Clinical trial results:
Phase III study of Palbociclib (PD-0332991) in combination with Exemestane versus chemotherapy (capecitabine) in Hormonal Receptor (HR) positive/HER2 negative Metastatic Breast Cancer (MBC) patients with Resistance to non-steroidal Aromatase inhibitors
The PEARL study

Summary

EudraCT number	2013-003170-27
Trial protocol	ES AT HU LV IE
Global end of trial date	11 January 2021

Results information

Result version number	v1
This version publication date	18 April 2022
First version publication date	18 April 2022

Trial information

Trial identification

Sponsor protocol code	GEICAM/2013-02

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02028507
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GEICAM (FUNDACIÓN GRUPO ESPAÑOL DE INVESTIGACIÓN EN CÁNCER DE MAMA)
Sponsor organisation address	Avenida de los Pirineos 7, San Sebastián de los Reyes / Madrid, Spain, 28703
Public contact	Clinical Operations Department, GEICAM (Fundación Grupo Español de Investigación en Cáncer de Mama), 34 916592870, geicam@geicam.org
Scientific contact	Clinical Operations Department, GEICAM (Fundación Grupo Español de Investigación en Cáncer de Mama), +34 916592870, geicam@geicam.org

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 May 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 January 2019
Global end of trial reached?	Yes
Global end of trial date	11 January 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that palbociclib in combination with exemestane is superior to capecitabine in prolonging Progression-Free Survival (PFS) in postmenopausal women with HR positive/HER2 negative MBC whose disease was resistant to non-steroidal aromatase inhibitors.

Protection of trial subjects:

Not applicable. It was not necessary to applied extra measures for protection of the subjects out of the good clinical practice environment.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 March 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 15
Country: Number of subjects enrolled	Spain: 488
Country: Number of subjects enrolled	Hungary: 59
Country: Number of subjects enrolled	Israel: 39
Worldwide total number of subjects	601
EEA total number of subjects	562

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0

Adolescents (12-17 years)	0
Adults (18-64 years)	391
From 65 to 84 years	205
85 years and over	5

Subject disposition

Recruitment

Recruitment details:

92 patients were screening failure. A total of 601 patients were included in this study from March 2014 to July 2018. Cohort 1 included 296 patients (153 on palbociclib plus exemestane and 143 on capecitabine) and cohort 2 included 305 patients (149 on palbociclib plus fulvestrant and 156 on capecitabine).

Pre-assignment

Screening details:

92 patients were screening failure. A total of 601 patients were included in this study from March 2014 to July 2018. Cohort 1 included 296 patients (153 on palbociclib plus exemestane and 143 on capecitabine) and cohort 2 included 305 patients (149 on palbociclib plus fulvestrant and 156 on capecitabine).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1: Arm A: Palbociclib Plus Exemestane

Arm description:

Palbociclib 125 mg orally once daily on Day 1 to Day 21 followed by 7 days off treatment on every 28 days cycles in combination with Exemestane 25 mg orally once daily

Arm type	Experimental
Investigational medicinal product name	Palbociclib
Investigational medicinal product code	
Other name	Ibrance
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Palbociclib will be administered at a dose of 125mg PO daily on Day 1 to Day 21 following a 1 week of rest period, given as 4 weeks cycles.

Investigational medicinal product name	Exemestane
Investigational medicinal product code	
Other name	Aromasil
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Exemestane will be administered at a dose of 25 mg PO daily (continuously).

Arm title	Cohort 1: Arm B: Capecitabine

Arm description:

Capecitabine, 1,250 mg/m2 twice daily for 2 weeks followed by a 1 week rest period, given as 3 weeks cycles. Capecitabine must be administered at a dose of 1,000 mg/m2 twice daily for 2 weeks followed by a 1 week of rest period, given as 3 weeks cycles, in patients over 70 years of age.

