NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Ribociclib/LEE011

Trial Indication(s)

Hormone receptor-positive HER2 negative locally advanced or metastatic breast cancer in postmenopausal women

Protocol Number

CLEE011X2106

Protocol Title

A phase Ib trial of LEE011 in combination with everolimus (RAD001) and exemestane in the treatment of postmenopausal women with hormone receptor positive, HER2 negative locally advanced or metastatic breast cancer

Clinical Trial Phase

Phase 1

Phase of Drug Development

Ib

Study Start/End Dates

Study Start Date: September 2013 (Actual)
Primary Completion Date: March 2018 (Actual)
Study Completion Date: April 2020 (Actual)

Reason for Termination (If applicable)

Study Design/Methodology

This was a multi-center, open-label, Phase Ib study consisting of a dose escalation and dose expansion parts. Dose escalation part of the trial was conducted in postmenopausal women with ER+ HER2 negative advanced breast cancer and dose expansion part in postmenopausal women with HR+ HER2 negative advanced breast cancer that was resistant to previous letrozole or anastrozole, defined as recurrence during or within 12 months after the end of adjuvant treatment or progression during or within 1 month after the end of treatment for advanced disease.

In the dose escalation part, the triplet (ribociclib+everolimus+exemestane) combination was explored in both fasted and fed states. Upon determination of recommended Phase 2 Dose (RP2D) in the dose escalation part of the study, for triplet (ribociclib+everolimus+exemestane) and doublet (ribociclib+exemestane) combinations, the dose expansion part of the study was initiated. Patients were enrolled into three treatment groups receiving triplet or doublet combination at RP2D given with food:

Two triplet combinations:

- Group 1: LEE011 + everolimus + exemestane in patients naive to CDK4/6 inhibitors
- Group 2: LEE011 + everolimus + exemestane in patients refractory to CDK4/6 inhibitor based therapy

One doublet combination:

- Group 3: LEE011 + exemestane in patients refractory to CDK4/6 inhibitor based therapy (except patients treated with prior LEE011 were not allowed in Group 3)

In the dose expansion phase, the clinical safety, tolerability, and efficacy of two investigational treatments in each of the above 3 groups of fed patients with HR+ HER2− advanced breast cancer refractory to prior Non-steroidal aromatase inhibitor (NSAI) treatment were assessed.

Centers

13 centers in 5 countries: United States(8), Spain(2), Belgium(1), Hong Kong(1), France(1)

Objectives:

Primary objectives:

Dose escalation

- To estimate the maximum tolerated dose (MTD(s)) and/or recommended Phase 2 dose (RP2D) of ribociclib in combination with everolimus and exemestane in patients with estrogen receptor-positive (ER-positive) human epidermal growth factor receptor 2-negative (HER2-negative) advanced breast cancer.*

Expansion

- To characterize the safety and tolerability of the triplet combination of ribociclib + everolimus + exemestane in patients naive or refractory to cyclin-dependent kinase 4/6 (CDK4/6) inhibitor based therapy.

Secondary objectives:

Dose escalation

- To characterize the safety and tolerability of the triplet combination of everolimus + exemestane + ribociclib and the doublet combination of exemestane + ribociclib.
- To determine the PK profile of everolimus and ribociclib in the triplet combination and of ribociclib and exemestane in the doublet combination
- To assess the preliminary anti-tumor activity of the triplet combination of ribociclib + everolimus + exemestane and the doublet combination of ribociclib + exemestane.

Expansion

- To assess the preliminary antitumor activity in each of the 2 groups of the triplet combination of ribociclib + everolimus + exemestane (Group 1 patients naive to CDK4/6 inhibitors and Group 2 patients refractory to CDK4/6 inhibitor based therapy).

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

Ribociclib capsules at dose strengths of 50 mg and 200 mg. Everolimus tablets at dose strengths of 1 mg, 2.5 mg, and 5 mg. Exemestane tablets at dose strengths of 25 mg.

Statistical Methods

In the dose escalation part, the primary variable was the incidence of dose limiting toxicity (DLTs) in Cycle 1. DLT is defined as treatment-related toxicity, occurring within the first 28 days of treatment (Cycle 1) with ribociclib + everolimus + exemestane or ribociclib + exemestane and meeting the criteria defined in protocol.

In the expansion part, the primary variables were the incidence and severity of AEs and SAEs.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:
- Adult women (≥ 18 years of age) with metastatic or locally advanced breast cancer
- Histological or cytological confirmation of ER+ breast cancer in dose escalation and HR+ breast cancer in dose expansion
- A representative tumor specimen must be available for molecular testing.
- Postmenopausal women. Postmenopausal status is defined either by:
- Age ≥ 18 with prior bilateral oophorectomy
- Age ≥ 60 years
- Age <60 years with amenorrhea for at least 12 months and both follicle-stimulating hormone (FSH) and estradiol levels are in postmenopausal range (according to the local laboratory)
- Recurrence while on, or within 12 months of end of adjuvant treatment with letrozole or anastrozole,
or
- Progression while on, or within one month of end of letrozole or anastrozole treatment for locally advanced or metastatic breast cancer.
-Patients must have:
• Measurable disease*: At least one lesion that can be accurately measured in at least one dimension ≥ 20 mm with conventional imaging techniques or ≥ 10 mm with spiral CT or MRI
or
• Bone lesions: lytic or mixed (lytic + sclerotic) in the absence of measurable disease as defined above.
- ECOG Performance Status 0-1.
- Fasting serum cholesterol ≤ 300 mg/dl or 7.75 mmol/L and fasting triglycerides ≤ 2.5 × ULN. In case one or both of these thresholds are exceeded, the patient can only be included after initiation of statin therapy and when the above mentioned values have been achieved

- Standard 12-lead ECG values defined as the mean of the triplicate ECGs and assessed by the central laboratory.
• QTcF interval at screening < 450 msec (using Fridericia's correction).
• Resting heart rate 50-90 bpm

Exclusion Criteria:
- HER2-overexpressing patients by local laboratory testing (IHC 3+ staining or in situ hybridization positive).
- Patients who received more than one chemotherapy line for advanced breast cancer.
- Previous treatment with exemestane or mTOR inhibitors* (Note: Patients with disease refractory to prior LEE011 are excluded for dose expansion Group 3 only).
- History of brain or other CNS metastases.
- Clinically significant, uncontrolled heart disease and/or recent cardiac repolarization abnormality including any of the following:
- History of myocardial infarction (MI), angina pectoris, symptomatic pericarditis, or coronary artery bypass graft (CABG) within 6 months prior to study entry
- Documented cardiomyopathy
- Left ventricular ejection fraction (LVEF) < 50% as determined by Multiple Gated acquisition scan (MUGA) or echocardiogram (ECHO)
- Long QT syndrome or family history of idiopathic sudden death or congenital long QT syndrome, and etc.
- Clinically significant cardiac arrhythmias, complete left bundle branch block, high-grade AV block
- Systolic Blood Pressure (SBP) >160 or <90 mmHg
- Patients who are currently receiving treatment with agents that are known to cause QTc prolongation in humans
- Patients who are currently receiving treatment (within 7 days prior to starting study treatment) with strong and moderate inhibitors or inducers of CYP3A4/5, substrates of CYP3A4/5 with a narrow therapeutic index or Herbal preparations/medications (Refer to Section 6.4 and Appendix 3)

Inclusion Criteria Exceptions for Phase Ib Dose Expansion patients:
Dose Expansion part of the study has 3 groups, following are the Inclusion Criteria exceptions for these 3 groups
a. Group 1 - Patients must not have received prior treatment with any CDK4/6 inhibitors
b. Group 2 - Patients must have disease progression while on or within one month after CDK4/6 inhibitor based therapy
c. Group 3 - Patients must have disease progression while on or within one month after CDK4/6 inhibitor based therapy (except those patients who received prior LEE011 based therapy).

Other protocol-defined Inclusion/Exclusion may apply.

Participant Flow Table

Overall Study

	LEE011(200 mg)+eve(2.5 mg)+exe (25mg) (fasting) esc naive	LEE011(200 mg)+eve(2.5 mg)+exe (25mg) (FED) esc refractory	LEE011(600 mg)+exe(25 mg) esc refractory	LEE011(300 mg)+eve(2.5 mg)+exe (25mg) exp naive	LEE011(300 mg)+eve(2.5 mg)+exe (25mg) exp refractory	LEE011(600 mg)+exe(25 mg) exp refractory	Total
Arm/Group Description	Triplet combination of LEE011 200 mg + everolimus (RAD001) 2.5 mg + exemestane 25 mg was administered in fasting to the naive to CDK4/6 inhibitors group	Triplet combination of LEE011 200 mg + everolimus (RAD001) 2.5 mg + exemestane 25 mg was administered with food to the refractory to CDK4/6 inhibitor based therapy group	Doublet combination, LEE011 600 mg + exemestane 25 mg was administered with food to the refractory to CDK4/6 inhibitor based therapy group	Following RP2D declaration for the triplet combination, LEE011 300 mg + everolimus 2.5 mg + exemestane 25 mg was administered with food to the naive to CDK4/6 inhibitors group	Following RP2D declaration for the triplet combination, LEE011 300 mg + everolimus 2.5 mg + exemestane 25 mg was administered with food to the refractory to CDK4/6 inhibitor based therapy group	Following RP2D declaration for the doublet combination, LEE011 600 mg + exemestane 25 mg was administered with food to the refractory to CDK4/6 inhibitor based therapy group (except patients with disease refractory to prior LEE011)	
Started	41	42	14	16	17	2	132
Completed	0	0	0	0	0	0	0
Not Completed	41	42	14	16	17	2	132
Adverse Event	3	3	1	2	1	1	11

Physician Decision	5	9	0	2	2	0	18
Subject withdrew consent	1	3	1	1	0	0	6
Administrative problems	0	1	0	0	0	0	1
Disease progression	32	26	12	11	14	1	96

