Median	132	143
	Min-Max	71.3-386	82.4-198
Cmax (ng/mL)	n	17	5
	Mean (SD)	18.8 (7.02)	13.2 (5.09)
	CV%	37.4	38.6
	Geo-mean	17.6	12.4
	Geo-CV%	36.8	39.4
	Median	15.6	12.2
	Min-Max	9.75-34.6	7.88-20.8
Tmax (hr)	n	17	5
	Mean (SD)	NA	NA

Timepoint: Cycle 1 Day 7

Parameter	Statistics	Alpelisib 250mg + Everolimus 2.5mg N=19	Alpelisib 300mg + Everolimus 2.5mg N=6
Tmax (hr)	CV%	NA	NA
	Geo-mean	NA	NA
	Geo-CV%	NA	NA
	Median	2.00	1.50
	Min-Max	0.967-4.00	0.500-3.00

Timepoint: Cycle 1 Day 15

Parameter	Statistics	Alpelisib 250mg + Everolimus 2.5mg N=19	Alpelisib 300mg + Everolimus 2.5mg N=6
AUClast (ng*hr/mL)	n	12	4
	Mean (SD)	148 (72.8)	180 (143)
	CV%	49.0	79.5
	Geo-mean	137	145
	Geo-CV%	39.2	87.4
	Median	139	133
	Min-Max	82.6-362	71.5-385
AUCtau (ng*hr/mL)	n	12	4
	Mean (SD)	155 (68.8)	182 (142)
	CV%	44.5	78.0
	Geo-mean	144	147
	Geo-CV%	37.5	84.8
	Median	142	134
	Min-Max	82.3-352	75.2-385
Cmax (ng/mL)	n	12	4
	Mean (SD)	19.9 (9.00)	21.2 (9.33)
	CV%	45.1	44.1
	Geo-mean	18.4	19.3
	Geo-CV%	42.5	56.3
	Median	16.4	22.1
	Min-Max	11.7-38.1	9.37-31.1
Tmax (hr)	n	12	4
	Mean (SD)	NA	NA

Timepoint: Cycle 1 Day 15

Parameter	Statistics	Alpelisib 250mg + Everolimus 2.5mg N=19	Alpelisib 300mg + Everolimus 2.5mg N=6
Tmax (hr)	CV%	NA	NA
	Geo-mean	NA	NA
	Geo-CV%	NA	NA
	Median	1.53	1.96
	Min-Max	0.500-3.35	0.500-4.00

Timepoint: Cycle 2 Day 1

Parameter	Statistics	Alpelisib 250mg + Everolimus 2.5mg N=19	Alpelisib 300mg + Everolimus 2.5mg N=6
AUClast (ng*hr/mL)	n	12	2
	Mean (SD)	117 (68.8)	118 (62.6)
	CV%	59.0	53.0
	Geo-mean	101	109
	Geo-CV%	60.1	60.3
	Median	115	118
	Min-Max	42.4-295	73.8-162
AUCtau (ng*hr/mL)	n	12	2
	Mean (SD)	123 (64.8)	114 (51.7)
	CV%	52.9	45.3
	Geo-mean	110	108
	Geo-CV%	50.6	49.7
	Median	116	114
	Min-Max	55.1-295	77.5-151
Cmax (ng/mL)	n	12	2
	Mean (SD)	20.9 (9.37)	13.2 (2.62)
	CV%	44.9	19.9
	Geo-mean	18.7	13.0
	Geo-CV%	56.0	20.2
	Median	20.9	13.2
	Min-Max	6.51-38.6	11.3-15.0
Tmax (hr)	n	12	2
	Mean (SD)	NA	NA

Timepoint: Cycle 2 Day 1

Parameter	Statistics	Alpelisib 250mg + Everolimus 2.5mg N=19	Alpelisib 300mg + Everolimus 2.5mg N=6
Tmax (hr)	CV%	NA	NA
	Geo-mean	NA	NA
	Geo-CV%	NA	NA
	Median	1.50	1.42
	Min-Max	0.633-3.02	1.00-1.83

n = number of subjects with corresponding evaluable PK parameters.
One subject with planned dose level Alpelisib 300mg + Everolimus 2.5mg received Alpelisib 200mg + Everolimus 2.5mg (actual dose level) and is not included in the table.

Primary PK parameters for blood everolimus by dose level - Triplet escalation (full PK) Pharmacokinetic analysis set

Timepoint: Cycle 1 Day 7

Parameter	Statistics	Alpelisib 200mg + Everolimus 2.5mg + Exemestane 25mg N=7
AUClast (ng*hr/mL)	n	7
	Mean (SD)	123 (23.4)
	CV%	19.1
	Geo-mean	121
	Geo-CV%	20.0
	Median	121
	Min-Max	85.8-152
AUCtau (ng*hr/mL)	n	7
	Mean (SD)	123 (23.4)
	CV%	19.1
	Geo-mean	121
	Geo-CV%	20.0
	Median	121
	Min-Max	85.9-153
Cmax (ng/mL)	n	7
	Mean (SD)	14.1 (2.55)
	CV%	18.1
	Geo-mean	14.0
	Geo-CV%	17.8
	Median	14.2
	Min-Max	11.1-18.6
Tmax (hr)	n	7
	Mean (SD)	NA
	CV%	NA

Timepoint: Cycle 1 Day 7

Parameter	Statistics	Alpelisib 200mg + Everolimus 2.5mg + Exemestane 25mg N=7
Tmax (hr)	Geo-mean	NA
	Geo-CV%	NA
	Median	1.50
	Min-Max	1.00-4.00

Timepoint: Cycle 1 Day 15

Parameter	Statistics	Alpelisib 200mg + Everolimus 2.5mg + Exemestane 25mg N=7
AUClast (ng*hr/mL)	n	7
	Mean (SD)	166 (44.4)
	CV%	26.9
	Geo-mean	160
	Geo-CV%	27.5
	Median	155
	Min-Max	110-234
AUCtau (ng*hr/mL)	n	7
	Mean (SD)	166 (44.1)
	CV%	26.6
	Geo-mean	161
	Geo-CV%	27.2
	Median	155
	Min-Max	110-234
Cmax (ng/mL)	n	7
	Mean (SD)	20.3 (6.34)
	CV%	31.2
	Geo-mean	19.6
	Geo-CV%	29.5
	Median	18.9
	Min-Max	13.3-32.7
Tmax (hr)	n	7
	Mean (SD)	NA
	CV%	NA

Timepoint: Cycle 1 Day 15

Parameter	Statistics	Alpelisib 200mg + Everolimus 2.5mg + Exemestane 25mg N=7
Tmax (hr)	Geo-mean	NA
	Geo-CV%	NA
	Median	1.50
	Min-Max	1.00-3.00

Timepoint: Cycle 2 Day 1

Parameter	Statistics	Alpelisib 200mg + Everolimus 2.5mg + Exemestane 25mg N=7
AUClast (ng*hr/mL)	n	6
	Mean (SD)	130 (33.5)
	CV%	25.8
	Geo-mean	126
	Geo-CV%	25.4
	Median	131
	Min-Max	95.8-187
AUCtau (ng*hr/mL)	n	6
	Mean (SD)	131 (33.0)
	CV%	25.2
	Geo-mean	128
	Geo-CV%	24.7
	Median	133
	Min-Max	95.9-188
Cmax (ng/mL)	n	6
	Mean (SD)	18.7 (5.61)
	CV%	30.1
	Geo-mean	18.0
	Geo-CV%	30.6
	Median	17.0
	Min-Max	12.0-26.5
Tmax (hr)	n	6
	Mean (SD)	NA
	CV%	NA

Timepoint: Cycle 2 Day 1

Parameter	Statistics	Alpelisib 200mg + Everolimus 2.5mg + Exemestane 25mg N=7
Tmax (hr)	Geo-mean	NA
	Geo-CV%	NA
	Median	2.00
	Min-Max	0.500-3.00

Primary PK parameters for plasma exemestane by dose level - Triplet escalation (full PK) (Pharmacokinetic analysis set)

Timepoint: Cycle 1 Day 7

Parameter	Statistics	Alpelisib 200mg + Everolimus 2.5mg + Exemestane 25mg N=7
AUClast (ng*hr/mL)	n	7
	Mean (SD)	58.7 (27.1)
	CV%	46.1
	Geo-mean	53.0
	Geo-CV%	54.1
	Median	61.6
	Min-Max	24.8-103
AUCtau (ng*hr/mL)	n	7
	Mean (SD)	58.7 (27.1)
	CV%	46.2
	Geo-mean	53.0
	Geo-CV%	54.1
	Median	61.6
	Min-Max	24.8-103
Cmax (ng/mL)	n	7
	Mean (SD)	20.7 (13.5)
	CV%	65.1
	Geo-mean	17.7
	Geo-CV%	65.0
	Median	18.6
	Min-Max	8.29-47.7
Tmax (hr)	n	7
	Mean (SD)	NA
	CV%	NA

Timepoint: Cycle 1 Day 7

Parameter	Statistics	Alpelisib 200mg + Everolimus 2.5mg + Exemestane 25mg N=7
Tmax (hr)	Geo-mean	NA
	Geo-CV%	NA
	Median	2.00
	Min-Max	1.00-2.00

Timepoint: Cycle 1 Day 15

Parameter	Statistics	Alpelisib 200mg + Everolimus 2.5mg + Exemestane 25mg N=7
AUClast (ng*hr/mL)	n	7
	Mean (SD)	57.5 (28.9)
	CV%	50.2
	Geo-mean	48.9
	Geo-CV%	79.7
	Median	55.4
	Min-Max	11.7-97.8
AUCtau (ng*hr/mL)	n	7
	Mean (SD)	57.5 (28.9)
	CV%	50.2
	Geo-mean	49.0
	Geo-CV%	79.7
	Median	55.4
	Min-Max	11.7-97.8
Cmax (ng/mL)	n	7
	Mean (SD)	17.7 (15.2)
	CV%	85.5
	Geo-mean	12.0
	Geo-CV%	153.7
	Median	12.0
	Min-Max	1.42-47.9
Tmax (hr)	n	7
	Mean (SD)	NA
	CV%	NA