Arm type	Active comparator

Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	Xeloda
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Capecitabine will be administered at a dose of 1,250mg/m2 twice daily for 2 weeks followed by a 1 week of rest period, given as 3 weeks cycles.
Capecitabine must be administered at a dose of 1,000mg/m2 twice daily for 2 weeks followed by a 1 week of rest period, given as 3 weeks cycles, in patients over 70 years of age.
Capecitabine Dose will be calculated for each patient in mg/m2, it is recommeded to calculate the dose according to the Protocol Attachment 4. The real Body Surface Area (BSA) of the
patient determined in the baseline visit will be the reference BSA throughout the study. The BSA and the capecitabine dose will be recalculated in the event that patients experience body
weight variations greater than 10% during the treatment period.

Arm title	Cohort 2: Palbociclib Plus Fulvestrant

Arm description:

Palbociclib 125 mg orally once daily on Day 1 to Day 21 followed by 7 days off treatment on every 28 days cycles in combination with Fulvestrant 500 mg on Days 1 and 15 of Cycle 1, and Day 1 of each subsequent 28 days Cycle.

Arm type	Experimental
Investigational medicinal product name	Palbociclib
Investigational medicinal product code	
Other name	Ibrance
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Palbociclib will be administered at a dose of 125mg PO daily on Day 1 to Day 21 following a 1 week of rest period, given as 4 weeks cycles.

Investigational medicinal product name	Fulvestrant
Investigational medicinal product code	
Other name	Faslodex
Pharmaceutical forms	Emulsion for injection/infusion in pre-filled syringe
Routes of administration	Concentrate for solution for infusion

Dosage and administration details:

Fulvestrant will be administered at a dose of 500mg, as two 5ml intramuscular injections (one in each buttock), on days 1 and 15 (±3 days) of Cycle 1, and then on Day 1 of each subsequent 28 days Cycle (± 3 days). Time windows extended to ±7 days after 24 weeks.

Arm title	Cohort 2: Arm B: Capecitabine

Arm description:

Capecitabine, 1,250 mg/m2 twice daily for 2 weeks followed by a 1 week rest period, given as 3 weeks cycles. Capecitabine must be administered at a dose of 1,000 mg/m2 twice daily for 2 weeks followed by a 1 week of rest period, given as 3 weeks cycles, in patients over 70 years of age

Arm type	Active comparator
Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	Xeloda
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Capecitabine will be administered at a dose of 1,250mg/m2 twice daily for 2 weeks followed by a 1 week of rest period, given as 3 weeks cycles.
Capecitabine must be administered at a dose of 1,000mg/m2 twice daily for 2 weeks followed by a 1 week of rest period, given as 3 weeks cycles, in patients over 70 years of age.
Capecitabine Dose will be calculated for each patient in mg/m2, it is recommeded to calculate the dose according to the Protocol Attachment 4. The real Body Surface Area (BSA) of the
patient determined in the baseline visit will be the reference BSA throughout the study. The BSA and the

capecitabine dose will be recalculated in the event that patients experience body weight variations greater than 10% during the treatment period.

Number of subjects in period 1	Cohort 1: Arm A: Palbociclib Plus Exemestane	Cohort 1: Arm B: Capecitabine	Cohort 2: Palbociclib Plus Fulvestrant
Started	153	143	149
Completed	0	0	0
Not completed	153	143	149
Consent withdrawn by subject	6	8	5
Physician decision	-	4	-
Enzyme defect	-	-	-
Adverse event, non-fatal	8	25	3
Death	1	-	1
Progressive Disease	122	90	102
Second Invasive Primary Malignancy	1	-	-
Patient Required Therapy/ Procedure Not Permitted	-	1	-
Randomized But Not Treated	3	6	-
Ongoing at date of cut-off 30-May-2019	10	5	37
Protocol deviation	2	4	1
Patient was not able to take whole dose of capecit	-	-	-

Number of subjects in period 1	Cohort 2: Arm B: Capecitabine
Started	156
Completed	0
Not completed	156
Consent withdrawn by subject	9
Physician decision	-
Enzyme defect	1
Adverse event, non-fatal	16
Death	3
Progressive Disease	89
Second Invasive Primary Malignancy	1
Patient Required Therapy/ Procedure Not Permitted	1
Randomized But Not Treated	4