Baseline Characteristics

	LEE011(200 mg)+eve(2.5 mg)+exe (25mg) (fasting) esc naive	**LEE011(200 mg)+eve(2.5 mg)+exe (25mg) (FED) esc refractory**	**LEE011(600 mg)+exe(25 mg) esc refractory**	**LEE011(300 mg)+eve(2.5 mg)+exe (25mg) exp naive**	**LEE011(300 mg)+eve(2.5 mg)+exe (25mg) exp refractory**	**LEE011(600 mg)+exe(25 mg) exp refractory**	**Total**
Arm/Group Description	Triplet combination of LEE011 200 mg + everolimus (RAD001) 2.5 mg + exemestane 25 mg was administered in fasting to the naive to CDK4/6 inhibitors group	Triplet combination of LEE011 200 mg + everolimus (RAD001) 2.5 mg + exemestane 25 mg was administered with food to the refractory to CDK4/6 inhibitor based therapy group	Doublet combination, LEE011 600 mg + exemestane 25 mg was administered with food to the refractory to CDK4/6 inhibitor based therapy group	Following RP2D declaration for the triplet combination, LEE011 300 mg + everolimus 2.5 mg + exemestane 25 mg was administered with food to the naive to CDK4/6 inhibitors group	Following RP2D declaration for the triplet combination, LEE011 300 mg + everolimus 2.5 mg + exemestane 25 mg was administered with food to the refractory to CDK4/6 inhibitor	Following RP2D declaration for the doublet combination, LEE011 600 mg + exemestane 25 mg was administered with food to the refractory to CDK4/6 inhibitor based therapy group (except patients with	

					based therapy group	disease refractory to prior LEE011)	
Number of Participants [units: participants]	41	42	14	16	17	2	132
Age Continuous (units: Years) Mean ± Standard Deviation							
	57.2±11.03	56.6±9.89	60.4±9.31	60.6±6.90	52.9±11.48	64.0±11.31	57.3±10.23
Sex: Female, Male (units: Participants) Count of Participants (Not Applicable)							
Female	41	42	14	16	17	2	132
Male	0	0	0	0	0	0	0
Race/Ethnicity, Customized (units: Participants) Count of Participants (Not Applicable)							
Caucasian	29	28	11	12	14	2	96
Black	3	4	0	1	0	0	8
Asian	4	4	0	0	0	0	8
Native American	0	0	0	1	0	0	1
Other	2	0	1	0	3	0	6
Missing	3	6	2	2	0	0	13

Primary Outcome Result(s)

Dose Escalation: Incidence of Dose Limiting Toxicity (DLT)

(Time Frame: At the end of Cycle 1 (each cycle is 28 days))

	Doublet Escalation: LEE011 (600 mg) exe (25 mg) (Fasting)	Triplet Escalation ALL
Arm/Group Description	Doublet Escalation: LEE011 (600 mg) exe (25 mg) (Fasting)	Triplet Escalation ALL
Number of Participants Analyzed [units: participants]	14	70
Dose Escalation: Incidence of Dose Limiting Toxicity (DLT) (units: Participants)		
	2	7

Dose Expansion: Number of participants with Adverse Events (AEs) and Serious Adverse Events (SAEs)

(Time Frame: Approximately 4.5 years after FPFV)

	LEE011(300 mg)+eve(2.5 mg)+exe (25mg) exp naive	LEE011(300 mg)+eve(2.5 mg)+exe (25mg) exp refractory	LEE011(600 mg)+exe(25 mg) exp refractory
Arm/Group Description	Following RP2D declaration for the triplet combination, LEE011 300 mg + everolimus 2.5 mg +	Following RP2D declaration for the triplet combination, LEE011 300 mg + everolimus 2.5 mg +	Following RP2D declaration for the doublet combination, LEE011 600 mg + exemestane 25 mg was

	exemestane 25 mg was administered with food to the naive to CDK4/6 inhibitors group	exemestane 25 mg was administered with food to the refractory to CDK4/6 inhibitor based therapy group	administered with food to the refractory to CDK4/6 inhibitor based therapy group (except patients with disease refractory to prior LEE011)
Number of Participants Analyzed [units: participants]	16	17	2
Dose Expansion: Number of participants with Adverse Events (AEs) and Serious Adverse Events (SAEs) (units: Participants) Count of Participants (Not Applicable)			
Adverse Events (AEs)	16 (100%)	17 (100%)	2 (100%)
Serious Adverse Events (SAEs)	4 (25%)	1 (5.88%)	1 (50%)

Secondary Outcome Result(s)

Dose Escalation: Number of participants with Adverse Events (AEs) and Serious Adverse Events (SAEs)

(Time Frame: Approximately 6.5 years after FPFV)

	LEE011(200 mg)+eve(2.5 mg)+exe (25mg) (fasting) esc naive	**LEE011(200 mg)+eve(2.5 mg)+exe (25mg) (FED) esc refractory**	**LEE011(600 mg)+exe(25 mg) esc refractory**
Arm/Group Description	Triplet combination	Triplet combination	Doublet combination,

	of LEE011 200 mg + everolimus (RAD001) 2.5 mg + exemestane 25 mg was administered in fasting to the naive to CDK4/6 inhibitors group	of LEE011 200 mg + everolimus (RAD001) 2.5 mg + exemestane 25 mg was administered with food to the refractory to CDK4/6 inhibitor based therapy group	LEE011 600 mg + exemestane 25 mg was administered with food to the refractory to CDK4/6 inhibitor based therapy group
Number of Participants Analyzed [units: participants]	41	42	14
Dose Escalation: Number of participants with Adverse Events (AEs) and Serious Adverse Events (SAEs) (units: Participants) Count of Participants (Not Applicable)			
Adverse Events (AEs)	41 (100%)	42 (100%)	14 (100%)
Serious Adverse Events (SAEs)	14 (34.15%)	12 (28.57%)	6 (42.86%)

Dose Escalation and Expansion: Overall Response Rate (ORR)

(Time Frame: Approximately 6.5 years for Dose Escalation and 4.5 years for Dose Espansion after FPFV)

	LEE011(200 mg)+eve(2.5 mg)+exe (25mg) (fasting) esc naive	**LEE011(200 mg)+eve(2.5 mg)+exe (25mg) (FED) esc refractory**	**LEE011(600 mg)+exe(25 mg) esc refractory**	**LEE011(300 mg)+eve(2.5 mg)+exe (25mg) exp naive**	**LEE011(300 mg)+eve(2.5 mg)+exe (25mg) exp refractory**	**LEE011(600 mg)+exe(25 mg) exp refractory**
Arm/Group Description	Triplet combination of LEE011	Triplet combination of LEE011	Doublet combination, LEE011 600	Following RP2D declaration for	Following RP2D declaration for	Following RP2D declaration for

	200 mg + everolimus (RAD001) 2.5 mg + exemestane 25 mg was administered in fasting to the naive to CDK4/6 inhibitors group	200 mg + everolimus (RAD001) 2.5 mg + exemestane 25 mg was administered with food to the refractory to CDK4/6 inhibitor based therapy group	mg + exemestane 25 mg was administered with food to the refractory to CDK4/6 inhibitor based therapy group	the triplet combination, LEE011 300 mg + everolimus 2.5 mg + exemestane 25 mg was administered with food to the naive to CDK4/6 inhibitors group	the triplet combination, LEE011 300 mg + everolimus 2.5 mg + exemestane 25 mg was administered with food to the refractory to CDK4/6 inhibitor based therapy group	the doublet combination, LEE011 600 mg + exemestane 25 mg was administered with food to the refractory to CDK4/6 inhibitor based therapy group (except patients with disease refractory to prior LEE011)
Number of Participants Analyzed [units: participants]	41	42	14	16	17	2
Dose Escalation and Expansion: Overall Response Rate (ORR) (units: Participants) Count of Participants (Not Applicable)						
	4 (9.76%)	5 (11.9%)	2 (14.29%)	0 (%)	0 (%)	0 (%)

Dose Escalation and Expansion: Disease Control Rate (DCR)

(Time Frame: Approximately 6.5 years for Dose Escalation and 4.5 years for Dose expansion after FPFV)

	LEE011(200 mg)+eve(2.5 mg)+exe (25mg) (fasting) esc naive	**LEE011(200 mg)+eve(2.5 mg)+exe (25mg) (FED) esc refractory**	**LEE011(600 mg)+exe(25 mg) esc refractory**	**LEE011(300 mg)+eve(2.5 mg)+exe (25mg) exp naive**	**LEE011(300 mg)+eve(2.5 mg)+exe (25mg) exp refractory**	**LEE011(600 mg)+exe(25 mg) exp refractory**

Arm/Group Description	Triplet combination of LEE011 200 mg + everolimus (RAD001) 2.5 mg + exemestane 25 mg was administered in fasting to the naive to CDK4/6 inhibitors group	Triplet combination of LEE011 200 mg + everolimus (RAD001) 2.5 mg + exemestane 25 mg was administered with food to the refractory to CDK4/6 inhibitor based therapy group	Doublet combination, LEE011 600 mg + exemestane 25 mg was administered with food to the refractory to CDK4/6 inhibitor based therapy group	Following RP2D declaration for the triplet combination, LEE011 300 mg + everolimus 2.5 mg + exemestane 25 mg was administered with food to the naive to CDK4/6 inhibitors group	Following RP2D declaration for the triplet combination, LEE011 300 mg + everolimus 2.5 mg + exemestane 25 mg was administered with food to the refractory to CDK4/6 inhibitor based therapy group	Following RP2D declaration for the doublet combination, LEE011 600 mg + exemestane 25 mg was administered with food to the refractory to CDK4/6 inhibitor based therapy group (except patients with disease refractory to prior LEE011)
Number of Participants Analyzed [units: participants]	41	42	14	16	17	2
Dose Escalation and Expansion: Disease Control Rate (DCR) (units: Participants) Count of Participants (Not Applicable)						
	27 (65.85%)	33 (78.57%)	12 (85.71%)	13 (81.25%)	7 (41.18%)	0 (%)

Dose Escalation and Expansion: Clinical Benefit Rate (CBR)

(Time Frame: Approximately 6.5 years for Dose Escalation and 4.5 years for Dose Espansion after FPFV)

	LEE011(200 mg)+eve(2.5 mg)+exe (25mg)	LEE011(200 mg)+eve(2.5 mg)+exe (25mg) (FED)	LEE011(600 mg)+exe(25	LEE011(300 mg)+eve(2.5 mg)+exe	LEE011(300 mg)+eve(2.5 mg)+exe	LEE011(600 mg)+exe(25