Timepoint: Cycle 1 Day 15

Parameter	Statistics	Alpelisib 200mg + Everolimus 2.5mg + Exemestane 25mg N=7
Tmax (hr)	Geo-mean	NA
	Geo-CV%	NA
	Median	2.00
	Min-Max	1.00-4.00

Secondary PK parameters for plasma alpelisib by dose level - Doublet escalation and Doublet expansion with full PK Pharmacokinetic analysis set

Timepoint: Cycle 1 Day 15

Parameter	Statistics	Alpelisib 250mg + Everolimus 2.5mg N=19	Alpelisib 300mg + Everolimus 2.5mg N=6
T1/2 (hr)	n	13	2
	Mean (SD)	7.43 (2.27)	10.6 (7.38)
	CV%	30.5	69.6
	Geo-mean	7.12	9.24
	Geo-CV%	31.1	88.7
	Median	7.12	10.6
	Min-Max	3.89-12.2	5.39-15.8
CLss/F (L/hr)	n	14	3
	Mean (SD)	13.2 (8.56)	9.58 (2.89)
	CV%	64.9	30.2
	Geo-mean	11.4	9.24
	Geo-CV%	56.6	34.8
	Median	9.27	10.9
	Min-Max	5.80-37.1	6.27-11.6
Vz/F (L)	n	13	2
	Mean (SD)	138 (81.0)	169 (111)
	CV%	58.7	65.9
	Geo-mean	123	150
	Geo-CV%	48.1	81.6
	Median	107	169
	Min-Max	72.8-369	90.3-248

Timepoint: Cycle 2 Day 1

Parameter	Statistics	Alpelisib 250mg + Everolimus 2.5mg N=19	Alpelisib 300mg + Everolimus 2.5mg N=6
T1/2 (hr)	n	12	1
	Mean (SD)	6.61 (1.51)	8.30
	CV%	22.8	
	Geo-mean	6.46	8.30
	Geo-CV%	22.9	
	Median	6.54	8.30
	Min-Max	3.97-10.2	8.30-8.30
CLss/F (L/hr)	n	12	1
	Mean (SD)	12.0 (6.12)	33.7
	CV%	51.1	
	Geo-mean	10.8	33.7
	Geo-CV%	47.2	
	Median	9.18	33.7
	Min-Max	6.73-26.3	33.7-33.7
Vz/F (L)	n	12	1
	Mean (SD)	109 (48.6)	404
	CV%	44.5	
	Geo-mean	101	404
	Geo-CV%	41.4	
	Median	77.8	404
	Min-Max	66.3-222	404-404

n = number of subjects with corresponding evaluable PK parameters.
One subject with planned dose level Alpelisib 300mg + Everolimus 2.5mg received Alpelisib 200mg + Everolimus 2.5mg (actual dose level) and is not included in the table.

Secondary PK parameters for plasma alpelisib by dose level - Triplet escalation (full PK) (Pharmacokinetic analysis set)

Timepoint: Cycle 1 Day 15

Parameter	Statistics	Alpelisib 200mg + Everolimus 2.5mg + Exemestane 25mg N=7
T1/2 (hr)	n	7
	Mean (SD)	8.59 (1.88)
	CV%	21.9
	Geo-mean	8.40
	Geo-CV%	23.5
	Median	8.96
	Min-Max	6.01-10.5
CLss/F (L/hr)	n	7
	Mean (SD)	8.85 (1.92)
	CV%	21.7
	Geo-mean	8.66
	Geo-CV%	22.9
	Median	9.68
	Min-Max	6.38-10.9
Vz/F (L)	n	7
	Mean (SD)	110 (33.0)
	CV%	30.1
	Geo-mean	105
	Geo-CV%	34.5
	Median	108
	Min-Max	55.3-163

Timepoint: Cycle 2 Day 1

Parameter	Statistics	Alpelisib 200mg + Everolimus 2.5mg + Exemestane 25mg N=7
T1/2 (hr)	n	6
	Mean (SD)	7.26 (1.12)
	CV%	15.4
	Geo-mean	7.19
	Geo-CV%	15.1
	Median	7.01
	Min-Max	6.07-9.02
CLss/F (L/hr)	n	6
	Mean (SD)	9.07 (2.26)
	CV%	24.9
	Geo-mean	8.83
	Geo-CV%	25.8
	Median	8.97
	Min-Max	6.57-11.8
Vz/F (L)	n	6
	Mean (SD)	94.1 (23.5)
	CV%	24.9
	Geo-mean	91.6
	Geo-CV%	26.4
	Median	96.0
	Min-Max	65.4-121

n = number of subjects with corresponding evaluable PK parameters.

Secondary PK parameters for blood everolimus by dose level - Doublet escalation and Doublet expansion with full PK (Pharmacokinetic analysis set)

Timepoint: Cycle 1 Day 7

Parameter	Statistics	Alpelisib 250mg + Everolimus 2.5mg N=19	Alpelisib 300mg + Everolimus 2.5mg N=6
T1/2 (hr)	n	17	5
	Mean (SD)	18.2 (6.04)	16.7 (6.33)
	CV%	33.2	37.9
	Geo-mean	16.9	15.3
	Geo-CV%	48.4	56.1
	Median	19.4	18.5
	Min-Max	4.09-31.6	6.15-23.0
CLss/F (L/hr)	n	17	5
	Mean (SD)	19.1 (8.18)	18.7 (7.03)
	CV%	42.9	37.6
	Geo-mean	17.2	17.8
	Geo-CV%	52.1	35.4
	Median	18.9	17.4
	Min-Max	6.48-35.1	12.6-30.3
Vz/F (L)	n	17	5
	Mean (SD)	481 (253)	446 (247)
	CV%	52.5	55.4
	Geo-mean	419	393
	Geo-CV%	60.6	62.7
	Median	386	422
	Min-Max	122-922	171-840

Timepoint: Cycle 1 Day 15

Parameter	Statistics	Alpelisib 250mg + Everolimus 2.5mg N=19	Alpelisib 300mg + Everolimus 2.5mg N=6
T1/2 (hr)	n	12	4
	Mean (SD)	17.2 (3.22)	13.9 (9.20)
	CV%	18.7	66.3
	Geo-mean	16.9	9.74
	Geo-CV%	21.8	176.2
	Median	17.2	14.9
	Min-Max	9.53-21.5	1.70-23.9
CLss/F (L/hr)	n	12	4
	Mean (SD)	18.3 (5.91)	20.2 (12.1)
	CV%	32.3	59.9
	Geo-mean	17.3	17.0
	Geo-CV%	37.5	84.8
	Median	17.6	20.6
	Min-Max	7.09-30.4	6.49-33.2
Vz/F (L)	n	12	4
	Mean (SD)	454 (176)	331 (266)
	CV%	38.9	80.4
	Geo-mean	422	238
	Geo-CV%	42.3	129.6
	Median	459	310
	Min-Max	203-862	81.3-623

Timepoint: Cycle 2 Day 1

Parameter	Statistics	Alpelisib 250mg + Everolimus 2.5mg N=19	Alpelisib 300mg + Everolimus 2.5mg N=6
T1/2 (hr)	n	12	1
	Mean (SD)	12.5 (5.79)	22.3
	CV%	46.1	
	Geo-mean	10.8	22.3
	Geo-CV%	70.1	
	Median	13.6	22.3
	Min-Max	3.67-21.0	22.3-22.3
CLss/F (L/hr)	n	12	1
	Mean (SD)	25.1 (11.5)	32.3
	CV%	45.9	
	Geo-mean	22.7	32.3
	Geo-CV%	50.6	
	Median	21.6	32.3
	Min-Max	8.47-45.4	32.3-32.3
Vz/F (L)	n	12	1
	Mean (SD)	408 (233)	1040
	CV%	57.1	
	Geo-mean	355	1040
	Geo-CV%	59.4	
	Median	388	1040
	Min-Max	140-951	1040-1040

n = number of subjects with corresponding evaluable PK parameters.
One subject with planned dose level Alpelisib 300mg + Everolimus 2.5mg received Alpelisib 200mg + Everolimus 2.5mg (actual dose level) and is not included in the table.

Secondary PK parameters for blood everolimus by dose level - Triplet escalation (full PK) (Pharmacokinetic analysis set)

Timepoint: Cycle 1 Day 7

Parameter	Statistics	Alpelisib 200mg + Everolimus 2.5mg + Exemestane 25mg N=7
T1/2 (hr)	n	7
	Mean (SD)	20.0 (3.49)
	CV%	17.5
	Geo-mean	19.8
	Geo-CV%	16.0
	Median	18.8
	Min-Max	17.3-27.3
CLss/F (L/hr)	n	7
	Mean (SD)	21.1 (4.33)
	CV%	20.5
	Geo-mean	20.7
	Geo-CV%	20.0
	Median	20.6
	Min-Max	16.4-29.1
Vz/F (L)	n	7
	Mean (SD)	601 (114)
	CV%	19.0
	Geo-mean	591
	Geo-CV%	20.4
	Median	589
	Min-Max	409-755

Timepoint: Cycle 1 Day 15

Parameter	Statistics	Alpelisib 200mg + Everolimus 2.5mg + Exemestane 25mg N=7
T1/2 (hr)	n	7
	Mean (SD)	19.8 (4.19)
	CV%	21.2
	Geo-mean	19.4
	Geo-CV%	21.5
	Median	20.0
	Min-Max	14.8-27.0
CLss/F (L/hr)	n	7
	Mean (SD)	16.0 (4.26)
	CV%	26.6
	Geo-mean	15.5
	Geo-CV%	27.2
	Median	16.2
	Min-Max	10.7-22.6
Vz/F (L)	n	7
	Mean (SD)	438 (61.2)
	CV%	14.0
	Geo-mean	435
	Geo-CV%	14.5
	Median	427
	Min-Max	339-513

Timepoint: Cycle 2 Day 1

Parameter	Statistics	Alpelisib 200mg + Everolimus 2.5mg + Exemestane 25mg N=7
T1/2 (hr)	n	6
	Mean (SD)	19.5 (3.32)
	CV%	17.1
	Geo-mean	19.2
	Geo-CV%	16.3
	Median	18.4
	Min-Max	16.1-25.2
CLss/F (L/hr)	n	6
	Mean (SD)	20.1 (4.73)
	CV%	23.6
	Geo-mean	19.6
	Geo-CV%	24.7
	Median	18.9
	Min-Max	13.3-26.1
Vz/F (L)	n	6
	Mean (SD)	551 (107)
	CV%	19.3
	Geo-mean	543
	Geo-CV%	19.2
	Median	530
	Min-Max	423-716