Ongoing at date of cut-off 30-May-2019	28
Protocol deviation	3
Patient was not able to take whole dose of capecit	1

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1: Arm A: Palbociclib Plus Exemestane
Reporting group description:	
Palbociclib 125 mg orally once daily on Day 1 to Day 21 followed by 7 days off treatment on every 28 days cycles in combination with Exemestane 25 mg orally once daily	
Reporting group title	Cohort 1: Arm B: Capecitabine
Reporting group description:	
Capecitabine, 1,250 mg/m2 twice daily for 2 weeks followed by a 1 week rest period, given as 3 weeks cycles. Capecitabine must be administered at a dose of 1,000 mg/m2 twice daily for 2 weeks followed by a 1 week of rest period, given as 3 weeks cycles, in patients over 70 years of age.	
Reporting group title	Cohort 2: Palbociclib Plus Fulvestrant
Reporting group description:	
Palbociclib 125 mg orally once daily on Day 1 to Day 21 followed by 7 days off treatment on every 28 days cycles in combination with Fulvestrant 500 mg on Days 1 and 15 of Cycle 1, and Day 1 of each subsequent 28 days Cycle.	
Reporting group title	Cohort 2: Arm B: Capecitabine
Reporting group description:	
Capecitabine, 1,250 mg/m2 twice daily for 2 weeks followed by a 1 week rest period, given as 3 weeks cycles. Capecitabine must be administered at a dose of 1,000 mg/m2 twice daily for 2 weeks followed by a 1 week of rest period, given as 3 weeks cycles, in patients over 70 years of age	

Reporting group values	Cohort 1: Arm A: Palbociclib Plus Exemestane	Cohort 1: Arm B: Capecitabine	Cohort 2: Palbociclib Plus Fulvestrant
Number of subjects	153	143	149
Age categorical Units: Subjects			
Adults (18-64 years)	97	98	93
From 65-84 years	55	44	54
85 years and over	1	1	2
Age continuous Units: years			
median	60	60	62
full range (min-max)	31 to 89	38 to 87	38 to 86
Gender categorical Units: Subjects			
Female	153	143	149
Male	0	0	0
Race/Ethnicity Units: Subjects			
Hispanic Or Latino	20	21	16
Not Hispanic Or Latino	128	118	129
Unknown	5	4	4
Region of Enrollment Units: Subjects			
Austria	5	1	4
Hungary	10	8	22
Israel	7	6	12
Spain	131	128	111

Eastern Cooperative Oncology Group (ECOG) status			
Measure Description: ECOG score runs from 0 to 5, with 0 denoting perfect health and 5 death. 0. - Asymptomatic 1. - Symptomatic but completely ambulatory 2. - Symptomatic, <50% in bed during the day 3. - Symptomatic, >50% in bed, but not bedbound 4. - Bedbound 5. - Death			
Units: Subjects			
ECOG 0	85	84	90
ECOG 1	68	59	59
Visceral disease Units: Subjects			
Yes	103	94	97
No	50	48	52
Not available	0	1	0
Hormone receptor status			
Estrogen receptor (ER) Progesterone receptor (PR)			
Units: Subjects			
ER positive and PR positive	114	103	114
ER positive and PR negative	36	38	33
ER negative and PR positive/ ER positive and PR NA	2	2	2
Triple negative	1	0	0
ESR1 mutational status Units: Subjects			
Wild-type	104	89	102
Mutant	41	37	38
Not available	8	17	9
Sensitivity to prior endocrine therapy Units: Subjects			
Yes	107	104	119
No	46	39	30
Number of prior lines of endocrine therapy for metastatic breast cancer Units: Subjects			
1 prior line	82	70	85
2 prior line	35	34	12
3 prior line	3	4	1
Maintenance after chemotherapy	3	4	12
Combination	0	0	1
No prior endocrine therapy for MBC	30	31	38
Prior chemotherapy for metastatic breast cancer Units: Subjects			
Yes	48	41	41
No	105	102	108
Line at study entry Units: Subjects			
1st line	27	31	38
2nd line	63	50	76
≥3rd line	63	62	35