	(fasting) esc naive	esc refractory	mg) esc refractory	(25mg) exp naive	(25mg) exp refractory	mg) exp refractory
Arm/Group Description	Triplet combination of LEE011 200 mg + everolimus (RAD001) 2.5 mg + exemestane 25 mg was administered in fasting to the naive to CDK4/6 inhibitors group	Triplet combination of LEE011 200 mg + everolimus (RAD001) 2.5 mg + exemestane 25 mg was administered with food to the refractory to CDK4/6 inhibitor based therapy group	Doublet combination, LEE011 600 mg + exemestane 25 mg was administered with food to the refractory to CDK4/6 inhibitor based therapy group	Following RP2D declaration for the triplet combination, LEE011 300 mg + everolimus 2.5 mg + exemestane 25 mg was administered with food to the naive to CDK4/6 inhibitors group	Following RP2D declaration for the triplet combination, LEE011 300 mg + everolimus 2.5 mg + exemestane 25 mg was administered with food to the refractory to CDK4/6 inhibitor based therapy group	Following RP2D declaration for the doublet combination, LEE011 600 mg + exemestane 25 mg was administered with food to the refractory to CDK4/6 inhibitor based therapy group (except patients with disease refractory to prior LEE011)
Number of Participants Analyzed [units: participants]	41	42	14	16	17	2
Dose Escalation and Expansion: Clinical Benefit Rate (CBR) (units: Participants) Count of Participants (Not Applicable)						
	18 (43.9%)	20 (47.62%)	10 (71.43%)	10 (62.5%)	4 (23.53%)	0 (%)

Dose Expansion: Duration of Response (DOR)

(Time Frame: Approximately 4.5 years for dose expansion after FPFV)

	LEE011(300 mg)+eve(2.5 mg)+exe (25mg) exp naive	LEE011(300 mg)+eve(2.5 mg)+exe (25mg) exp refractory	LEE011(600 mg)+exe(25 mg) exp refractory
Arm/Group Description	Following RP2D declaration for the triplet combination, LEE011 300 mg + everolimus 2.5 mg + exemestane 25 mg was administered with food to the naive to CDK4/6 inhibitors group	Following RP2D declaration for the triplet combination, LEE011 300 mg + everolimus 2.5 mg + exemestane 25 mg was administered with food to the refractory to CDK4/6 inhibitor based therapy group	Following RP2D declaration for the doublet combination, LEE011 600 mg + exemestane 25 mg was administered with food to the refractory to CDK4/6 inhibitor based therapy group (except patients with disease refractory to prior LEE011)
Number of Participants Analyzed [units: participants]	16	17	2
Dose Expansion: Duration of Response (DOR) (units: Participants) Count of Participants (Not Applicable)			
	0 (%)	0 (%)	0 (%)

Dose Expansion: Progression Free Survival (PFS)

(Time Frame: Approximately 4.5 years after FPFV)

	LEE011(300 mg)+eve(2.5 mg)+exe (25mg) exp naive	LEE011(300 mg)+eve(2.5 mg)+exe (25mg) exp refractory	LEE011(600 mg)+exe(25 mg) exp refractory
Arm/Group Description	Following RP2D declaration for the triplet combination, LEE011 300 mg + everolimus 2.5 mg + exemestane 25 mg was administered with food to the naive to CDK4/6 inhibitors group	Following RP2D declaration for the triplet combination, LEE011 300 mg + everolimus 2.5 mg + exemestane 25 mg was administered with food to the refractory to CDK4/6 inhibitor based therapy group	Following RP2D declaration for the doublet combination, LEE011 600 mg + exemestane 25 mg was administered with food to the refractory to CDK4/6 inhibitor based therapy group (except patients with disease refractory to prior LEE011)
Number of Participants Analyzed [units: participants]	16	17	2
Dose Expansion: Progression Free Survival (PFS) (units: months) Median (95% Confidence Interval)			
	12.7 (3.7 to 20.2)	1.9 (1.7 to 7.3)	1.7 (NA to NA)[1]

[1] NOT ESTIMABLE

Dose Escalation: Pharmacokinetics (PK) parameter: AUC0-24h at Day 1 of Cycle 1

(Time Frame: 6 Cycles of treatment (28 day cycles): Cycle 1 Day 1)

	LEE011 (200 mg) + eve (2.5 mg) + exe (25 mg) (fasting)	**LEE011 (200 mg) + eve (2.5 mg) + exe (25 mg) (fed)**	**LEE011 (250 mg) + eve (2.5 mg) + exe (25 mg) (fasting)**	**LEE011 (250 mg) + eve (2.5 mg) + exe (25 mg) (fed)**	**LEE011 (300 mg) + eve (2.5 mg) + exe (25mg) (fasting)**	**LEE011 (300 mg) + eve (2.5 mg) + exe (25mg) (fed)**	**LEE011 (350 mg) + eve (1 mg) + exe (25mg) (fasting)**	**LEE011 (350 mg) + eve (2.5 mg) + exe (25mg) (fed)**	**LEE011 (200 mg) + eve (5 mg) + exe (25 mg) (fed)**
Arm/Group Description	LEE011 (200 mg) + eve (2.5 mg) + exe (25 mg) (fasting)	LEE011 (200 mg) + eve (2.5 mg) + exe (25 mg) (fed)	LEE011 (250 mg) + eve (2.5 mg) + exe (25 mg) (fasting)	LEE011 (250 mg) + eve (2.5 mg) + exe (25 mg) (fed)	LEE011 (300 mg) + eve (2.5 mg) + exe (25mg) (fasting)	LEE011 (300 mg) + eve (2.5 mg) + exe (25mg) (fed)	LEE011 (350 mg) + eve (1 mg) + exe (25mg) (fasting)	LEE011 (350 mg) + eve (2.5 mg) + exe (25mg) (fed)	LEE011 (200 mg) + eve (5 mg) + exe (25 mg) (fed)
Number of Participants Analyzed [units: participants]	6	2	18	6	9	17	6	9	6
Dose Escalation: Pharmacokinetics (PK) parameter: AUC0-24h at Day 1 of Cycle 1 (units: hr*ng/mL) Mean ± Standard Deviation									
	2170 ± 854	2580 ± 2340	3750 ± 1840	2820 ± 1260	6810 ± 2280	5440 ± 2810	6060 ± 2730	6380 ± 3630	2440 ± 1270

Dose Escalation: Pharmacokinetics (PK) parameter: AUC0-24h at at Day 15 of Cycle 1

(Time Frame: 6 Cycles of treatment (28 day cycles): Cycle 1 Day 15)

	LEE011 (200 mg) + eve (2.5 mg) + exe	**LEE011 (200 mg) + eve (2.5 mg) + exe**	**LEE011 (250 mg) + eve (2.5 mg) + exe**	**LEE011 (250 mg) + eve (2.5 mg) + exe**	**LEE011 (300 mg) + eve (2.5 mg) + exe**	**LEE011 (300 mg) + eve (2.5 mg) + exe**	**LEE011 (350 mg) + eve (1 mg) + exe**	**LEE011 (350 mg) + eve (2.5 mg) + exe**	**LEE011 (200 mg) + eve (5 mg)**

	(25 mg) (fasting)	(25 mg) (fed)	(25 mg) (fasting)	(25 mg) (fed)	(25mg) (fasting)	(25mg) (fed)	(25mg) (fasting)	(25mg) (fed)	+ exe (25 mg) (fed)
Arm/Group Description	LEE011 (200 mg) + eve (2.5 mg) + exe (25 mg) (fasting)	LEE011 (200 mg) + eve (2.5 mg) + exe (25 mg) (fed)	LEE011 (250 mg) + eve (2.5 mg) + exe (25 mg) (fasting)	LEE011 (250 mg) + eve (2.5 mg) + exe (25 mg) (fed)	LEE011 (300 mg) + eve (2.5 mg) + exe (25mg) (fasting)	LEE011 (300 mg) + eve (2.5 mg) + exe (25mg) (fed)	LEE011 (350 mg) + eve (1 mg) + exe (25mg) (fasting)	LEE011 (350 mg) + eve (2.5 mg) + exe (25mg) (fed)	LEE011 (200 mg) + eve (5 mg) + exe (25 mg) (fed)
Number of Participants Analyzed [units: participants]	5	3	13	6	8	16	5	8	5
Dose Escalation: Pharmacokinetics (PK) parameter: AUC0-24h at at Day 15 of Cycle 1 (units: hr*ng/mL) Mean ± Standard Deviation									
	5310 ± 3760	4770 ± 3590	11100 ± 6030	7120 ± 4240	14600 ± 9320	11500 ± 6550	10800 ± 3820	15200 ± 8250	6710 ± 2520

Dose Escalation: Pharmacokinetics (PK) parameter: Cmax at Day 1 of Cycle 1

(Time Frame: 6 Cycles of treatment (28 day cycles): Cycle 1 Day 1)

	LEE011 (200 mg) + eve (2.5 mg) + exe (25 mg) (fasting)	LEE011 (200 mg) + eve (2.5 mg) + exe (25 mg) (fed)	LEE011 (250 mg) + eve (2.5 mg) + exe (25 mg) (fasting)	LEE011 (250 mg) + eve (2.5 mg) + exe (25 mg) (fed)	LEE011 (300 mg) + eve (2.5 mg) + exe (25mg) (fasting)	LEE011 (300 mg) + eve (2.5 mg) + exe (25mg) (fed)	LEE011 (350 mg) + eve (1 mg) + exe (25mg) (fasting)	LEE011 (350 mg) + eve (2.5 mg) + exe (25mg) (fed)	LEE011 (200 mg) + eve (5 mg) + exe (25 mg) (fed)
Arm/Group Description	LEE011 (200 mg) + eve (2.5 mg) + exe (25 mg) (fasting)	LEE011 (200 mg) + eve (2.5 mg) + exe (25 mg) (fed)	LEE011 (250 mg) + eve (2.5 mg) + exe (25 mg) (fasting)	LEE011 (250 mg) + eve (2.5 mg) + exe (25 mg) (fed)	LEE011 (300 mg) + eve (2.5 mg) + exe (25mg) (fasting)	LEE011 (300 mg) + eve (2.5 mg) + exe (25mg) (fed)	LEE011 (350 mg) + eve (1 mg) + exe (25mg) (fasting)	LEE011 (350 mg) + eve (2.5 mg) + exe (25mg) (fed)	LEE011 (200 mg) + eve (5 mg) + exe (25 mg) (fed)

Number of Participants Analyzed [units: participants]	6	2	18	6	11	18	6	9	6
Dose Escalation: Pharmacokinetics (PK) parameter: Cmax at Day 1 of Cycle 1 (units: ng/mL) Mean ± Standard Deviation									
	245 ± 148	238 ± 180	397 ± 205	358 ± 133	510 ± 173	513 ± 206	512 ± 178	625 ± 310	268 ± 178