Progression Free Survival rate at 16 weeks as per local investigator assessment by cohort - Doublet expansion phase (Full analysis set)

	RCC N=21			pNET N=17			Prior mTOR N=10		
	n (%)	90% CI	95% CI	n (%)	90% CI	95% CI	n (%)	90% CI	95% CI
Overall response at 16 weeks									
Partial Response (PR)	4 (19.0)			0			0		
Stable Disease (SD)	7 (33.3)			6 (35.3)			3 (30.0)		
Progressive Disease (PD)	7 (33.3)			6 (35.3)			4 (40.0)		
Unknown (UNK)	1 (4.8)			4 (23.5)			1 (10.0)		
Not Assessed	2 (9.5)			1 (5.9)			2 (20.0)		
PFS rate at 16 weeks	11 (52.4)	(32.8, 71.4)	(29.8, 74.3)	6 (35.3)	(16.6, 58.0)	(14.2, 61.7)	3 (30.0)	(8.7, 60.7)	(6.7, 65.2)

Planned starting doses for the Doublet are BYL719 250 mg + Everolimus 2.5 mg. N: The total number of subjects in the treatment group. It is the denominator for percentage (%) calculation. n: Number of subjects who are at the corresponding category. Subjects are progression free after 16 weeks if they have an overall response of CR, PR, Non-CR/Non-PD or SD at their 2nd post-baseline scan. This scan should occur between Day 106 and Day 120. The 90% and 95% CIs for the frequency distribution were computed using Clopper-Pearson method.

Best overall response as per local investigator assessment by cohort - Doublet expansion phase (Full analysis set)

	RCC N=21			pNET N=17		
	n (%)	90% CI	95% CI	n (%)	90% CI	95% CI
Subject with measurable disease at baseline	21 (100)			17 (100)		
Best overall response						
Partial Response (PR)	4 (19.0)			1 (5.9)		
Stable Disease (SD)	9 (42.9)			11 (64.7)		
Progressive Disease (PD)	5 (23.8)			3 (17.6)		
Unknown (UNK)	3 (14.3)			2 (11.8)		
Overall Response Rate (ORR: CR+PR)	4 (19.0)	(6.8,38.4)	(5.4,41.9)	1 (5.9)	(0.3,25.0)	(0.1,28.7)
Disease Control Rate (DCR: CR, PR, SD or Non-CR/Non-PD)	13 (61.9)	(41.7,79.4)	(38.4,81.9)	12 (70.6)	(47.8,87.6)	(44.0,89.7)

	Prior mTOR N=10		
	n (%)	90% CI	95% CI
Subject with measurable disease at baseline	10 (100)		
Best overall response			
Partial Response (PR)	0		
Stable Disease (SD)	6 (60.0)		
Progressive Disease (PD)	2 (20.0)		
Unknown (UNK)	2 (20.0)		
Overall Response Rate (ORR: CR+PR)	0	(0.0,25.9)	(0.0,30.8)
Disease Control Rate (DCR: CR, PR, SD or Non-CR/Non-PD)	6 (60.0)	(30.4,85.0)	(26.2,87.8)

Planned starting doses for the Doublet are BYL719 250 mg + Everolimus 2.5 mg
N: The total number of subjects in the treatment group. It is the denominator for percentage (%) calculation.
n: Number of subjects who are at the corresponding category.
The 90% and 95% CIs for the frequency distribution of each variable were computed using Clopper-Pearson method.

Best overall response as per local investigator assessment by treatment - Breast cancer expansion phase (Full analysis set)

	Alpelisib 200mg + Everolimus 2.5mg + Exemestane 25mg N=8			Alpelisib 250mg + Exemestane 25mg N=3		
	n (%)	90% CI	95% CI	n (%)	90% CI	95% CI
Subject with measurable disease at baseline	7 (87.5)			2 (66.7)		
Subject with non-measurable disease only at baseline	1 (12.5)			1 (33.3)		
Best overall response						
Partial Response (PR)	2 (25.0)			0		
Non-CR/Non-PD	1 (12.5)			1 (33.3)		
Stable Disease (SD)	2 (25.0)			1 (33.3)		
Progressive Disease (PD)	1 (12.5)			0		
Unknown (UNK)	2 (25.0)			1 (33.3)		
Overall Response Rate (ORR: CR+PR)	2 (25.0)	(4.6,60.0)	(3.2,65.1)	0	(0.0,63.2)	(0.0,70.8)
Disease Control Rate (DCR: CR, PR, SD or Non-CR/Non-PD)	5 (62.5)	(28.9,88.9)	(24.5,91.5)	2 (66.7)	(13.5,98.3)	(9.4,99.2)
Clinical Benefit Rate (CBR: CR, PR, SD or Non-CR/Non-PD > 24 weeks)	4 (50.0)	(19.3,80.7)	(15.7,84.3)	0	(0.0,63.2)	(0.0,70.8)

N: The total number of subjects in the treatment group. It is the denominator for percentage (%) calculation.
n: Number of subjects who are at the corresponding category.
The 90% and 95% CIs for the frequency distribution of each variable were computed using Clopper-Pearson method.

Safety Results

Adverse events by system organ class and preferred term by dose level - Doublet escalation phase (Safety set)

Primary system organ class Preferred term	Alpelisib 300mg + Everolimus 2.5mg N=6 All Grades n (%)	 Grade 3 n (%)	 Grade 4 n (%)	Alpelisib 250mg + Everolimus 2.5mg N=6 All Grades n (%)	 Grade 3 n (%)	 Grade 4 n (%)
Number of subjects with at least one event	6 (100)	3 (50.0)	2 (33.3)	6 (100)	3 (50.0)	2 (33.3)
Blood and lymphatic system disorders	2 (33.3)	0	0	2 (33.3)	1 (16.7)	0
Anaemia	2 (33.3)	0	0	1 (16.7)	0	0
Leukopenia	0	0	0	1 (16.7)	0	0
Lymphopenia	0	0	0	1 (16.7)	1 (16.7)	0
Thrombocytopenia	0	0	0	1 (16.7)	0	0
Gastrointestinal disorders	5 (83.3)	2 (33.3)	1 (16.7)	5 (83.3)	1 (16.7)	0
Diarrhoea	4 (66.7)	3 (50.0)	0	3 (50.0)	0	0
Stomatitis	4 (66.7)	0	0	3 (50.0)	0	0
Nausea	4 (66.7)	0	0	2 (33.3)	0	0
Abdominal pain	3 (50.0)	0	0	1 (16.7)	0	0
Vomiting	3 (50.0)	0	0	1 (16.7)	0	0
Abdominal pain upper	1 (16.7)	0	0	1 (16.7)	0	0
Aphthous ulcer	0	0	0	2 (33.3)	0	0
Constipation	0	0	0	2 (33.3)	0	0
Abdominal distension	1 (16.7)	0	0	0	0	0
Anal fissure	0	0	0	1 (16.7)	0	0
Anal inflammation	1 (16.7)	0	0	0	0	0
Ascites	1 (16.7)	0	0	0	0	0
Dry mouth	0	0	0	1 (16.7)	0	0
Dyspepsia	1 (16.7)	0	0	0	0	0

Primary system organ class Preferred term	Alpelisib 200mg + Everolimus 2.5mg N=1 All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All subjects N=13 All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Number of subjects with at least one event	1 (100)	1 (100)	0	13 (100)	7 (53.8)	4 (30.8)
Blood and lymphatic system disorders	0	0	0	4 (30.8)	1 (7.7)	0
Anaemia	0	0	0	3 (23.1)	0	0
Leukopenia	0	0	0	1 (7.7)	0	0
Lymphopenia	0	0	0	1 (7.7)	1 (7.7)	0
Thrombocytopenia	0	0	0	1 (7.7)	0	0
Gastrointestinal disorders	1 (100)	1 (100)	0	11 (84.6)	4 (30.8)	1 (7.7)
Diarrhoea	1 (100)	1 (100)	0	8 (61.5)	4 (30.8)	0
Stomatitis	1 (100)	1 (100)	0	8 (61.5)	1 (7.7)	0
Nausea	1 (100)	0	0	7 (53.8)	0	0
Abdominal pain	1 (100)	0	0	5 (38.5)	0	0
Vomiting	1 (100)	0	0	5 (38.5)	0	0
Abdominal pain upper	0	0	0	2 (15.4)	0	0
Aphthous ulcer	0	0	0	2 (15.4)	0	0
Constipation	0	0	0	2 (15.4)	0	0
Abdominal distension	0	0	0	1 (7.7)	0	0
Anal fissure	0	0	0	1 (7.7)	0	0
Anal inflammation	0	0	0	1 (7.7)	0	0
Ascites	0	0	0	1 (7.7)	0	0
Dry mouth	0	0	0	1 (7.7)	0	0
Dyspepsia	0	0	0	1 (7.7)	0	0

Primary system organ class Preferred term	Alpelisib 300mg + Everolimus 2.5mg N=6 All Grades n (%)	 Grade 3 n (%)	 Grade 4 n (%)	Alpelisib 250mg + Everolimus 2.5mg N=6 All Grades n (%)	 Grade 3 n (%)	 Grade 4 n (%)
Gastrointestinal disorders						
Gastric haemorrhage	1 (16.7)	0	1 (16.7)	0	0	0
Gastritis	0	0	0	1 (16.7)	0	0
Gingival pain	0	0	0	1 (16.7)	0	0
Haemorrhoids	0	0	0	1 (16.7)	0	0
Lip ulceration	1 (16.7)	0	0	0	0	0
Rectal haemorrhage	0	0	0	1 (16.7)	1 (16.7)	0
General disorders and administration site conditions	4 (66.7)	1 (16.7)	0	5 (83.3)	1 (16.7)	0
Asthenia	4 (66.7)	1 (16.7)	0	2 (33.3)	1 (16.7)	0
Pyrexia	3 (50.0)	0	0	1 (16.7)	0	0
Fatigue	1 (16.7)	1 (16.7)	0	2 (33.3)	0	0
Non-cardiac chest pain	2 (33.3)	0	0	1 (16.7)	0	0
Oedema peripheral	1 (16.7)	0	0	1 (16.7)	0	0
Hyperpyrexia	0	0	0	1 (16.7)	0	0
Malaise	1 (16.7)	0	0	0	0	0
Pain	0	0	0	1 (16.7)	0	0
Infections and infestations	4 (66.7)	1 (16.7)	0	5 (83.3)	0	0
Urinary tract infection	2 (33.3)	0	0	1 (16.7)	0	0
Clostridium difficile infection	1 (16.7)	1 (16.7)	0	0	0	0
Cystitis	0	0	0	1 (16.7)	0	0
Folliculitis	0	0	0	1 (16.7)	0	0
Fungal infection	1 (16.7)	0	0	0	0	0