Status at initial diagnosis Units: Subjects			
M0: Cancer not spread to other parts of the body	127	109	115
M1: Cancer has spread to other parts of the body	26	34	34
Histopathology type Units: Subjects			
Breast Invasive Ductal Carcinoma	122	117	117
Breast Invasive Lobular Carcinoma	23	24	24
Other	3	1	4
Not Available/ Not Done	5	1	4
Histologic grade			
Cancer cells are given a Grade (G) when they are removed from the breast and checked under a microscope. The G is based on how much the cancer cells look like normal cells. G1 or well differentiated (score 3, 4, or 5): cells are slower-growing, and look more like normal breast tissue. G2 or moderately differentiated (score 6, 7): cells are growing at a speed of and look like cells somewhere between G1 and 3. G3 or poorly differentiated (score 8, 9): cells look very different from normal and will probably grow and spread faster.			
Units: Subjects			
G1, Well Differentiated	17	15	13
G2, Moderately Differentiated	68	57	70
G3, Poorly Differentiated	36	37	38
GX, Unknown	23	23	19
Not Available/ Not Done	9	11	9

Reporting group values	Cohort 2: Arm B: Capecitabine	Total	
Number of subjects	156	601	
Age categorical Units: Subjects			
Adults (18-64 years)	103	391	
From 65-84 years	52	205	
85 years and over	1	5	
Age continuous Units: years			
median	60		
full range (min-max)	33 to 85	-	
Gender categorical Units: Subjects			
Female	156	601	
Male	0	0	
Race/Ethnicity Units: Subjects			
Hispanic Or Latino	18	75	
Not Hispanic Or Latino	136	511	
Unknown	2	15	
Region of Enrollment Units: Subjects			
Austria	5	15	
Hungary	19	59	
Israel	14	39	

Spain	118	488	
Eastern Cooperative Oncology Group (ECOG) status			
Measure Description: ECOG score runs from 0 to 5, with 0 denoting perfect health and 5 death. 0. - Asymptomatic 1. - Symptomatic but completely ambulatory 2. - Symptomatic, <50% in bed during the day 3. - Symptomatic, >50% in bed, but not bedbound 4. - Bedbound 5. - Death			
Units: Subjects			
ECOG 0	93	352	
ECOG 1	63	249	
Visceral disease Units: Subjects			
Yes	102	396	
No	54	204	
Not available	0	1	
Hormone receptor status			
Estrogen receptor (ER) Progesterone receptor (PR)			
Units: Subjects			
ER positive and PR positive	118	449	
ER positive and PR negative	33	140	
ER negative and PR positive/ ER positive and PR NA	5	11	
Triple negative	0	1	
ESR1 mutational status Units: Subjects			
Wild-type	98	393	
Mutant	48	164	
Not available	10	44	
Sensitivity to prior endocrine therapy Units: Subjects			
Yes	122	452	
No	34	149	
Number of prior lines of endocrine therapy for metastatic breast cancer Units: Subjects			
1 prior line	90	327	
2 prior line	9	90	
3 prior line	1	9	
Maintenance after chemotherapy	12	31	
Combination	0	1	
No prior endocrine therapy for MBC	44	143	
Prior chemotherapy for metastatic breast cancer Units: Subjects			
Yes	41	171	
No	115	430	
Line at study entry Units: Subjects			
1st line	43	139	
2nd line	79	268	

≥3rd line	34	194	
Status at initial diagnosis Units: Subjects			
M0: Cancer not spread to other parts of the body	120	471	
M1: Cancer has spread to other parts of the body	36	130	
Histopathology type Units: Subjects			
Breast Invasive Ductal Carcinoma	125	481	
Breast Invasive Lobular Carcinoma	20	91	
Other	8	16	
Not Available/ Not Done	3	13	
Histologic grade			
Cancer cells are given a Grade (G) when they are removed from the breast and checked under a microscope. The G is based on how much the cancer cells look like normal cells. G1 or well differentiated (score 3, 4, or 5): cells are slower-growing, and look more like normal breast tissue. G2 or moderately differentiated (score 6, 7): cells are growing at a speed of and look like cells somewhere between G1 and 3. G3 or poorly differentiated (score 8, 9): cells look very different from normal and will probably grow and spread faster.			
Units: Subjects			
G1, Well Differentiated	14	59	
G2, Moderately Differentiated	72	267	
G3, Poorly Differentiated	40	151	
GX, Unknown	19	84	
Not Available/ Not Done	11	40	