Dose Escalation: Pharmacokinetics (PK) parameter: Cmax at Day 15 of Cycle 1

(Time Frame: 6 Cycles of treatment (28 day cycles): Cycle 1 Day 15)

	LEE011 (200 mg) + eve (2.5 mg) + exe (25 mg) (fasting)	**LEE011 (200 mg) + eve (2.5 mg) + exe (25 mg) (fed)**	**LEE011 (250 mg) + eve (2.5 mg) + exe (25 mg) (fasting)**	**LEE011 (250 mg) + eve (2.5 mg) + exe (25 mg) (fed)**	**LEE011 (300 mg) + eve (2.5 mg) + exe (25mg) (fasting)**	**LEE011 (300 mg) + eve (2.5 mg) + exe (25mg) (fed)**	**LEE011 (350 mg) + eve (1 mg) + exe (25mg) (fasting)**	**LEE011 (350 mg) + eve (2.5 mg) + exe (25mg) (fed)**	**LEE011 (200 mg) + eve (5 mg) + exe (25 mg) (fed)**
Arm/Group Description	LEE011 (200 mg) + eve (2.5 mg) + exe (25 mg) (fasting)	LEE011 (200 mg) + eve (2.5 mg) + exe (25 mg) (fed)	LEE011 (250 mg) + eve (2.5 mg) + exe (25 mg) (fasting)	LEE011 (250 mg) + eve (2.5 mg) + exe (25 mg) (fed)	LEE011 (300 mg) + eve (2.5 mg) + exe (25mg) (fasting)	LEE011 (300 mg) + eve (2.5 mg) + exe (25mg) (fed)	LEE011 (350 mg) + eve (1 mg) + exe (25mg) (fasting)	LEE011 (350 mg) + eve (2.5 mg) + exe (25mg) (fed)	LEE011 (200 mg) + eve (5 mg) + exe (25 mg) (fed)
Number of Participants Analyzed [units: participants]	6	3	14	6	8	16	5	8	6
Dose Escalation: Pharmacokinetics (PK) parameter: Cmax at Day 15 of Cycle 1 (units: ng/mL) Mean ± Standard Deviation									

	473 ± 305	315 ± 163	840 ± 528	533 ± 277	1250 ± 690	859 ± 459	893 ± 379	1030 ± 390	550 ± 207

Dose Escalation: Pharmacokinetics (PK) parameter: Tmax at Day 1 of Cycle 1

(Time Frame: 6 Cycles of treatment (28 day cycles): Cycle 1 Day 1)

	LEE011 (200 mg) + eve (2.5 mg) + exe (25 mg) (fasting)	**LEE011 (200 mg) + eve (2.5 mg) + exe (25 mg) (fed)**	**LEE011 (250 mg) + eve (2.5 mg) + exe (25 mg) (fasting)**	**LEE011 (250 mg) + eve (2.5 mg) + exe (25 mg) (fed)**	**LEE011 (300 mg) + eve (2.5 mg) + exe (25mg) (fasting)**	**LEE011 (300 mg) + eve (2.5 mg) + exe (25mg) (fed)**	**LEE011 (350 mg) + eve (1 mg) + exe (25mg) (fasting)**	**LEE011 (350 mg) + eve (2.5 mg) + exe (25mg) (fed)**	**LEE011 (200 mg) + eve (5 mg) + exe (25 mg) (fed)**
Arm/Group Description	LEE011 (200 mg) + eve (2.5 mg) + exe (25 mg) (fasting)	LEE011 (200 mg) + eve (2.5 mg) + exe (25 mg) (fed)	LEE011 (250 mg) + eve (2.5 mg) + exe (25 mg) (fasting)	LEE011 (250 mg) + eve (2.5 mg) + exe (25 mg) (fed)	LEE011 (300 mg) + eve (2.5 mg) + exe (25mg) (fasting)	LEE011 (300 mg) + eve (2.5 mg) + exe (25mg) (fed)	LEE011 (350 mg) + eve (1 mg) + exe (25mg) (fasting)	LEE011 (350 mg) + eve (2.5 mg) + exe (25mg) (fed)	LEE011 (200 mg) + eve (5 mg) + exe (25 mg) (fed)
Number of Participants Analyzed [units: participants]	6	2	18	6	11	18	6	9	6
Dose Escalation: Pharmacokinetics (PK) parameter: Tmax at Day 1 of Cycle 1 (units: hour) Median (Full Range)									
	2.56 (1.02 to 4.2)	4.03 (4 to 4.07)	2.81 (0.967 to 4.5)	1.13 (1 to 2.17)	4 (1 to 23)	4 (1.95 to 8)	2.82 (1 to 8)	2.1 (1.02 to 4)	3.04 (1 to 4.02)

Dose Escalation: Pharmacokinetics (PK) parameter: Tmax at Day 15 of Cycle 1

(Time Frame: 6 Cycles of treatment (28 day cycles): Cycle 15 Day 1)

	LEE011 (200 mg) + eve (2.5 mg) + exe	**LEE011 (200 mg) + eve (2.5 mg) + exe**	**LEE011 (250 mg) + eve (2.5 mg) + exe**	**LEE011 (250 mg) + eve (2.5 mg) + exe**	**LEE011 (300 mg) + eve (2.5 mg) + exe**	**LEE011 (300 mg) + eve (2.5 mg) + exe**	**LEE011 (350 mg) + eve (1 mg) + exe**	**LEE011 (350 mg) + eve (2.5 mg) + exe**	**LEE011 (200 mg) + eve (5 mg)**

	(25 mg) (fasting)	(25 mg) (fed)	(25 mg) (fasting)	(25 mg) (fed)	(25mg) (fasting)	(25mg) (fed)	(25mg) (fasting)	(25mg) (fed)	+ exe (25 mg) (fed)
Arm/Group Description	LEE011 (200 mg) + eve (2.5 mg) + exe (25 mg) (fasting)	LEE011 (200 mg) + eve (2.5 mg) + exe (25 mg) (fed)	LEE011 (250 mg) + eve (2.5 mg) + exe (25 mg) (fasting)	LEE011 (250 mg) + eve (2.5 mg) + exe (25 mg) (fed)	LEE011 (300 mg) + eve (2.5 mg) + exe (25mg) (fasting)	LEE011 (300 mg) + eve (2.5 mg) + exe (25mg) (fed)	LEE011 (350 mg) + eve (1 mg) + exe (25mg) (fasting)	LEE011 (350 mg) + eve (2.5 mg) + exe (25mg) (fed)	LEE011 (200 mg) + eve (5 mg) + exe (25 mg) (fed)
Number of Participants Analyzed [units: participants]	6	3	14	6	8	16	5	8	6
Dose Escalation: Pharmacokinetics (PK) parameter: Tmax at Day 15 of Cycle 1 (units: hour) Median (Full Range)									
	2.03 (1.03 to 4.12)	2.17 (2.12 to 4.02)	2.19 (0.983 to 4.08)	3.93 (2 to 4.03)	3 (1.03 to 4.33)	3.07 (0.983 to 8)	1.98 (1 to 4)	4 (2.05 to 23.4)	2 (1 to 4.03)

Dose Escalation: Pharmacokinetics (PK) parameter: Racc at Day 15 of Cycle 1

(Time Frame: 6 Cycles of treatment (28 day cycles): Cycle 15 Day 1)

	LEE011 (200 mg) + eve (2.5 mg) + exe (25 mg) (fasting)	LEE011 (200 mg) + eve (2.5 mg) + exe (25 mg) (fed)	LEE011 (250 mg) + eve (2.5 mg) + exe (25 mg) (fasting)	LEE011 (250 mg) + eve (2.5 mg) + exe (25 mg) (fed)	LEE011 (300 mg) + eve (2.5 mg) + exe (25mg) (fasting)	LEE011 (300 mg) + eve (2.5 mg) + exe (25mg) (fed)	LEE011 (350 mg) + eve (1 mg) + exe (25mg) (fasting)	LEE011 (350 mg) + eve (2.5 mg) + exe (25mg) (fed)	LEE011 (200 mg) + eve (5 mg) + exe (25 mg) (fed)
Arm/Group Description	LEE011 (200 mg) + eve (2.5 mg) + exe (25 mg) (fasting)	LEE011 (200 mg) + eve (2.5 mg) + exe (25 mg) (fed)	LEE011 (250 mg) + eve (2.5 mg) + exe (25 mg) (fasting)	LEE011 (250 mg) + eve (2.5 mg) + exe (25 mg) (fed)	LEE011 (300 mg) + eve (2.5 mg) + exe (25mg) (fasting)	LEE011 (300 mg) + eve (2.5 mg) + exe (25mg) (fed)	LEE011 (350 mg) + eve (1 mg) + exe (25mg) (fasting)	LEE011 (350 mg) + eve (2.5 mg) + exe (25mg) (fed)	LEE011 (200 mg) + eve (5 mg) + exe (25 mg) (fed)

Number of Participants Analyzed [units: participants]	5	2	13	6	7	16	5	8	5
Dose Escalation: Pharmacokinetics (PK) parameter: Racc at Day 15 of Cycle 1 (units: Ratio) Mean ± Standard Deviation									
	2.22 ± 0.774	1.55 ± 1.09	3.54 ± 1.54	2.54 ± 0.94	2.77 ± 0.846	2.55 ± 1.02	2.2 ± 0.618	2.85 ± 1.17	3.61 ± 0.82

Safety Results

All-Cause Mortality

	LEE011(200 mg)+eve(2.5 mg)+exe (25mg) (fasting) esc naive N = 41	**LEE011(200 mg)+eve(2.5 mg)+exe (25mg) (FED) esc refractory N = 42**	**Triplet: ESCALATION ALL N = 83**	**LEE011(300 mg)+eve(2.5 mg)+exe (25mg) exp naive N = 16**	**LEE011(300 mg)+eve(2.5 mg)+exe (25mg) exp refractory N = 17**	**LEE011(600 mg)+exe(25 mg) esc refractory N = 14**	**LEE011(600 mg)+exe(25 mg) exp refractory N = 2**	**All subjects N = 132**
Arm/Group Description	Triplet combination of LEE011 200 mg + everolimus (RAD001) 2.5 mg + exemestane	Triplet combination of LEE011 200 mg + everolimus (RAD001) 2.5 mg + exemestane	Triplet: ESCALATION ALL	Following RP2D declaration for the triplet combination, LEE011 300 mg + everolimus	Following RP2D declaration for the triplet combination, LEE011 300 mg + everolimus	Doublet combination, LEE011 600 mg + exemestane 25 mg was administered with food to	Following RP2D declaration for the doublet combination, LEE011 600 mg +	All subjects