Primary system organ class Preferred term	Alpelisib 200mg + Everolimus 2.5mg N=1 All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All subjects N=13 All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Gastrointestinal disorders						
Gastric haemorrhage	0	0	0	1 (7.7)	0	1 (7.7)
Gastritis	0	0	0	1 (7.7)	0	0
Gingival pain	0	0	0	1 (7.7)	0	0
Haemorrhoids	0	0	0	1 (7.7)	0	0
Lip ulceration	0	0	0	1 (7.7)	0	0
Rectal haemorrhage	0	0	0	1 (7.7)	1 (7.7)	0
General disorders and administration site conditions	1 (100)	0	0	10 (76.9)	2 (15.4)	0
Asthenia	1 (100)	0	0	7 (53.8)	2 (15.4)	0
Pyrexia	1 (100)	0	0	5 (38.5)	0	0
Fatigue	0	0	0	3 (23.1)	1 (7.7)	0
Non-cardiac chest pain	0	0	0	3 (23.1)	0	0
Oedema peripheral	0	0	0	2 (15.4)	0	0
Hyperpyrexia	0	0	0	1 (7.7)	0	0
Malaise	0	0	0	1 (7.7)	0	0
Pain	0	0	0	1 (7.7)	0	0
Infections and infestations	1 (100)	0	0	10 (76.9)	1 (7.7)	0
Urinary tract infection	0	0	0	3 (23.1)	0	0
Clostridium difficile infection	0	0	0	1 (7.7)	1 (7.7)	0
Cystitis	0	0	0	1 (7.7)	0	0
Folliculitis	0	0	0	1 (7.7)	0	0
Fungal infection	0	0	0	1 (7.7)	0	0

Primary system organ class Preferred term	Alpelisib 300mg + Everolimus 2.5mg N=6 All Grades n (%)	 Grade 3 n (%)	 Grade 4 n (%)	Alpelisib 250mg + Everolimus 2.5mg N=6 All Grades n (%)	 Grade 3 n (%)	 Grade 4 n (%)
Infections and infestations						
Hordeolum	0	0	0	1 (16.7)	0	0
Oral candidiasis	0	0	0	1 (16.7)	0	0
Oral fungal infection	0	0	0	0	0	0
Pneumonia	1 (16.7)	0	0	0	0	0
Sinusitis	0	0	0	1 (16.7)	0	0
Vulvitis	1 (16.7)	0	0	0	0	0
Vulvovaginal mycotic infection	0	0	0	1 (16.7)	0	0
Injury, poisoning and procedural complications	1 (16.7)	0	0	1 (16.7)	0	0
Fall	1 (16.7)	0	0	0	0	0
Muscle rupture	0	0	0	1 (16.7)	0	0
Spinal compression fracture	1 (16.7)	0	0	0	0	0
Spinal fracture	1 (16.7)	0	0	0	0	0
Investigations	3 (50.0)	0	1 (16.7)	4 (66.7)	2 (33.3)	0
Blood creatinine increased	2 (33.3)	0	0	3 (50.0)	0	0
Weight decreased	2 (33.3)	0	0	3 (50.0)	0	0
Lipase increased	1 (16.7)	0	1 (16.7)	1 (16.7)	1 (16.7)	0
Aspartate aminotransferase increased	1 (16.7)	0	0	0	0	0
Blood potassium decreased	0	0	0	1 (16.7)	1 (16.7)	0
International normalised ratio increased	1 (16.7)	0	0	0	0	0

Primary system organ class Preferred term	Alpelisib 200mg + Everolimus 2.5mg N=1 All Grades n (%)	 Grade 3 n (%)	 Grade 4 n (%)	All subjects N=13 All Grades n (%)	 Grade 3 n (%)	 Grade 4 n (%)
Infections and infestations						
Hordeolum	0	0	0	1 (7.7)	0	0
Oral candidiasis	0	0	0	1 (7.7)	0	0
Oral fungal infection	1 (100)	0	0	1 (7.7)	0	0
Pneumonia	0	0	0	1 (7.7)	0	0
Sinusitis	0	0	0	1 (7.7)	0	0
Vulvitis	0	0	0	1 (7.7)	0	0
Vulvovaginal mycotic infection	0	0	0	1 (7.7)	0	0
Injury, poisoning and procedural complications	0	0	0	2 (15.4)	0	0
Fall	0	0	0	1 (7.7)	0	0
Muscle rupture	0	0	0	1 (7.7)	0	0
Spinal compression fracture	0	0	0	1 (7.7)	0	0
Spinal fracture	0	0	0	1 (7.7)	0	0
Investigations	0	0	0	7 (53.8)	2 (15.4)	1 (7.7)
Blood creatinine increased	0	0	0	5 (38.5)	0	0
Weight decreased	0	0	0	5 (38.5)	0	0
Lipase increased	0	0	0	2 (15.4)	1 (7.7)	1 (7.7)
Aspartate aminotransferase increased	0	0	0	1 (7.7)	0	0
Blood potassium decreased	0	0	0	1 (7.7)	1 (7.7)	0
International normalised ratio increased	0	0	0	1 (7.7)	0	0

Primary system organ class Preferred term	Alpelisib 300mg + Everolimus 2.5mg N=6 All Grades n (%)	 Grade 3 n (%)	 Grade 4 n (%)	Alpelisib 250mg + Everolimus 2.5mg N=6 All Grades n (%)	 Grade 3 n (%)	 Grade 4 n (%)
Metabolism and nutrition disorders	6 (100)	2 (33.3)	1 (16.7)	4 (66.7)	3 (50.0)	1 (16.7)
Hyperglycaemia	6 (100)	3 (50.0)	0	4 (66.7)	3 (50.0)	0
Decreased appetite	3 (50.0)	0	0	3 (50.0)	1 (16.7)	0
Dehydration	3 (50.0)	0	0	0	0	0
Hyponatraemia	2 (33.3)	0	1 (16.7)	1 (16.7)	1 (16.7)	0
Hypokalaemia	2 (33.3)	1 (16.7)	0	0	0	0
Hypertriglyceridaemia	0	0	0	1 (16.7)	0	0
Hyperuricaemia	1 (16.7)	0	0	0	0	0
Hypocalcaemia	0	0	0	1 (16.7)	0	1 (16.7)
Hypoglycaemia	1 (16.7)	0	0	0	0	0
Hypomagnesaemia	1 (16.7)	0	0	0	0	0
Hypophosphataemia	1 (16.7)	1 (16.7)	0	0	0	0
Musculoskeletal and connective tissue disorders	4 (66.7)	1 (16.7)	0	1 (16.7)	0	0
Arthralgia	2 (33.3)	0	0	1 (16.7)	0	0
Back pain	3 (50.0)	1 (16.7)	0	0	0	0
Coccydynia	1 (16.7)	0	0	0	0	0
Muscle spasms	0	0	0	1 (16.7)	0	0
Musculoskeletal chest pain	1 (16.7)	0	0	0	0	0
Sacroiliitis	1 (16.7)	0	0	0	0	0
Nervous system disorders	2 (33.3)	0	0	4 (66.7)	1 (16.7)	0
Dysgeusia	0	0	0	2 (33.3)	0	0
Neuralgia	1 (16.7)	0	0	1 (16.7)	1 (16.7)	0

Primary system organ class Preferred term	Alpelisib 200mg + Everolimus 2.5mg N=1 All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All subjects N=13 All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Metabolism and nutrition disorders	1 (100)	0	0	11 (84.6)	5 (38.5)	2 (15.4)
Hyperglycaemia	1 (100)	0	0	11 (84.6)	6 (46.2)	0
Decreased appetite	1 (100)	0	0	7 (53.8)	1 (7.7)	0
Dehydration	0	0	0	3 (23.1)	0	0
Hyponatraemia	0	0	0	3 (23.1)	1 (7.7)	1 (7.7)
Hypokalaemia	0	0	0	2 (15.4)	1 (7.7)	0
Hypertriglyceridaemia	0	0	0	1 (7.7)	0	0
Hyperuricaemia	0	0	0	1 (7.7)	0	0
Hypocalcaemia	0	0	0	1 (7.7)	0	1 (7.7)
Hypoglycaemia	0	0	0	1 (7.7)	0	0
Hypomagnesaemia	0	0	0	1 (7.7)	0	0
Hypophosphataemia	0	0	0	1 (7.7)	1 (7.7)	0
Musculoskeletal and connective tissue disorders	0	0	0	5 (38.5)	1 (7.7)	0
Arthralgia	0	0	0	3 (23.1)	0	0
Back pain	0	0	0	3 (23.1)	1 (7.7)	0
Coccydynia	0	0	0	1 (7.7)	0	0
Muscle spasms	0	0	0	1 (7.7)	0	0
Musculoskeletal chest pain	0	0	0	1 (7.7)	0	0
Sacroiliitis	0	0	0	1 (7.7)	0	0
Nervous system disorders	0	0	0	6 (46.2)	1 (7.7)	0
Dysgeusia	0	0	0	2 (15.4)	0	0
Neuralgia	0	0	0	2 (15.4)	1 (7.7)	0