End points

End points reporting groups

Reporting group title	Cohort 1: Arm A: Palbociclib Plus Exemestane

Reporting group description:

Palbociclib 125 mg orally once daily on Day 1 to Day 21 followed by 7 days off treatment on every 28 days cycles in combination with Exemestane 25 mg orally once daily

Reporting group title	Cohort 1: Arm B: Capecitabine

Reporting group description:

Capecitabine, 1,250 mg/m2 twice daily for 2 weeks followed by a 1 week rest period, given as 3 weeks cycles. Capecitabine must be administered at a dose of 1,000 mg/m2 twice daily for 2 weeks followed by a 1 week of rest period, given as 3 weeks cycles, in patients over 70 years of age.

Reporting group title	Cohort 2: Palbociclib Plus Fulvestrant

Reporting group description:

Palbociclib 125 mg orally once daily on Day 1 to Day 21 followed by 7 days off treatment on every 28 days cycles in combination with Fulvestrant 500 mg on Days 1 and 15 of Cycle 1, and Day 1 of each subsequent 28 days Cycle.

Reporting group title	Cohort 2: Arm B: Capecitabine

Reporting group description:

Capecitabine, 1,250 mg/m2 twice daily for 2 weeks followed by a 1 week rest period, given as 3 weeks cycles. Capecitabine must be administered at a dose of 1,000 mg/m2 twice daily for 2 weeks followed by a 1 week of rest period, given as 3 weeks cycles, in patients over 70 years of age

Subject analysis set title	Exemestane or Fulvestrant + Palbo ESR1 wild type population
Subject analysis set type	Per protocol

Subject analysis set description:

The ESR1 wild type population will include all patients who are randomized, with study drug/medication assignment designated according to initial randomization and whose tumor had estrogen receptor (ESR1) mutational status as wild type at study entry.
ESR1 wild type population include patients with ESR1 mutational status as wild type at study entry.
• Exemestane or Fulvestrant plus Palbociclib ESR1 wild type population: Cohort 1 (n=153) of which ESR1 wild type (n=104) and cohort 2 (n=149) of which ESR1 wild type (n=102). Total ESR1 wild type 206
• Capecitabine ESR1 wild type population: Cohort 1 (n=143) of which ESR1 wild type (n=89) and cohort 2 (n=156) of which ESR1 wild type (n=98). Total ESR1 wild type 187

Subject analysis set title	Capecitabine ESR1 Wild Type Population
Subject analysis set type	Per protocol

Subject analysis set description:

The ESR1 wild type population will include all patients who are randomized, with study drug/medication assignment designated according to initial randomization and whose tumor had estrogen receptor (ESR1) mutational status as wild type at study entry.
ESR1 wild type population include patients with ESR1 mutational status as wild type at study entry.
• Exemestane or Fulvestrant plus Palbociclib ESR1 wild type population: Cohort 1 (n=153) of which ESR1 wild type (n=104) and cohort 2 (n=149) of which ESR1 wild type (n=102). Total ESR1 wild type 206
• Capecitabine ESR1 wild type population: Cohort 1 (n=143) of which ESR1 wild type (n=89) and cohort 2 (n=156) of which ESR1 wild type (n=98). Total ESR1 wild type 187

Subject analysis set title	Cohort 1 and 2: (Exemestane or Fulvestrant) Plus Palbociclib
Subject analysis set type	Per protocol

Subject analysis set description:

• Cohort 1: Palbociclib 125 mg orally once daily on Day 1 to Day 21 followed by 7 days off treatment on every 28 days cycles in combination with Exemestane 25 mg orally once daily.
• Cohort 2: Palbociclib 125 mg orally once daily on Day 1 to Day 21 followed by 7 days off treatment on every 28 days cycles in combination with Fulvestrant 500 mg on Days 1 and 15 of Cycle 1, and Day 1 of each subsequent 28 days Cycle.