	25 mg was administered in fasting to the naive to CDK4/6 inhibitors group	25 mg was administered with food to the refractory to CDK4/6 inhibitor based therapy group		2.5 mg + exemestane 25 mg was administered with food to the naive to CDK4/6 inhibitors group	2.5 mg + exemestane 25 mg was administered with food to the refractory to CDK4/6 inhibitor based therapy group	the refractory to CDK4/6 inhibitor based therapy group	exemestane 25 mg was administered with food to the refractory to CDK4/6 inhibitor based therapy group (except patients with disease refractory to prior LEE011)	
Total participants affected	4 (9.76%)	2 (4.76%)	6 (7.23%)	0 (0.00%)	0 (0.00%)	3 (21.43%)	0 (0.00%)	9 (6.82%)

Serious Adverse Events by System Organ Class

Time Frame	Adverse events were collected for approximately 6.5 years for dose escalation and 4.5 years for dose expansion including the 30 days safety follow-up period.
Additional Description	Any undesirable sign(s), symptom(s), or medical condition(s) that occurred after patient's signed informed consent up to roughly 6.5 years for dose escalation and 4.5 years for dose expansion including the 30 days safety follow-up period.
Source Vocabulary for Table Default	MedDRA (23.0)
Assessment Type for Table Default	Systematic Assessment

	LEE011(200 mg)+eve(2.5 mg)+exe (25mg) (fasting) esc naive N = 41	**LEE011(200 mg)+eve(2.5 mg)+exe (25mg) (FED) esc refractory N = 42**	**Triplet: ESCALATION ALL N = 83**	**LEE011(300 mg)+eve(2.5 mg)+exe (25mg) exp naive N = 16**	**LEE011(300 mg)+eve(2.5 mg)+exe (25mg) exp refractory N = 17**	**LEE011(600 mg)+exe(25 mg) esc refractory N = 14**	**LEE011(600 mg)+exe(25 mg) exp refractory N = 2**	**All subjects N = 132**

Arm/Group Description	Triplet combination of LEE011 200 mg + everolimus (RAD001) 2.5 mg + exemestane 25 mg was administered in fasting to the naive to CDK4/6 inhibitors group	Triplet combination of LEE011 200 mg + everolimus (RAD001) 2.5 mg + exemestane 25 mg was administered with food to the refractory to CDK4/6 inhibitor based therapy group	Triplet: ESCALATION ALL	Following RP2D declaration for the triplet combination, LEE011 300 mg + everolimus 2.5 mg + exemestane 25 mg was administered with food to the naive to CDK4/6 inhibitors group	Following RP2D declaration for the triplet combination, LEE011 300 mg + everolimus 2.5 mg + exemestane 25 mg was administered with food to the refractory to CDK4/6 inhibitor based therapy group	Doublet combination, LEE011 600 mg + exemestane 25 mg was administered with food to the refractory to CDK4/6 inhibitor based therapy group	Following RP2D declaration for the doublet combination, LEE011 600 mg + exemestane 25 mg was administered with food to the refractory to CDK4/6 inhibitor based therapy group (except patients with disease refractory to prior LEE011)	All subjects
Total participants affected	14 (34.15%)	12 (28.57%)	26 (31.33%)	4 (25.00%)	1 (5.88%)	6 (42.86%)	1 (50.00%)	38 (28.79%)
Blood and lymphatic system disorders								
Anaemia	1 (2.44%)	1 (2.38%)	2 (2.41%)	0 (0.00%)	0 (0.00%)	1 (7.14%)	0 (0.00%)	3 (2.27%)
Febrile neutropenia	1 (2.44%)	0 (0.00%)	1 (1.20%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.76%)
Lymphopenia	1 (2.44%)	0 (0.00%)	1 (1.20%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.76%)
Thrombocytopenia	1 (2.44%)	0 (0.00%)	1 (1.20%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.76%)
Cardiac disorders								
Acute myocardial infarction	1 (2.44%)	0 (0.00%)	1 (1.20%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.76%)
Cardiac arrest	1 (2.44%)	0 (0.00%)	1 (1.20%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.76%)

Gastrointestinal disorders								
Abdominal pain	1 (2.44%)	1 (2.38%)	2 (2.41%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (1.52%)
Diarrhoea	0 (0.00%)	1 (2.38%)	1 (1.20%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.76%)
Enterocolitis	0 (0.00%)	1 (2.38%)	1 (1.20%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.76%)
Gastrointestinal haemorrhage	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (7.14%)	0 (0.00%)	1 (0.76%)
Small intestinal obstruction	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.88%)	0 (0.00%)	0 (0.00%)	1 (0.76%)
Stomatitis	1 (2.44%)	0 (0.00%)	1 (1.20%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.76%)
Upper gastrointestinal haemorrhage	0 (0.00%)	1 (2.38%)	1 (1.20%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.76%)
General disorders and administration site conditions								
Peripheral swelling	1 (2.44%)	0 (0.00%)	1 (1.20%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.76%)
Pyrexia	0 (0.00%)	1 (2.38%)	1 (1.20%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.76%)
Infections and infestations								
Cellulitis	0 (0.00%)	1 (2.38%)	1 (1.20%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.76%)
Device related infection	0 (0.00%)	1 (2.38%)	1 (1.20%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.76%)
Gastroenteritis viral	1 (2.44%)	0 (0.00%)	1 (1.20%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.76%)
Infectious colitis	0 (0.00%)	1 (2.38%)	1 (1.20%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.76%)
Localised infection	1 (2.44%)	0 (0.00%)	1 (1.20%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.76%)
Pneumocystis jirovecii infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.76%)
Pneumonia	1 (2.44%)	2 (4.76%)	3 (3.61%)	1 (6.25%)	0 (0.00%)	2 (14.29%)	0 (0.00%)	6 (4.55%)
Urinary tract infection	1 (2.44%)	0 (0.00%)	1 (1.20%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.76%)

Viral infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.88%)	0 (0.00%)	1 (50.00%)	2 (1.52%)
Wound infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.76%)
Injury, poisoning and procedural complications								
Transfusion reaction	0 (0.00%)	1 (2.38%)	1 (1.20%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.76%)
Investigations								
Alanine aminotransferase increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (7.14%)	0 (0.00%)	1 (0.76%)
Aspartate aminotransferase increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (7.14%)	0 (0.00%)	1 (0.76%)
Blood bilirubin increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (7.14%)	0 (0.00%)	1 (0.76%)
Electrocardiogram QT prolonged	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.76%)
White blood cell count decreased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (7.14%)	0 (0.00%)	1 (0.76%)
Metabolism and nutrition disorders								
Hyperkalaemia	0 (0.00%)	1 (2.38%)	1 (1.20%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.76%)
Hyponatraemia	1 (2.44%)	1 (2.38%)	2 (2.41%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (1.52%)
Musculoskeletal and connective tissue disorders								
Arthralgia	1 (2.44%)	0 (0.00%)	1 (1.20%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.76%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)								

Malignant peritoneal neoplasm	0 (0.00%)	1 (2.38%)	1 (1.20%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.76%)
Metastases to peritoneum	0 (0.00%)	1 (2.38%)	1 (1.20%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.76%)
Nervous system disorders								
Central nervous system inflammation	1 (2.44%)	0 (0.00%)	1 (1.20%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.76%)
Encephalopathy	1 (2.44%)	0 (0.00%)	1 (1.20%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.76%)
Spinal cord compression	1 (2.44%)	1 (2.38%)	2 (2.41%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (1.52%)
Syncope	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (7.14%)	0 (0.00%)	1 (0.76%)
Psychiatric disorders								
Mental status changes	1 (2.44%)	0 (0.00%)	1 (1.20%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.76%)
Renal and urinary disorders								
Acute kidney injury	1 (2.44%)	1 (2.38%)	2 (2.41%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (1.52%)
Renal failure	1 (2.44%)	0 (0.00%)	1 (1.20%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.76%)
Respiratory, thoracic and mediastinal disorders								
Acute respiratory failure	2 (4.88%)	0 (0.00%)	2 (2.41%)	0 (0.00%)	0 (0.00%)	1 (7.14%)	0 (0.00%)	3 (2.27%)
Aspiration	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (7.14%)	0 (0.00%)	1 (0.76%)
Dyspnoea	0 (0.00%)	1 (2.38%)	1 (1.20%)	1 (6.25%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (1.52%)
Haemoptysis	0 (0.00%)	1 (2.38%)	1 (1.20%)	1 (6.25%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (1.52%)
Pleural effusion	0 (0.00%)	1 (2.38%)	1 (1.20%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.76%)
Pneumonitis	1 (2.44%)	0 (0.00%)	1 (1.20%)	2 (12.50%)	0 (0.00%)	1 (7.14%)	0 (0.00%)	4 (3.03%)

Skin and subcutaneous tissue disorders								
Rash	1 (2.44%)	0 (0.00%)	1 (1.20%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.76%)
Vascular disorders								
Superior vena cava syndrome	1 (2.44%)	0 (0.00%)	1 (1.20%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.76%)

Other Adverse Events by System Organ Class

Time Frame	Adverse events were collected for approximately 6.5 years for dose escalation and 4.5 years for dose expansion including the 30 days safety follow-up period.
Additional Description	Any undesirable sign(s), symptom(s), or medical condition(s) that occurred after patient's signed informed consent up to roughly 6.5 years for dose escalation and 4.5 years for dose expansion including the 30 days safety follow-up period.
Source Vocabulary for Table Default	MedDRA (23.0)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	5%