Primary system organ class Preferred term	Alpelisib 300mg + Everolimus 2.5mg N=6 All Grades n (%)	 Grade 3 n (%)	 Grade 4 n (%)	Alpelisib 250mg + Everolimus 2.5mg N=6 All Grades n (%)	 Grade 3 n (%)	 Grade 4 n (%)
Nervous system disorders						
Dizziness	1 (16.7)	0	0	0	0	0
Headache	0	0	0	1 (16.7)	0	0
Memory impairment	0	0	0	1 (16.7)	0	0
Paraesthesia	0	0	0	1 (16.7)	0	0
Peripheral sensory neuropathy	1 (16.7)	0	0	0	0	0
Phantom pain	0	0	0	1 (16.7)	0	0
Radicular pain	1 (16.7)	0	0	0	0	0
Psychiatric disorders	2 (33.3)	0	0	0	0	0
Agitation	1 (16.7)	0	0	0	0	0
Insomnia	1 (16.7)	0	0	0	0	0
Renal and urinary disorders	2 (33.3)	1 (16.7)	0	1 (16.7)	0	0
Acute kidney injury	1 (16.7)	0	0	1 (16.7)	0	0
Anuria	1 (16.7)	1 (16.7)	0	0	0	0
Dysuria	0	0	0	1 (16.7)	0	0
Micturition disorder	1 (16.7)	0	0	0	0	0
Renal impairment	1 (16.7)	1 (16.7)	0	0	0	0
Urethral haemorrhage	1 (16.7)	0	0	0	0	0
Respiratory, thoracic and mediastinal disorders	3 (50.0)	0	0	3 (50.0)	0	0
Catarrh	1 (16.7)	0	0	1 (16.7)	0	0
Cough	0	0	0	2 (33.3)	0	0

Primary system organ class Preferred term	Alpelisib 200mg + Everolimus 2.5mg N=1 All Grades n (%)	 Grade 3 n (%)	 Grade 4 n (%)	All subjects N=13 All Grades n (%)	 Grade 3 n (%)	 Grade 4 n (%)
Nervous system disorders						
Dizziness	0	0	0	1 (7.7)	0	0
Headache	0	0	0	1 (7.7)	0	0
Memory impairment	0	0	0	1 (7.7)	0	0
Paraesthesia	0	0	0	1 (7.7)	0	0
Peripheral sensory neuropathy	0	0	0	1 (7.7)	0	0
Phantom pain	0	0	0	1 (7.7)	0	0
Radicular pain	0	0	0	1 (7.7)	0	0
Psychiatric disorders	0	0	0	2 (15.4)	0	0
Agitation	0	0	0	1 (7.7)	0	0
Insomnia	0	0	0	1 (7.7)	0	0
Renal and urinary disorders	0	0	0	3 (23.1)	1 (7.7)	0
Acute kidney injury	0	0	0	2 (15.4)	0	0
Anuria	0	0	0	1 (7.7)	1 (7.7)	0
Dysuria	0	0	0	1 (7.7)	0	0
Micturition disorder	0	0	0	1 (7.7)	0	0
Renal impairment	0	0	0	1 (7.7)	1 (7.7)	0
Urethral haemorrhage	0	0	0	1 (7.7)	0	0
Respiratory, thoracic and mediastinal disorders	0	0	0	6 (46.2)	0	0
Catarrh	0	0	0	2 (15.4)	0	0
Cough	0	0	0	2 (15.4)	0	0

Primary system organ class Preferred term	Alpelisib 300mg + Everolimus 2.5mg N=6 All Grades n (%)	 Grade 3 n (%)	 Grade 4 n (%)	Alpelisib 250mg + Everolimus 2.5mg N=6 All Grades n (%)	 Grade 3 n (%)	 Grade 4 n (%)
Respiratory, thoracic and mediastinal disorders						
Dyspnoea	2 (33.3)	0	0	0	0	0
Chronic obstructive pulmonary disease	1 (16.7)	0	0	0	0	0
Hypoxia	1 (16.7)	0	0	0	0	0
Pleural effusion	1 (16.7)	0	0	0	0	0
Productive cough	1 (16.7)	0	0	0	0	0
Wheezing	1 (16.7)	0	0	0	0	0
Skin and subcutaneous tissue disorders	3 (50.0)	0	0	3 (50.0)	0	0
Dry skin	1 (16.7)	0	0	1 (16.7)	0	0
Rash	0	0	0	1 (16.7)	0	0
Skin ulcer	1 (16.7)	0	0	1 (16.7)	0	0
Dermatitis acneiform	1 (16.7)	0	0	0	0	0
Erythema	0	0	0	1 (16.7)	0	0
Night sweats	1 (16.7)	0	0	0	0	0
Pruritus	0	0	0	1 (16.7)	0	0
Rash maculo-papular	0	0	0	1 (16.7)	0	0
Skin fissures	0	0	0	1 (16.7)	0	0
Skin lesion	0	0	0	0	0	0
Vascular disorders	2 (33.3)	2 (33.3)	0	2 (33.3)	1 (16.7)	1 (16.7)
Hypertension	2 (33.3)	2 (33.3)	0	1 (16.7)	0	1 (16.7)

Primary system organ class Preferred term	Alpelisib 200mg + Everolimus 2.5mg N=1 All Grades n (%)	 Grade 3 n (%)	 Grade 4 n (%)	All subjects N=13 All Grades n (%)	 Grade 3 n (%)	 Grade 4 n (%)
Respiratory, thoracic and mediastinal disorders						
Dyspnoea	0	0	0	2 (15.4)	0	0
Chronic obstructive pulmonary disease	0	0	0	1 (7.7)	0	0
Hypoxia	0	0	0	1 (7.7)	0	0
Pleural effusion	0	0	0	1 (7.7)	0	0
Productive cough	0	0	0	1 (7.7)	0	0
Wheezing	0	0	0	1 (7.7)	0	0
Skin and subcutaneous tissue disorders	1 (100)	1 (100)	0	7 (53.8)	1 (7.7)	0
Dry skin	0	0	0	2 (15.4)	0	0
Rash	1 (100)	1 (100)	0	2 (15.4)	1 (7.7)	0
Skin ulcer	0	0	0	2 (15.4)	0	0
Dermatitis acneiform	0	0	0	1 (7.7)	0	0
Erythema	0	0	0	1 (7.7)	0	0
Night sweats	0	0	0	1 (7.7)	0	0
Pruritus	0	0	0	1 (7.7)	0	0
Rash maculo-papular	0	0	0	1 (7.7)	0	0
Skin fissures	0	0	0	1 (7.7)	0	0
Skin lesion	1 (100)	0	0	1 (7.7)	0	0
Vascular disorders	0	0	0	4 (30.8)	3 (23.1)	1 (7.7)
Hypertension	0	0	0	3 (23.1)	2 (15.4)	1 (7.7)

Primary system organ class Preferred term	Alpelisib 300mg + Everolimus 2.5mg N=6 All Grades n (%)	 Grade 3 n (%)	 Grade 4 n (%)	Alpelisib 250mg + Everolimus 2.5mg N=6 All Grades n (%)	 Grade 3 n (%)	 Grade 4 n (%)
Vascular disorders						
Peripheral artery aneurysm	0	0	0	1 (16.7)	1 (16.7)	0

Primary system organ class Preferred term	Alpelisib 200mg + Everolimus 2.5mg N=1 All Grades n (%)	 Grade 3 n (%)	 Grade 4 n (%)	All subjects N=13 All Grades n (%)	 Grade 3 n (%)	 Grade 4 n (%)
Vascular disorders						
Peripheral artery aneurysm	0	0	0	1 (7.7)	1 (7.7)	0

Numbers (n) represent counts of subjects.

A subject with multiple severity grades for an AE is only counted under the maximum grade.

MedDRA version 20.1, CTCAE version 4.03.

Adverse events by system organ class and preferred term by dose level - Triplet escalation phase (Safety set)

Primary system organ class Preferred term	Alpelisib 200mg + Everolimus 2.5mg + Exemestane 25mg N=7 All Grades n (%)	 Grade 3 n (%)	 Grade 4 n (%)
Number of subjects with at least one event	7 (100)	1 (14.3)	2 (28.6)
Blood and lymphatic system disorders	2 (28.6)	2 (28.6)	0
Anaemia	2 (28.6)	2 (28.6)	0
Leukopenia	1 (14.3)	0	0
Lymphopenia	1 (14.3)	1 (14.3)	0
Cardiac disorders	1 (14.3)	0	0
Atrial fibrillation	1 (14.3)	0	0
Eye disorders	1 (14.3)	0	0
Eczema eyelids	1 (14.3)	0	0
Gastrointestinal disorders	7 (100)	1 (14.3)	0
Stomatitis	5 (71.4)	1 (14.3)	0
Nausea	4 (57.1)	0	0
Vomiting	3 (42.9)	0	0
Constipation	2 (28.6)	0	0
Diarrhoea	2 (28.6)	0	0
Dyspepsia	2 (28.6)	0	0
Abdominal pain	1 (14.3)	0	0
Anal pruritus	1 (14.3)	0	0

Primary system organ class Preferred term	Alpelisib 200mg + Everolimus 2.5mg + Exemestane 25mg N=7 All Grades n (%)	 Grade 3 n (%)	 Grade 4 n (%)
Gastrointestinal disorders			
Dry mouth	1 (14.3)	0	0
Gastritis	1 (14.3)	0	0
Gastrointestinal pain	1 (14.3)	0	0
Gastrooesophageal reflux disease	1 (14.3)	0	0
Oral mucosal erythema	1 (14.3)	0	0
General disorders and administration site conditions	7 (100)	3 (42.9)	0
Pyrexia	6 (85.7)	0	0
Asthenia	4 (57.1)	0	0
Fatigue	4 (57.1)	3 (42.9)	0
Non-cardiac chest pain	2 (28.6)	0	0
Oedema peripheral	1 (14.3)	0	0
Infections and infestations	5 (71.4)	0	0
Conjunctivitis	1 (14.3)	0	0
Gingivitis	1 (14.3)	0	0
Herpes simplex	1 (14.3)	0	0
Influenza	1 (14.3)	0	0
Klebsiella infection	1 (14.3)	0	0
Pharyngitis	1 (14.3)	0	0
Tooth abscess	1 (14.3)	0	0

Primary system organ class Preferred term	Alpelisib 200mg + Everolimus 2.5mg + Exemestane 25mg N=7 All Grades n (%)	 Grade 3 n (%)	 Grade 4 n (%)
Injury, poisoning and procedural complications	1 (14.3)	0	0
Accidental overdose	1 (14.3)	0	0
Investigations	4 (57.1)	1 (14.3)	2 (28.6)
Gamma-glutamyltransferase increased	4 (57.1)	0	2 (28.6)
Alanine aminotransferase increased	2 (28.6)	0	0
Blood alkaline phosphatase increased	2 (28.6)	0	0
Blood creatinine increased	2 (28.6)	1 (14.3)	0
Aspartate aminotransferase increased	1 (14.3)	1 (14.3)	0
Blood cholesterol increased	1 (14.3)	0	0
Blood insulin increased	1 (14.3)	0	0
Prothrombin time prolonged	1 (14.3)	0	0
Metabolism and nutrition disorders	7 (100)	1 (14.3)	0
Hyperglycaemia	7 (100)	0	0
Decreased appetite	3 (42.9)	0	0
Hypercalcaemia	1 (14.3)	0	0
Hypokalaemia	1 (14.3)	1 (14.3)	0
Hyponatraemia	1 (14.3)	0	0

Primary system organ class Preferred term	Alpelisib 200mg + Everolimus 2.5mg + Exemestane 25mg N=7 All Grades n (%)	 Grade 3 n (%)	 Grade 4 n (%)
Metabolism and nutrition disorders			
Polydipsia	1 (14.3)	0	0
Musculoskeletal and connective tissue disorders	4 (57.1)	0	0
Myalgia	2 (28.6)	0	0
Arthralgia	1 (14.3)	0	0
Back pain	1 (14.3)	0	0
Bone pain	1 (14.3)	0	0
Coccydynia	1 (14.3)	0	0
Muscle spasms	1 (14.3)	0	0
Nervous system disorders	3 (42.9)	0	0
Aphonia	1 (14.3)	0	0
Headache	1 (14.3)	0	0
Neuropathy peripheral	1 (14.3)	0	0
Psychiatric disorders	1 (14.3)	0	0
Depression	1 (14.3)	0	0
Panic attack	1 (14.3)	0	0
Renal and urinary disorders	2 (28.6)	1 (14.3)	0
Acute kidney injury	1 (14.3)	1 (14.3)	0
Cystitis noninfective	1 (14.3)	0	0

Primary system organ class Preferred term	Alpelisib 200mg + Everolimus 2.5mg + Exemestane 25mg N=7 All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Renal and urinary disorders			
Renal failure	1 (14.3)	0	0
Reproductive system and breast disorders	1 (14.3)	0	0
Breast pain	1 (14.3)	0	0
Respiratory, thoracic and mediastinal disorders	4 (57.1)	0	0
Oropharyngeal pain	3 (42.9)	0	0
Cough	2 (28.6)	0	0
Dysphonia	2 (28.6)	0	0
Dyspnoea	1 (14.3)	0	0
Skin and subcutaneous tissue disorders	4 (57.1)	0	0
Rash	2 (28.6)	0	0
Rash maculo-papular	2 (28.6)	0	0
Erythema	1 (14.3)	0	0
Nail disorder	1 (14.3)	0	0
Vascular disorders	1 (14.3)	0	0
Lymphoedema	1 (14.3)	0	0

Numbers (n) represent counts of subjects.
A subject with multiple severity grades for an AE is only counted under the maximum grade.
MedDRA version 20.1, CTCAE version 4.03

Adverse events by system organ class by cohort - Doublet expansion phase (Safety set)

Primary system organ class	RCC N=21		pNET N=17		Prior mTOR N=10		All subjects N=48	
	All Grades n (%)	Grade >=3 n (%)	All Grades n (%)	Grade >=3 n (%)	All Grades n (%)	Grade >=3 n (%)	All Grades n (%)	Grade >=3 n (%)
Number of subjects with at least one event	21 (100)	19 (90.5)	17 (100)	14 (82.4)	10 (100)	5 (50.0)	48 (100)	38 (79.2)
Metabolism and nutrition disorders	19 (90.5)	10 (47.6)	15 (88.2)	7 (41.2)	8 (80.0)	4 (40.0)	42 (87.5)	21 (43.8)
Gastrointestinal disorders	18 (85.7)	3 (14.3)	13 (76.5)	6 (35.3)	8 (80.0)	0	39 (81.3)	9 (18.8)
General disorders and administration site conditions	17 (81.0)	3 (14.3)	10 (58.8)	2 (11.8)	5 (50.0)	1 (10.0)	32 (66.7)	6 (12.5)
Investigations	13 (61.9)	4 (19.0)	7 (41.2)	2 (11.8)	4 (40.0)	1 (10.0)	24 (50.0)	7 (14.6)
Infections and infestations	11 (52.4)	2 (9.5)	7 (41.2)	4 (23.5)	4 (40.0)	1 (10.0)	22 (45.8)	7 (14.6)
Skin and subcutaneous tissue disorders	12 (57.1)	2 (9.5)	9 (52.9)	0	1 (10.0)	0	22 (45.8)	2 (4.2)
Musculoskeletal and connective tissue disorders	10 (47.6)	2 (9.5)	6 (35.3)	1 (5.9)	4 (40.0)	1 (10.0)	20 (41.7)	4 (8.3)
Respiratory, thoracic and mediastinal disorders	12 (57.1)	4 (19.0)	7 (41.2)	2 (11.8)	1 (10.0)	0	20 (41.7)	6 (12.5)
Blood and lymphatic system disorders	9 (42.9)	3 (14.3)	7 (41.2)	0	3 (30.0)	2 (20.0)	19 (39.6)	5 (10.4)
Nervous system disorders	10 (47.6)	1 (4.8)	6 (35.3)	0	2 (20.0)	1 (10.0)	18 (37.5)	2 (4.2)
Psychiatric disorders	8 (38.1)	0	4 (23.5)	1 (5.9)	1 (10.0)	0	13 (27.1)	1 (2.1)
Renal and urinary disorders	5 (23.8)	1 (4.8)	4 (23.5)	0	3 (30.0)	1 (10.0)	12 (25.0)	2 (4.2)
Eye disorders	4 (19.0)	0	3 (17.6)	0	1 (10.0)	0	8 (16.7)	0
Vascular disorders	2 (9.5)	1 (4.8)	4 (23.5)	1 (5.9)	1 (10.0)	0	7 (14.6)	2 (4.2)
Cardiac disorders	3 (14.3)	0	2 (11.8)	1 (5.9)	0	0	5 (10.4)	1 (2.1)

Primary system organ class	RCC N=21		pNET N=17		Prior mTOR N=10		All subjects N=48	
	All Grades n (%)	Grade >=3 n (%)	All Grades n (%)	Grade >=3 n (%)	All Grades n (%)	Grade >=3 n (%)	All Grades n (%)	Grade >=3 n (%)
Injury, poisoning and procedural complications	3 (14.3)	1 (4.8)	2 (11.8)	0	0	0	5 (10.4)	1 (2.1)
Reproductive system and breast disorders	3 (14.3)	1 (4.8)	1 (5.9)	0	1 (10.0)	0	5 (10.4)	1 (2.1)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	4 (19.0)	2 (9.5)	0	0	0	0	4 (8.3)	2 (4.2)
Hepatobiliary disorders	1 (4.8)	0	1 (5.9)	0	0	0	2 (4.2)	0
Congenital, familial and genetic disorders	1 (4.8)	0	0	0	0	0	1 (2.1)	0
Ear and labyrinth disorders	0	0	0	0	1 (10.0)	0	1 (2.1)	0
Endocrine disorders	1 (4.8)	0	0	0	0	0	1 (2.1)	0
Social circumstances	1 (4.8)	0	0	0	0	0	1 (2.1)	0

Planned starting doses for the Doublet are BYL719 250 mg + Everolimus 2.5 mg
Numbers (n) represent counts of subjects.
A subject with multiple severity grades for an AE is only counted under the maximum grade.
MedDRA version 20.1, CTCAE version 4.03.

Adverse events by system organ class and preferred term by treatment - Breast cancer expansion phase (Safety set)

Primary system organ class Preferred term	Alpelisib 200mg + Everolimus 2.5mg + Exemestane 25mg N=8 All Grades n (%)	 Grade 3 n (%)	 Grade 4 n (%)	Alpelisib 250mg + Exemestane 25mg N=3 All Grades n (%)	 Grade 3 n (%)	 Grade 4 n (%)
Number of subjects with at least one event	8 (100)	2 (25.0)	2 (25.0)	3 (100)	1 (33.3)	0
Blood and lymphatic system disorders	1 (12.5)	0	0	1 (33.3)	1 (33.3)	0
Leukopenia	1 (12.5)	0	0	0	0	0
Neutropenia	1 (12.5)	0	0	0	0	0
Anaemia	0	0	0	1 (33.3)	1 (33.3)	0
Eye disorders	1 (12.5)	0	0	1 (33.3)	0	0
Eyelid oedema	1 (12.5)	0	0	0	0	0
Vision blurred	0	0	0	1 (33.3)	0	0
Gastrointestinal disorders	8 (100)	0	0	3 (100)	1 (33.3)	0
Stomatitis	6 (75.0)	0	0	1 (33.3)	0	0
Nausea	5 (62.5)	0	0	0	0	0
Diarrhoea	3 (37.5)	0	0	3 (100)	1 (33.3)	0
Constipation	2 (25.0)	0	0	0	0	0
Vomiting	2 (25.0)	0	0	0	0	0
Abdominal pain	1 (12.5)	0	0	1 (33.3)	0	0
Abdominal pain upper	1 (12.5)	0	0	0	0	0
Anal fissure	1 (12.5)	0	0	0	0	0
Aphthous ulcer	1 (12.5)	0	0	0	0	0
Dyspepsia	1 (12.5)	0	0	0	0	0

Primary system organ class Preferred term	Alpelisib 200mg + Everolimus 2.5mg + Exemestane 25mg N=8 All Grades n (%)	 Grade 3 n (%)	 Grade 4 n (%)	Alpelisib 250mg + Exemestane 25mg N=3 All Grades n (%)	 Grade 3 n (%)	 Grade 4 n (%)
Gastrointestinal disorders						
Gastritis	1 (12.5)	0	0	0	0	0
Haemorrhoids	1 (12.5)	0	0	0	0	0
Food poisoning	0	0	0	1 (33.3)	0	0
General disorders and administration site conditions	5 (62.5)	1 (12.5)	0	2 (66.7)	0	0
Asthenia	2 (25.0)	1 (12.5)	0	0	0	0
Non-cardiac chest pain	2 (25.0)	0	0	0	0	0
Face oedema	1 (12.5)	0	0	0	0	0
Fatigue	1 (12.5)	0	0	2 (66.7)	0	0
Pyrexia	1 (12.5)	0	0	0	0	0
Hepatobiliary disorders	1 (12.5)	0	0	0	0	0
Hyperbilirubinaemia	1 (12.5)	0	0	0	0	0
Hypertransaminasaemia	1 (12.5)	0	0	0	0	0
Infections and infestations	4 (50.0)	0	0	1 (33.3)	0	0
Conjunctivitis	1 (12.5)	0	0	0	0	0
Folliculitis	1 (12.5)	0	0	0	0	0
Fungal infection	1 (12.5)	0	0	0	0	0
Herpes zoster	1 (12.5)	0	0	0	0	0
Influenza	1 (12.5)	0	0	0	0	0
Pneumonia	1 (12.5)	0	0	0	0	0