	LEE011(200 mg)+eve(2.5 mg)+exe (25mg) (fasting) esc naive N = 41	**LEE011(200 mg)+eve(2.5 mg)+exe (25mg) (FED) esc refractory N = 42**	**Triplet: ESCALATION ALL N = 83**	**LEE011(300 mg)+eve(2.5 mg)+exe (25mg) exp naive N = 16**	**LEE011(300 mg)+eve(2.5 mg)+exe (25mg) exp refractory N = 17**	**LEE011(600 mg)+exe(25 mg) esc refractory N = 14**	**LEE011(600 mg)+exe(25 mg) exp refractory N = 2**	**All subjects N = 132**
Arm/Group Description	Triplet combination of LEE011 200 mg +	Triplet combination of LEE011 200 mg +	Triplet: ESCALATION ALL	Following RP2D declaration for the triplet	Following RP2D declaration for the triplet	Doublet combination, LEE011 600 mg +	Following RP2D declaration for the	All subjects

	everolimus (RAD001) 2.5 mg + exemestane 25 mg was administered in fasting to the naive to CDK4/6 inhibitors group	everolimus (RAD001) 2.5 mg + exemestane 25 mg was administered with food to the refractory to CDK4/6 inhibitor based therapy group		combination, LEE011 300 mg + everolimus 2.5 mg + exemestane 25 mg was administered with food to the naive to CDK4/6 inhibitors group	combination, LEE011 300 mg + everolimus 2.5 mg + exemestane 25 mg was administered with food to the refractory to CDK4/6 inhibitor based therapy group	exemestane 25 mg was administered with food to the refractory to CDK4/6 inhibitor based therapy group	doublet combination, LEE011 600 mg + exemestane 25 mg was administered with food to the refractory to CDK4/6 inhibitor based therapy group (except patients with disease refractory to prior LEE011)	
Total participants affected	41 (100.00%)	42 (100.00%)	83 (100.00%)	16 (100.00%)	17 (100.00%)	14 (100.00%)	2 (100.00%)	132 (100.00%)
Blood and lymphatic system disorders								
Anaemia	26 (63.41%)	22 (52.38%)	48 (57.83%)	10 (62.50%)	5 (29.41%)	9 (64.29%)	0 (0.00%)	72 (54.55%)
Leukopenia	1 (2.44%)	3 (7.14%)	4 (4.82%)	1 (6.25%)	2 (11.76%)	1 (7.14%)	0 (0.00%)	8 (6.06%)
Lymphopenia	11 (26.83%)	5 (11.90%)	16 (19.28%)	2 (12.50%)	1 (5.88%)	4 (28.57%)	0 (0.00%)	23 (17.42%)
Neutropenia	18 (43.90%)	22 (52.38%)	40 (48.19%)	10 (62.50%)	11 (64.71%)	6 (42.86%)	0 (0.00%)	67 (50.76%)
Thrombocytopenia	12 (29.27%)	12 (28.57%)	24 (28.92%)	6 (37.50%)	4 (23.53%)	4 (28.57%)	0 (0.00%)	38 (28.79%)
Cardiac disorders								
Acute myocardial infarction	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (7.14%)	0 (0.00%)	1 (0.76%)
Bradycardia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.76%)
Palpitations	1 (2.44%)	1 (2.38%)	2 (2.41%)	0 (0.00%)	0 (0.00%)	1 (7.14%)	0 (0.00%)	3 (2.27%)

Tachycardia	0 (0.00%)	2 (4.76%)	2 (2.41%)	1 (6.25%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (2.27%)
Ventricular extrasystoles	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.76%)
Ear and labyrinth disorders								
Cerumen impaction	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.88%)	0 (0.00%)	0 (0.00%)	1 (0.76%)
Ear discomfort	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (7.14%)	0 (0.00%)	1 (0.76%)
Vertigo	0 (0.00%)	1 (2.38%)	1 (1.20%)	0 (0.00%)	1 (5.88%)	0 (0.00%)	0 (0.00%)	2 (1.52%)
Endocrine disorders								
Hypothyroidism	1 (2.44%)	0 (0.00%)	1 (1.20%)	2 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (2.27%)
Eye disorders								
Dry eye	2 (4.88%)	1 (2.38%)	3 (3.61%)	0 (0.00%)	0 (0.00%)	1 (7.14%)	0 (0.00%)	4 (3.03%)
Eyelid oedema	1 (2.44%)	1 (2.38%)	2 (2.41%)	0 (0.00%)	0 (0.00%)	1 (7.14%)	0 (0.00%)	3 (2.27%)
Lacrimation increased	1 (2.44%)	0 (0.00%)	1 (1.20%)	0 (0.00%)	1 (5.88%)	1 (7.14%)	0 (0.00%)	3 (2.27%)
Myopia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (7.14%)	0 (0.00%)	1 (0.76%)
Vision blurred	0 (0.00%)	1 (2.38%)	1 (1.20%)	0 (0.00%)	2 (11.76%)	0 (0.00%)	0 (0.00%)	3 (2.27%)
Visual impairment	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.76%)
Gastrointestinal disorders								
Abdominal distension	1 (2.44%)	0 (0.00%)	1 (1.20%)	0 (0.00%)	1 (5.88%)	1 (7.14%)	0 (0.00%)	3 (2.27%)
Abdominal pain	4 (9.76%)	5 (11.90%)	9 (10.84%)	0 (0.00%)	2 (11.76%)	0 (0.00%)	0 (0.00%)	11 (8.33%)
Abdominal pain upper	3 (7.32%)	1 (2.38%)	4 (4.82%)	1 (6.25%)	0 (0.00%)	2 (14.29%)	0 (0.00%)	7 (5.30%)
Anal incontinence	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.88%)	0 (0.00%)	0 (0.00%)	1 (0.76%)
Aphthous ulcer	0 (0.00%)	2 (4.76%)	2 (2.41%)	2 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	4 (3.03%)
Ascites	0 (0.00%)	3 (7.14%)	3 (3.61%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (2.27%)
Colitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.76%)

Constipation	10 (24.39%)	4 (9.52%)	14 (16.87%)	3 (18.75%)	3 (17.65%)	6 (42.86%)	1 (50.00%)	27 (20.45%)
Dental caries	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (7.14%)	0 (0.00%)	1 (0.76%)
Diarrhoea	9 (21.95%)	13 (30.95%)	22 (26.51%)	2 (12.50%)	5 (29.41%)	8 (57.14%)	0 (0.00%)	37 (28.03%)
Dry mouth	2 (4.88%)	5 (11.90%)	7 (8.43%)	1 (6.25%)	1 (5.88%)	1 (7.14%)	0 (0.00%)	10 (7.58%)
Dyspepsia	4 (9.76%)	4 (9.52%)	8 (9.64%)	2 (12.50%)	2 (11.76%)	1 (7.14%)	1 (50.00%)	14 (10.61%)
Flatulence	1 (2.44%)	0 (0.00%)	1 (1.20%)	2 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (2.27%)
Gastrooesophageal reflux disease	2 (4.88%)	1 (2.38%)	3 (3.61%)	4 (25.00%)	0 (0.00%)	3 (21.43%)	0 (0.00%)	10 (7.58%)
Haemorrhoidal haemorrhage	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.76%)
Haemorrhoids	1 (2.44%)	3 (7.14%)	4 (4.82%)	1 (6.25%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	5 (3.79%)
Mouth ulceration	1 (2.44%)	1 (2.38%)	2 (2.41%)	0 (0.00%)	1 (5.88%)	1 (7.14%)	0 (0.00%)	4 (3.03%)
Nausea	15 (36.59%)	12 (28.57%)	27 (32.53%)	5 (31.25%)	9 (52.94%)	6 (42.86%)	1 (50.00%)	48 (36.36%)
Odynophagia	1 (2.44%)	3 (7.14%)	4 (4.82%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	4 (3.03%)
Oral pain	0 (0.00%)	1 (2.38%)	1 (1.20%)	0 (0.00%)	1 (5.88%)	0 (0.00%)	0 (0.00%)	2 (1.52%)
Stomatitis	23 (56.10%)	25 (59.52%)	48 (57.83%)	9 (56.25%)	11 (64.71%)	4 (28.57%)	0 (0.00%)	72 (54.55%)
Vomiting	12 (29.27%)	7 (16.67%)	19 (22.89%)	3 (18.75%)	6 (35.29%)	4 (28.57%)	1 (50.00%)	33 (25.00%)
General disorders and administration site conditions								
Asthenia	7 (17.07%)	7 (16.67%)	14 (16.87%)	3 (18.75%)	1 (5.88%)	2 (14.29%)	0 (0.00%)	20 (15.15%)
Chest discomfort	0 (0.00%)	1 (2.38%)	1 (1.20%)	1 (6.25%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (1.52%)
Chills	2 (4.88%)	1 (2.38%)	3 (3.61%)	0 (0.00%)	2 (11.76%)	0 (0.00%)	1 (50.00%)	6 (4.55%)
Fatigue	15 (36.59%)	9 (21.43%)	24 (28.92%)	5 (31.25%)	9 (52.94%)	5 (35.71%)	0 (0.00%)	43 (32.58%)
Gait disturbance	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.76%)
Influenza like illness	0 (0.00%)	1 (2.38%)	1 (1.20%)	0 (0.00%)	0 (0.00%)	2 (14.29%)	0 (0.00%)	3 (2.27%)
Local swelling	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.88%)	0 (0.00%)	0 (0.00%)	1 (0.76%)

Malaise	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (7.14%)	0 (0.00%)	1 (0.76%)
Mucosal dryness	1 (2.44%)	0 (0.00%)	1 (1.20%)	1 (6.25%)	0 (0.00%)	1 (7.14%)	0 (0.00%)	3 (2.27%)
Non-cardiac chest pain	2 (4.88%)	1 (2.38%)	3 (3.61%)	1 (6.25%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	4 (3.03%)
Oedema peripheral	10 (24.39%)	5 (11.90%)	15 (18.07%)	5 (31.25%)	5 (29.41%)	2 (14.29%)	0 (0.00%)	27 (20.45%)
Pain	1 (2.44%)	3 (7.14%)	4 (4.82%)	0 (0.00%)	1 (5.88%)	0 (0.00%)	0 (0.00%)	5 (3.79%)
Pyrexia	7 (17.07%)	7 (16.67%)	14 (16.87%)	3 (18.75%)	0 (0.00%)	1 (7.14%)	2 (100.00%)	20 (15.15%)
Hepatobiliary disorders								
Hepatic necrosis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (7.14%)	0 (0.00%)	1 (0.76%)
Hyperbilirubinaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (11.76%)	0 (0.00%)	0 (0.00%)	2 (1.52%)
Infections and infestations								
Bronchitis	2 (4.88%)	0 (0.00%)	2 (2.41%)	1 (6.25%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (2.27%)
Clostridium difficile colitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (7.14%)	0 (0.00%)	1 (0.76%)
Diverticulitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (7.14%)	0 (0.00%)	1 (0.76%)
Folliculitis	1 (2.44%)	1 (2.38%)	2 (2.41%)	1 (6.25%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (2.27%)
Gastroenteritis	0 (0.00%)	1 (2.38%)	1 (1.20%)	0 (0.00%)	0 (0.00%)	1 (7.14%)	0 (0.00%)	2 (1.52%)
Gastroenteritis viral	1 (2.44%)	0 (0.00%)	1 (1.20%)	1 (6.25%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (1.52%)
Gastrointestinal infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.88%)	0 (0.00%)	0 (0.00%)	1 (0.76%)
Genital herpes	1 (2.44%)	0 (0.00%)	1 (1.20%)	0 (0.00%)	0 (0.00%)	1 (7.14%)	0 (0.00%)	2 (1.52%)
Lung infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (1.52%)
Nasopharyngitis	0 (0.00%)	1 (2.38%)	1 (1.20%)	1 (6.25%)	0 (0.00%)	1 (7.14%)	0 (0.00%)	3 (2.27%)
Onychomycosis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (7.14%)	0 (0.00%)	1 (0.76%)
Pneumonia	4 (9.76%)	2 (4.76%)	6 (7.23%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	6 (4.55%)
Rash pustular	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.88%)	0 (0.00%)	0 (0.00%)	1 (0.76%)

Rhinitis	1 (2.44%)	0 (0.00%)	1 (1.20%)	1 (6.25%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (1.52%)
Sinusitis	2 (4.88%)	2 (4.76%)	4 (4.82%)	0 (0.00%)	1 (5.88%)	1 (7.14%)	0 (0.00%)	6 (4.55%)
Skin infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.88%)	0 (0.00%)	0 (0.00%)	1 (0.76%)
Tooth infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)	1 (5.88%)	0 (0.00%)	0 (0.00%)	2 (1.52%)
Upper respiratory tract infection	1 (2.44%)	4 (9.52%)	5 (6.02%)	1 (6.25%)	1 (5.88%)	0 (0.00%)	0 (0.00%)	7 (5.30%)
Urinary tract infection	2 (4.88%)	3 (7.14%)	5 (6.02%)	1 (6.25%)	3 (17.65%)	1 (7.14%)	0 (0.00%)	10 (7.58%)
Viral infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.88%)	0 (0.00%)	0 (0.00%)	1 (0.76%)
Viral upper respiratory tract infection	1 (2.44%)	4 (9.52%)	5 (6.02%)	2 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	7 (5.30%)
Vulvovaginal mycotic infection	1 (2.44%)	0 (0.00%)	1 (1.20%)	0 (0.00%)	1 (5.88%)	0 (0.00%)	0 (0.00%)	2 (1.52%)
Wound infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.76%)
Injury, poisoning and procedural complications								
Arthropod bite	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.76%)
Ligament sprain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (7.14%)	0 (0.00%)	1 (0.76%)
Muscle rupture	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (7.14%)	0 (0.00%)	1 (0.76%)
Wound	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (7.14%)	0 (0.00%)	1 (0.76%)
Wrist fracture	0 (0.00%)	1 (2.38%)	1 (1.20%)	1 (6.25%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (1.52%)
Investigations								
Alanine aminotransferase decreased	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.76%)
Alanine aminotransferase increased	12 (29.27%)	13 (30.95%)	25 (30.12%)	5 (31.25%)	4 (23.53%)	5 (35.71%)	0 (0.00%)	39 (29.55%)

Aspartate aminotransferase increased	18 (43.90%)	16 (38.10%)	34 (40.96%)	4 (25.00%)	5 (29.41%)	8 (57.14%)	0 (0.00%)	51 (38.64%)
Blood alkaline phosphatase increased	11 (26.83%)	7 (16.67%)	18 (21.69%)	1 (6.25%)	1 (5.88%)	4 (28.57%)	0 (0.00%)	24 (18.18%)
Blood bilirubin increased	1 (2.44%)	0 (0.00%)	1 (1.20%)	0 (0.00%)	1 (5.88%)	2 (14.29%)	0 (0.00%)	4 (3.03%)
Blood cholesterol increased	4 (9.76%)	3 (7.14%)	7 (8.43%)	2 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	9 (6.82%)
Blood creatinine increased	4 (9.76%)	5 (11.90%)	9 (10.84%)	2 (12.50%)	1 (5.88%)	2 (14.29%)	1 (50.00%)	15 (11.36%)
Blood lactate dehydrogenase increased	3 (7.32%)	2 (4.76%)	5 (6.02%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	5 (3.79%)
Blood phosphorus decreased	1 (2.44%)	1 (2.38%)	2 (2.41%)	1 (6.25%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (2.27%)
Blood phosphorus increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (7.14%)	0 (0.00%)	1 (0.76%)
Blood thyroid stimulating hormone decreased	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.76%)
Blood thyroid stimulating hormone increased	1 (2.44%)	0 (0.00%)	1 (1.20%)	1 (6.25%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (1.52%)
Blood urea decreased	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.76%)
Electrocardiogram QT prolonged	2 (4.88%)	0 (0.00%)	2 (2.41%)	0 (0.00%)	1 (5.88%)	2 (14.29%)	0 (0.00%)	5 (3.79%)
Gamma-glutamyltransferase increased	5 (12.20%)	5 (11.90%)	10 (12.05%)	3 (18.75%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	13 (9.85%)
Haemoglobin decreased	2 (4.88%)	0 (0.00%)	2 (2.41%)	0 (0.00%)	1 (5.88%)	0 (0.00%)	0 (0.00%)	3 (2.27%)

Lymphocyte count decreased	12 (29.27%)	11 (26.19%)	23 (27.71%)	6 (37.50%)	1 (5.88%)	4 (28.57%)	0 (0.00%)	34 (25.76%)
Lymphocyte count increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (7.14%)	0 (0.00%)	1 (0.76%)
Neutrophil count decreased	20 (48.78%)	16 (38.10%)	36 (43.37%)	10 (62.50%)	8 (47.06%)	9 (64.29%)	1 (50.00%)	64 (48.48%)
Platelet count decreased	9 (21.95%)	8 (19.05%)	17 (20.48%)	1 (6.25%)	3 (17.65%)	3 (21.43%)	0 (0.00%)	24 (18.18%)
Platelet count increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.88%)	0 (0.00%)	0 (0.00%)	1 (0.76%)
Thyroxine decreased	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.76%)
Transaminases increased	1 (2.44%)	0 (0.00%)	1 (1.20%)	0 (0.00%)	1 (5.88%)	0 (0.00%)	0 (0.00%)	2 (1.52%)
Weight decreased	6 (14.63%)	3 (7.14%)	9 (10.84%)	2 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	11 (8.33%)
Weight increased	1 (2.44%)	1 (2.38%)	2 (2.41%)	0 (0.00%)	1 (5.88%)	1 (7.14%)	0 (0.00%)	4 (3.03%)
White blood cell count decreased	20 (48.78%)	17 (40.48%)	37 (44.58%)	5 (31.25%)	6 (35.29%)	12 (85.71%)	0 (0.00%)	60 (45.45%)
Metabolism and nutrition disorders								
Decreased appetite	10 (24.39%)	6 (14.29%)	16 (19.28%)	5 (31.25%)	6 (35.29%)	1 (7.14%)	0 (0.00%)	28 (21.21%)
Hyperglycaemia	10 (24.39%)	14 (33.33%)	24 (28.92%)	3 (18.75%)	4 (23.53%)	5 (35.71%)	0 (0.00%)	36 (27.27%)
Hyperkalaemia	2 (4.88%)	2 (4.76%)	4 (4.82%)	2 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	6 (4.55%)
Hypertriglyceridaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)	0 (0.00%)	1 (7.14%)	0 (0.00%)	2 (1.52%)
Hypocalcaemia	4 (9.76%)	5 (11.90%)	9 (10.84%)	0 (0.00%)	0 (0.00%)	1 (7.14%)	0 (0.00%)	10 (7.58%)
Hypoglycaemia	2 (4.88%)	0 (0.00%)	2 (2.41%)	0 (0.00%)	0 (0.00%)	2 (14.29%)	0 (0.00%)	4 (3.03%)
Hypokalaemia	5 (12.20%)	6 (14.29%)	11 (13.25%)	1 (6.25%)	1 (5.88%)	3 (21.43%)	0 (0.00%)	16 (12.12%)
Hypomagnesaemia	5 (12.20%)	4 (9.52%)	9 (10.84%)	1 (6.25%)	1 (5.88%)	1 (7.14%)	0 (0.00%)	12 (9.09%)
Hyponatraemia	5 (12.20%)	7 (16.67%)	12 (14.46%)	3 (18.75%)	0 (0.00%)	2 (14.29%)	0 (0.00%)	17 (12.88%)
Hypophosphataemia	10 (24.39%)	12 (28.57%)	22 (26.51%)	5 (31.25%)	4 (23.53%)	3 (21.43%)	0 (0.00%)	34 (25.76%)

Increased appetite	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (7.14%)	0 (0.00%)	1 (0.76%)
Iron deficiency	0 (0.00%)	3 (7.14%)	3 (3.61%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (2.27%)
Musculoskeletal and connective tissue disorders								
Arthralgia	5 (12.20%)	9 (21.43%)	14 (16.87%)	1 (6.25%)	5 (29.41%)	2 (14.29%)	0 (0.00%)	22 (16.67%)
Arthropathy	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.76%)
Back pain	6 (14.63%)	3 (7.14%)	9 (10.84%)	2 (12.50%)	1 (5.88%)	3 (21.43%)	1 (50.00%)	16 (12.12%)
Bone cyst	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.76%)
Bone pain	5 (12.20%)	2 (4.76%)	7 (8.43%)	1 (6.25%)	0 (0.00%)	1 (7.14%)	0 (0.00%)	9 (6.82%)
Intervertebral disc degeneration	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.76%)
Muscle spasms	2 (4.88%)	1 (2.38%)	3 (3.61%)	1 (6.25%)	1 (5.88%)	2 (14.29%)	0 (0.00%)	7 (5.30%)
Musculoskeletal chest pain	2 (4.88%)	2 (4.76%)	4 (4.82%)	1 (6.25%)	1 (5.88%)	1 (7.14%)	0 (0.00%)	7 (5.30%)
Musculoskeletal pain	3 (7.32%)	1 (2.38%)	4 (4.82%)	2 (12.50%)	1 (5.88%)	1 (7.14%)	0 (0.00%)	8 (6.06%)
Myalgia	2 (4.88%)	3 (7.14%)	5 (6.02%)	0 (0.00%)	1 (5.88%)	2 (14.29%)	0 (0.00%)	8 (6.06%)
Neck pain	2 (4.88%)	0 (0.00%)	2 (2.41%)	1 (6.25%)	1 (5.88%)	0 (0.00%)	0 (0.00%)	4 (3.03%)
Osteonecrosis	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.76%)
Osteopenia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)	0 (0.00%)	1 (7.14%)	0 (0.00%)	2 (1.52%)
Osteoporosis	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.76%)
Pain in extremity	3 (7.32%)	2 (4.76%)	5 (6.02%)	2 (12.50%)	1 (5.88%)	1 (7.14%)	0 (0.00%)	9 (6.82%)
Nervous system disorders								
Amnesia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.76%)
Dizziness	3 (7.32%)	1 (2.38%)	4 (4.82%)	0 (0.00%)	2 (11.76%)	0 (0.00%)	0 (0.00%)	6 (4.55%)
Dysaesthesia	0 (0.00%)	1 (2.38%)	1 (1.20%)	1 (6.25%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (1.52%)