Primary system organ class Preferred term	Alpelisib 200mg + Everolimus 2.5mg + Exemestane 25mg N=8			Alpelisib 250mg + Exemestane 25mg N=3		
	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Infections and infestations						
Staphylococcal infection	1 (12.5)	0	0	0	0	0
Gastric infection	0	0	0	1 (33.3)	0	0
Urinary tract infection	0	0	0	1 (33.3)	0	0
Investigations	4 (50.0)	1 (12.5)	2 (25.0)	1 (33.3)	0	0
Gamma-glutamyltransferase increased	3 (37.5)	0	2 (25.0)	0	0	0
Alanine aminotransferase increased	1 (12.5)	0	0	0	0	0
Aspartate aminotransferase increased	1 (12.5)	0	0	0	0	0
Blood alkaline phosphatase increased	1 (12.5)	0	0	0	0	0
Blood cholesterol increased	1 (12.5)	0	0	0	0	0
Weight decreased	1 (12.5)	1 (12.5)	0	1 (33.3)	0	0
Glycosylated haemoglobin increased	0	0	0	1 (33.3)	0	0
Metabolism and nutrition disorders	7 (87.5)	1 (12.5)	0	1 (33.3)	0	0
Hyperglycaemia	5 (62.5)	0	0	1 (33.3)	0	0
Decreased appetite	4 (50.0)	1 (12.5)	0	1 (33.3)	0	0
Hypercholesterolaemia	1 (12.5)	0	0	0	0	0
Hypokalaemia	1 (12.5)	0	0	1 (33.3)	0	0

Primary system organ class Preferred term	Alpelisib 200mg + Everolimus 2.5mg + Exemestane 25mg N=8 All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)	Alpelisib 250mg + Exemestane 25mg N=3 All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Musculoskeletal and connective tissue disorders	1 (12.5)	0	0	1 (33.3)	0	0
Musculoskeletal chest pain	1 (12.5)	0	0	0	0	0
Pain in extremity	1 (12.5)	0	0	0	0	0
Arthralgia	0	0	0	1 (33.3)	0	0
Nervous system disorders	4 (50.0)	0	0	2 (66.7)	0	0
Dysgeusia	4 (50.0)	0	0	1 (33.3)	0	0
Headache	1 (12.5)	0	0	1 (33.3)	0	0
Post herpetic neuralgia	1 (12.5)	0	0	0	0	0
Somnolence	1 (12.5)	0	0	0	0	0
Peripheral sensory neuropathy	0	0	0	1 (33.3)	0	0
Psychiatric disorders	2 (25.0)	0	0	0	0	0
Depression	2 (25.0)	0	0	0	0	0
Renal and urinary disorders	2 (25.0)	0	0	0	0	0
Micturition urgency	1 (12.5)	0	0	0	0	0
Proteinuria	1 (12.5)	0	0	0	0	0
Reproductive system and breast disorders	1 (12.5)	0	0	2 (66.7)	0	0
Breast pain	1 (12.5)	0	0	0	0	0
Pelvic pain	0	0	0	1 (33.3)	0	0

Primary system organ class Preferred term	Alpelisib 200mg + Everolimus 2.5mg + Exemestane 25mg N=8 All Grades n (%)	 Grade 3 n (%)	 Grade 4 n (%)	Alpelisib 250mg + Exemestane 25mg N=3 All Grades n (%)	 Grade 3 n (%)	 Grade 4 n (%)
Reproductive system and breast disorders						
Vulvovaginal dryness	0	0	0	1 (33.3)	0	0
Respiratory, thoracic and mediastinal disorders	2 (25.0)	0	0	0	0	0
Dyspnoea	1 (12.5)	0	0	0	0	0
Pharyngeal erythema	1 (12.5)	0	0	0	0	0
Skin and subcutaneous tissue disorders	6 (75.0)	0	0	1 (33.3)	0	0
Rash	3 (37.5)	0	0	0	0	0
Alopecia	1 (12.5)	0	0	1 (33.3)	0	0
Erythema	1 (12.5)	0	0	0	0	0
Nail discolouration	1 (12.5)	0	0	0	0	0
Pruritus	1 (12.5)	0	0	0	0	0
Eczema	0	0	0	1 (33.3)	0	0
Vascular disorders	2 (25.0)	0	0	0	0	0
Flushing	1 (12.5)	0	0	0	0	0
Lymphoedema	1 (12.5)	0	0	0	0	0

Serious adverse events by system organ class and preferred term by dose level - Doublet escalation phase (Safety set)

Primary system organ class Preferred term	Alpelisib 300mg + Everolimus 2.5mg N=6 All Grades n (%)	 Grade 3 n (%)	 Grade 4 n (%)	Alpelisib 250mg + Everolimus 2.5mg N=6 All Grades n (%)	 Grade 3 n (%)	 Grade 4 n (%)
Number of subjects with at least one event	4 (66.7)	0	1 (16.7)	2 (33.3)	0	2 (33.3)
Blood and lymphatic system disorders	1 (16.7)	0	0	0	0	0
Anaemia	1 (16.7)	0	0	0	0	0
Gastrointestinal disorders	2 (33.3)	0	1 (16.7)	1 (16.7)	1 (16.7)	0
Diarrhoea	2 (33.3)	1 (16.7)	0	0	0	0
Gastric haemorrhage	1 (16.7)	0	1 (16.7)	0	0	0
Rectal haemorrhage	0	0	0	1 (16.7)	1 (16.7)	0
Vomiting	1 (16.7)	0	0	0	0	0
Infections and infestations	1 (16.7)	0	0	0	0	0
Pneumonia	1 (16.7)	0	0	0	0	0
Metabolism and nutrition disorders	0	0	0	1 (16.7)	0	1 (16.7)
Hyperglycaemia	0	0	0	1 (16.7)	1 (16.7)	0
Hypocalcaemia	0	0	0	1 (16.7)	0	1 (16.7)
Renal and urinary disorders	1 (16.7)	1 (16.7)	0	0	0	0
Acute kidney injury	1 (16.7)	0	0	0	0	0
Anuria	1 (16.7)	1 (16.7)	0	0	0	0
Renal impairment	1 (16.7)	1 (16.7)	0	0	0	0

Primary system organ class Preferred term	Alpelisib 200mg + Everolimus 2.5mg N=1 All Grades n (%)	 Grade 3 n (%)	 Grade 4 n (%)	All subjects N=13 All Grades n (%)	 Grade 3 n (%)	 Grade 4 n (%)
Number of subjects with at least one event	0	0	0	6 (46.2)	0	3 (23.1)
Blood and lymphatic system disorders	0	0	0	1 (7.7)	0	0
Anaemia	0	0	0	1 (7.7)	0	0
Gastrointestinal disorders	0	0	0	3 (23.1)	1 (7.7)	1 (7.7)
Diarrhoea	0	0	0	2 (15.4)	1 (7.7)	0
Gastric haemorrhage	0	0	0	1 (7.7)	0	1 (7.7)
Rectal haemorrhage	0	0	0	1 (7.7)	1 (7.7)	0
Vomiting	0	0	0	1 (7.7)	0	0
Infections and infestations	0	0	0	1 (7.7)	0	0
Pneumonia	0	0	0	1 (7.7)	0	0
Metabolism and nutrition disorders	0	0	0	1 (7.7)	0	1 (7.7)
Hyperglycaemia	0	0	0	1 (7.7)	1 (7.7)	0
Hypocalcaemia	0	0	0	1 (7.7)	0	1 (7.7)
Renal and urinary disorders	0	0	0	1 (7.7)	1 (7.7)	0
Acute kidney injury	0	0	0	1 (7.7)	0	0
Anuria	0	0	0	1 (7.7)	1 (7.7)	0
Renal impairment	0	0	0	1 (7.7)	1 (7.7)	0

Primary system organ class Preferred term	Alpelisib 300mg + Everolimus 2.5mg N=6 All Grades n (%)	 Grade 3 n (%)	 Grade 4 n (%)	Alpelisib 250mg + Everolimus 2.5mg N=6 All Grades n (%)	 Grade 3 n (%)	 Grade 4 n (%)
Vascular disorders	0	0	0	2 (33.3)	1 (16.7)	1 (16.7)
Hypertension	0	0	0	1 (16.7)	0	1 (16.7)
Peripheral artery aneurysm	0	0	0	1 (16.7)	1 (16.7)	0

Primary system organ class Preferred term	Alpelisib 200mg + Everolimus 2.5mg N=1 All Grades n (%)	 Grade 3 n (%)	 Grade 4 n (%)	All subjects N=13 All Grades n (%)	 Grade 3 n (%)	 Grade 4 n (%)
Vascular disorders	0	0	0	2 (15.4)	1 (7.7)	1 (7.7)
Hypertension	0	0	0	1 (7.7)	0	1 (7.7)
Peripheral artery aneurysm	0	0	0	1 (7.7)	1 (7.7)	0

Serious adverse events by system organ class and preferred term by dose level - Triplet escalation phase (Safety set)

Primary system organ class Preferred term	Alpelisib 200mg + Everolimus 2.5mg + Exemestane 25mg N=7 All Grades n (%)	 Grade 3 n (%)	 Grade 4 n (%)
Number of subjects with at least one event	2 (28.6)	1 (14.3)	0
Injury, poisoning and procedural complications	1 (14.3)	0	0
Accidental overdose	1 (14.3)	0	0
Renal and urinary disorders	1 (14.3)	1 (14.3)	0
Acute kidney injury	1 (14.3)	1 (14.3)	0