Dysgeusia	8 (19.51%)	4 (9.52%)	12 (14.46%)	4 (25.00%)	2 (11.76%)	0 (0.00%)	0 (0.00%)	18 (13.64%)
Headache	6 (14.63%)	11 (26.19%)	17 (20.48%)	3 (18.75%)	3 (17.65%)	3 (21.43%)	1 (50.00%)	27 (20.45%)
Hyperaesthesia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.88%)	0 (0.00%)	0 (0.00%)	1 (0.76%)
Hypoaesthesia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.76%)
Intracranial aneurysm	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.88%)	0 (0.00%)	0 (0.00%)	1 (0.76%)
Neuropathy peripheral	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.76%)
Paraesthesia	0 (0.00%)	1 (2.38%)	1 (1.20%)	0 (0.00%)	0 (0.00%)	1 (7.14%)	0 (0.00%)	2 (1.52%)
Sciatica	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.76%)
Psychiatric disorders								
Anxiety	2 (4.88%)	0 (0.00%)	2 (2.41%)	1 (6.25%)	0 (0.00%)	1 (7.14%)	0 (0.00%)	4 (3.03%)
Delirium	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (7.14%)	0 (0.00%)	1 (0.76%)
Depression	1 (2.44%)	1 (2.38%)	2 (2.41%)	2 (12.50%)	1 (5.88%)	0 (0.00%)	0 (0.00%)	5 (3.79%)
Insomnia	2 (4.88%)	6 (14.29%)	8 (9.64%)	0 (0.00%)	2 (11.76%)	2 (14.29%)	0 (0.00%)	12 (9.09%)
Irritability	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (7.14%)	0 (0.00%)	1 (0.76%)
Restlessness	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (7.14%)	0 (0.00%)	1 (0.76%)
Renal and urinary disorders								
Dysuria	2 (4.88%)	1 (2.38%)	3 (3.61%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (50.00%)	4 (3.03%)
Pollakiuria	0 (0.00%)	1 (2.38%)	1 (1.20%)	0 (0.00%)	1 (5.88%)	0 (0.00%)	0 (0.00%)	2 (1.52%)
Urinary incontinence	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.88%)	0 (0.00%)	0 (0.00%)	1 (0.76%)
Reproductive system and breast disorders								
Breast haematoma	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.76%)
Breast pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.88%)	0 (0.00%)	0 (0.00%)	1 (0.76%)
Vulvovaginal burning sensation	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.76%)

Respiratory, thoracic and mediastinal disorders								
Allergic sinusitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (7.14%)	0 (0.00%)	1 (0.76%)
Cough	12 (29.27%)	11 (26.19%)	23 (27.71%)	3 (18.75%)	3 (17.65%)	4 (28.57%)	1 (50.00%)	34 (25.76%)
Dysphonia	3 (7.32%)	0 (0.00%)	3 (3.61%)	1 (6.25%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	4 (3.03%)
Dyspnoea	10 (24.39%)	10 (23.81%)	20 (24.10%)	4 (25.00%)	1 (5.88%)	2 (14.29%)	0 (0.00%)	27 (20.45%)
Dyspnoea exertional	4 (9.76%)	1 (2.38%)	5 (6.02%)	2 (12.50%)	1 (5.88%)	4 (28.57%)	0 (0.00%)	12 (9.09%)
Epistaxis	9 (21.95%)	7 (16.67%)	16 (19.28%)	4 (25.00%)	3 (17.65%)	1 (7.14%)	0 (0.00%)	24 (18.18%)
Nasal congestion	3 (7.32%)	2 (4.76%)	5 (6.02%)	1 (6.25%)	0 (0.00%)	1 (7.14%)	0 (0.00%)	7 (5.30%)
Oropharyngeal pain	3 (7.32%)	4 (9.52%)	7 (8.43%)	0 (0.00%)	2 (11.76%)	1 (7.14%)	0 (0.00%)	10 (7.58%)
Pharyngeal inflammation	1 (2.44%)	0 (0.00%)	1 (1.20%)	1 (6.25%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (1.52%)
Pneumonitis	4 (9.76%)	5 (11.90%)	9 (10.84%)	6 (37.50%)	1 (5.88%)	1 (7.14%)	0 (0.00%)	17 (12.88%)
Productive cough	0 (0.00%)	1 (2.38%)	1 (1.20%)	1 (6.25%)	0 (0.00%)	1 (7.14%)	0 (0.00%)	3 (2.27%)
Pulmonary embolism	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.76%)
Reflux laryngitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.88%)	0 (0.00%)	0 (0.00%)	1 (0.76%)
Rhinorrhoea	1 (2.44%)	1 (2.38%)	2 (2.41%)	3 (18.75%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	5 (3.79%)
Sinus congestion	1 (2.44%)	0 (0.00%)	1 (1.20%)	1 (6.25%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (1.52%)
Upper-airway cough syndrome	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (7.14%)	0 (0.00%)	1 (0.76%)
Wheezing	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.76%)
Skin and subcutaneous tissue disorders								
Acne	0 (0.00%)	1 (2.38%)	1 (1.20%)	0 (0.00%)	0 (0.00%)	1 (7.14%)	0 (0.00%)	2 (1.52%)
Alopecia	2 (4.88%)	3 (7.14%)	5 (6.02%)	1 (6.25%)	1 (5.88%)	3 (21.43%)	0 (0.00%)	10 (7.58%)
Dermal cyst	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (7.14%)	0 (0.00%)	1 (0.76%)

Dermatitis	1 (2.44%)	1 (2.38%)	2 (2.41%)	0 (0.00%)	0 (0.00%)	1 (7.14%)	0 (0.00%)	3 (2.27%)
Dermatitis acneiform	1 (2.44%)	2 (4.76%)	3 (3.61%)	0 (0.00%)	0 (0.00%)	1 (7.14%)	0 (0.00%)	4 (3.03%)
Dry skin	3 (7.32%)	2 (4.76%)	5 (6.02%)	2 (12.50%)	1 (5.88%)	2 (14.29%)	0 (0.00%)	10 (7.58%)
Ecchymosis	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.76%)
Hair texture abnormal	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (7.14%)	0 (0.00%)	1 (0.76%)
Madarosis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (7.14%)	0 (0.00%)	1 (0.76%)
Nail discolouration	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (7.14%)	0 (0.00%)	1 (0.76%)
Nail disorder	3 (7.32%)	1 (2.38%)	4 (4.82%)	2 (12.50%)	0 (0.00%)	1 (7.14%)	0 (0.00%)	7 (5.30%)
Nail dystrophy	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.76%)
Onychomalacia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (7.14%)	0 (0.00%)	1 (0.76%)
Palmoplantar keratoderma	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (7.14%)	0 (0.00%)	1 (0.76%)
Pruritus	3 (7.32%)	3 (7.14%)	6 (7.23%)	0 (0.00%)	1 (5.88%)	1 (7.14%)	0 (0.00%)	8 (6.06%)
Rash	8 (19.51%)	10 (23.81%)	18 (21.69%)	5 (31.25%)	4 (23.53%)	1 (7.14%)	0 (0.00%)	28 (21.21%)
Rash macular	0 (0.00%)	1 (2.38%)	1 (1.20%)	0 (0.00%)	1 (5.88%)	0 (0.00%)	0 (0.00%)	2 (1.52%)
Rash maculo-papular	3 (7.32%)	4 (9.52%)	7 (8.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	7 (5.30%)
Rash vesicular	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.76%)
Rosacea	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (7.14%)	0 (0.00%)	1 (0.76%)
Skin lesion	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)	0 (0.00%)	1 (7.14%)	0 (0.00%)	2 (1.52%)
Skin mass	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (7.14%)	0 (0.00%)	1 (0.76%)
Vascular disorders								
Deep vein thrombosis	0 (0.00%)	1 (2.38%)	1 (1.20%)	1 (6.25%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (1.52%)
Hot flush	0 (0.00%)	3 (7.14%)	3 (3.61%)	1 (6.25%)	2 (11.76%)	3 (21.43%)	1 (50.00%)	10 (7.58%)
Hypertension	3 (7.32%)	3 (7.14%)	6 (7.23%)	1 (6.25%)	1 (5.88%)	2 (14.29%)	0 (0.00%)	10 (7.58%)
Lymphoedema	3 (7.32%)	3 (7.14%)	6 (7.23%)	1 (6.25%)	0 (0.00%)	1 (7.14%)	0 (0.00%)	8 (6.06%)

Phlebitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.76%)

Other Relevant Findings

None

Conclusion:

- The efficacy and safety results of this final analysis are consistent with those of the primary analysis.
- Preliminary evidence of antitumor efficacy were observed in patients treated with the doublet combination (ribociclib + exemestane) and triplet combination (ribociclib + everolimus + exemestane) in the fasting and fed state as demonstrated by the efficacy results of PFS, ORR, and CBR.
- Modest evidence of antitumor efficacy was observed in the dose escalation cohorts with an overall response rate of 14.3% in the doublet escalation fasting cohort, 9.8% in the triplet escalation fasting cohort and 11.9% in the triplet escalation fed cohort.
- AEs reported were consistent with the known safety profile of ribociclib, everolimus and exemestane and no new safety findings were evident at the time of study completion.

Date of Clinical Trial Report

30 January, 2021