Serious adverse events regardless of study drug relationship by preferred term by cohort - Doublet expansion phase (Safety set)

Preferred term	RCC N=21		pNET N=17		Prior mTOR N=10		All subjects N=48	
	All Grades n (%)	Grade >=3 n (%)	All Grades n (%)	Grade >=3 n (%)	All Grades n (%)	Grade >=3 n (%)	All Grades n (%)	Grade >=3 n (%)
Number of subjects with at least one event	10 (47.6)	7 (33.3)	7 (41.2)	6 (35.3)	4 (40.0)	4 (40.0)	21 (43.8)	17 (35.4)
Hyperglycaemia	2 (9.5)	2 (9.5)	2 (11.8)	2 (11.8)	0	0	4 (8.3)	4 (8.3)
Pneumonia	1 (4.8)	1 (4.8)	2 (11.8)	2 (11.8)	0	0	3 (6.3)	3 (6.3)
Pneumonitis	0	0	2 (11.8)	2 (11.8)	0	0	2 (4.2)	2 (4.2)
Acute kidney injury	1 (4.8)	1 (4.8)	0	0	0	0	1 (2.1)	1 (2.1)
Acute myocardial infarction	0	0	1 (5.9)	1 (5.9)	0	0	1 (2.1)	1 (2.1)
Acute respiratory distress syndrome	0	0	1 (5.9)	1 (5.9)	0	0	1 (2.1)	1 (2.1)
Anal abscess	0	0	1 (5.9)	0	0	0	1 (2.1)	0
Anorectal infection	1 (4.8)	1 (4.8)	0	0	0	0	1 (2.1)	1 (2.1)
Back pain	1 (4.8)	1 (4.8)	0	0	0	0	1 (2.1)	1 (2.1)
Bone pain	1 (4.8)	1 (4.8)	0	0	0	0	1 (2.1)	1 (2.1)
Cancer pain	1 (4.8)	1 (4.8)	0	0	0	0	1 (2.1)	1 (2.1)
Condition aggravated	0	0	0	0	1 (10.0)	1 (10.0)	1 (2.1)	1 (2.1)
Constipation	0	0	1 (5.9)	0	0	0	1 (2.1)	0
Dyspnoea	1 (4.8)	1 (4.8)	0	0	0	0	1 (2.1)	1 (2.1)
Femur fracture	1 (4.8)	1 (4.8)	0	0	0	0	1 (2.1)	1 (2.1)
Flank pain	0	0	1 (5.9)	1 (5.9)	0	0	1 (2.1)	1 (2.1)
Hypocalcaemia	0	0	1 (5.9)	1 (5.9)	0	0	1 (2.1)	1 (2.1)
Ischaemic stroke	0	0	0	0	1 (10.0)	1 (10.0)	1 (2.1)	1 (2.1)

Preferred term	RCC N=21		pNET N=17		Prior mTOR N=10		All subjects N=48	
	All Grades n (%)	Grade >=3 n (%)	All Grades n (%)	Grade >=3 n (%)	All Grades n (%)	Grade >=3 n (%)	All Grades n (%)	Grade >=3 n (%)
Lower respiratory tract infection	0	0	1 (5.9)	1 (5.9)	0	0	1 (2.1)	1 (2.1)
Lung disorder	1 (4.8)	0	0	0	0	0	1 (2.1)	0
Metastases to lung	1 (4.8)	0	0	0	0	0	1 (2.1)	0
Oedema	1 (4.8)	0	0	0	0	0	1 (2.1)	0
Osteonecrosis	0	0	1 (5.9)	0	0	0	1 (2.1)	0
Osteonecrosis of jaw	0	0	0	0	1 (10.0)	1 (10.0)	1 (2.1)	1 (2.1)
Pain in extremity	1 (4.8)	1 (4.8)	0	0	0	0	1 (2.1)	1 (2.1)
Pleural effusion	1 (4.8)	0	0	0	0	0	1 (2.1)	0
Rash	0	0	1 (5.9)	0	0	0	1 (2.1)	0
Renal failure	0	0	0	0	1 (10.0)	1 (10.0)	1 (2.1)	1 (2.1)
Soft tissue necrosis	1 (4.8)	1 (4.8)	0	0	0	0	1 (2.1)	1 (2.1)
Tumour pain	1 (4.8)	1 (4.8)	0	0	0	0	1 (2.1)	1 (2.1)
Urinary incontinence	1 (4.8)	1 (4.8)	0	0	0	0	1 (2.1)	1 (2.1)
Urinary tract infection	0	0	0	0	1 (10.0)	1 (10.0)	1 (2.1)	1 (2.1)
Urosepsis	0	0	1 (5.9)	1 (5.9)	0	0	1 (2.1)	1 (2.1)

Planned starting doses for the Doublet are BYL719 250 mg + Everolimus 2.5 mg
Numbers (n) represent counts of subjects.
A subject with multiple severity grades for an AE is only counted under the maximum grade.
MedDRA version 22.0, CTCAE version 4.03.

Serious adverse events by system organ class and preferred term by treatment - Breast cancer expansion phase (Safety set)

Primary system organ class Preferred term	Alpelisib 200mg + Everolimus 2.5mg + Exemestane 25mg N=8			Alpelisib 250mg + Exemestane 25mg N=3		
	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Number of subjects with at least one event	1 (12.5)	0	0	0	0	0
General disorders and administration site conditions	1 (12.5)	0	0	0	0	0
Non-cardiac chest pain	1 (12.5)	0	0	0	0	0

Numbers (n) represent counts of subjects.
A subject with multiple severity grades for an AE is only counted under the maximum grade.
MedDRA version 20.1, CTCAE version 4.03.

All deaths, by system organ class and preferred term by dose level - Doublet escalation phase (Safety set)

Primary system organ class Primary reason (preferred term)	Alpelisib 300mg + Everolimus 2.5mg N=6 n (%)	Alpelisib 250mg + Everolimus 2.5mg N=6 n (%)	Alpelisib 200mg + Everolimus 2.5mg N=1 n (%)	All subjects N=13 n (%)
Number of subjects who died	6 (100)	4 (66.7)	1 (100)	11 (84.6)
Other	2 (33.3)	0	0	2 (15.4)
Study Indication	4 (66.7)	4 (66.7)	1 (100)	9 (69.2)
Gastrointestinal disorders	1 (16.7)	0	0	1 (7.7)
Gastric haemorrhage	1 (16.7)	0	0	1 (7.7)
General disorders and administration site conditions	5 (83.3)	4 (66.7)	1 (100)	10 (76.9)
Death	1 (16.7)	0	0	1 (7.7)
Disease progression	4 (66.7)	4 (66.7)	1 (100)	9 (69.2)

Includes both on-treatment deaths, and those that occurred more than 30 days after last treatment.
MedDRA version 20.1.

All deaths, by system organ class and preferred term by dose level - Triplet escalation phase (Safety set)

Primary system organ class Primary reason (preferred term)	Alpelisib 200mg + Everolimus 2.5mg + Exemestane 25mg N=7 n (%)
Number of subjects who died	4 (57.1)
Other	2 (28.6)
Study Indication	2 (28.6)
General disorders and administration site conditions	3 (42.9)
Death	1 (14.3)
Disease progression	2 (28.6)
Respiratory, thoracic and mediastinal disorders	1 (14.3)
Pulmonary embolism	1 (14.3)

All deaths, by system organ class and preferred term by cohort - Doublet expansion phase (Safety set)

Primary system organ class Primary reason (preferred term)	RCC N=21 n (%)	pNET N=17 n (%)	Prior mTOR N=10 n (%)	All subjects N=48 n (%)
Number of subjects who died	13 (61.9)	4 (23.5)	6 (60.0)	23 (47.9)
Other	1 (4.8)	1 (5.9)	1 (10.0)	3 (6.3)
Study Indication	12 (57.1)	3 (17.6)	5 (50.0)	20 (41.7)
Cardiac disorders	0	0	1 (10.0)	1 (2.1)
Myocardial infarction	0	0	1 (10.0)	1 (2.1)
General disorders and administration site conditions	13 (61.9)	3 (17.6)	5 (50.0)	21 (43.8)
Death	1 (4.8)	0	0	1 (2.1)
Disease progression	12 (57.1)	3 (17.6)	5 (50.0)	20 (41.7)
Respiratory, thoracic and mediastinal disorders	0	1 (5.9)	0	1 (2.1)
Pneumonitis	0	1 (5.9)	0	1 (2.1)

Planned starting doses for the Doublet are BYL719 250 mg + Everolimus 2.5 mg
Includes both on-treatment deaths, and those that occurred more than 30 days after last treatment.
MedDRA version 20.1.

All deaths, by system organ class and preferred term by treatment - Breast cancer expansion phase (Safety set)

Primary system organ class Primary reason (preferred term)	Alpelisib 200mg + Everolimus 2.5mg + Exemestane 25mg N=8 n (%)	Alpelisib 250mg + Exemestane 25mg N=3 n (%)
Number of subjects who died	0	1 (33.3)
Other	0	1 (33.3)
General disorders and administration site conditions	0	1 (33.3)
Death	0	1 (33.3)

Includes both on-treatment deaths, and those that occurred more than 30 days after last treatment.
MedDRA version 20.1.

Other Relevant Findings
NA

Conclusion:

- The combination of alpelisib 250 mg + everolimus 2.5 mg was declared as MTD in the doublet escalation phase.
- The combination of alpelisib 200 mg + everolimus 2.5 mg + exemestane 25 mg was declared as MTD in the triplet escalation phase.
- Pharmacokinetics of alpelisib, everolimus and/exemestane were largely unchanged in combination with each other (doublet or triplet combination).
- Based on the formal assessment of the drug-drug interaction of alpelisib on everolimus, the magnitude of changes (~10% increase in Cmax and decrease in AUCtau) in everolimus PK at steady state are not clinically relevant. There is no clinically relevant drug-drug interaction between alpelisib and everolimus.
- The overall safety profile of alpelisib with everolimus and exemestane is manageable and reversible; the AEs observed in this study are consistent with the known safety profiles from either single agent and combination studies. Synergistic safety signals occurred for AEs known to be induced by the inhibition of the PI3K/mTOR pathway (e.g. hyperglycemia, stomatitis). No new safety signals or safety concerns were noted for the combinations.

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