Subject analysis set title	Cohort 1 and 2: Capecitabine
Subject analysis set type	Per protocol

Subject analysis set description:

Capecitabine, 1,250 mg/m2 twice daily for 2 weeks followed by a 1 week rest period, given as 3 weeks cycles.
Capecitabine must be administered at a dose of 1,000 mg/m2 twice daily for 2 weeks followed by a 1 week of
rest period, given as 3 weeks cycles, in patients over 70 years of age.

Subject analysis set title	Cohort 1 & 2: (Exemestane or Fulvestrant) + Palbo & Cape
Subject analysis set type	Sub-group analysis

Subject analysis set description:

QoL population: a subset of enrolled patients with available QoL questionnaires (the baseline and at least one more).
- Cohort 1: Palbociclib 125 mg orally once daily on Day 1 to Day 21 followed by 7 days off treatment on every 28 days cycles in combination with Exemestane 25 mg orally once daily.
Capecitabine, 1,250 mg/m2 twice daily for 2 weeks followed by a 1 week rest period, given as 3 weeks cycles.
Capecitabine must be administered at a dose of 1,000 mg/m2 twice daily for 2 weeks followed by a 1 week of rest period, given as 3 weeks cycles, in patients over 70 years of age.
- Cohort 2: Palbociclib 125 mg orally once daily on Day 1 to Day 21 followed by 7 days off treatment on every 28 days cycles in combination with Fulvestrant 500 mg on Days 1 and 15 of Cycle 1, and Day 1 of each subsequent 28 days Cycle.
Capecitabine, 1,250 mg/m2 twice daily for 2 weeks followed by a 1 week rest period, given as 3 weeks cycles.

Primary: Progression-Free Survival (PFS)

End point title	Progression-Free Survival (PFS)[1]

End point description:

The primary efficacy variable is PFS based on the investigator's assessment. PFS is defined as the time from randomization to the first documented progressive disease based on the investigator's assessment, using RECIST version 1.1, or death from any cause, whichever occurs first.
Estrogen Receptor 1 (ESR1) mutational status will be determined in circulating free DNA (cDNA) obtained from.
Disease assessments will be performed at baseline and every 8 weeks (± 7 days) from the start of treatment and every 12 weeks (±7 days) after 120 weeks of treatment baseline plasma samples and will be prospectively determined before the interims or final analyses. ESR1 mutational status will be blinded to the patients, investigators and study team.

End point type	Primary

End point timeframe:

Through study treatment, and average of 8 months

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Primary objectives are to demonstrate that the combination of palbociclib-fulvestrant is superior to capecitabine in prolonging PFS and to demostrate that palbociclib in combination with endocrine therapy (exemestane or fulvestrant) is superior to capecitabine in prolonging PFS in wild type patients.

End point values	Cohort 2: Palbociclib Plus Fulvestrant	Cohort 2: Arm B: Capecitabine	Exemestane or Fulvestrant + Palbo ESR1 wild type population	Capecitabine ESR1 Wild Type Population
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	149	156	206	187
Units: months				
median (confidence interval 95%)	7.5 (5.7 to 10.9)	10 (6.3 to 12.9)	8 (6.5 to 10.9)	10.6 (7.4 to 13)

Statistical analyses

Statistical analysis title	Progression-Free survival analysis Cohort 2
Comparison groups	Cohort 2: Palbociclib Plus Fulvestrant v Cohort 2: Arm B: Capecitabine
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.597
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	1.44

Statistical analysis title	Progression-Free survival analysis Wild type
Comparison groups	Exemestane or Fulvestrant + Palbo ESR1 wild type population v Capecitabine ESR1 Wild Type Population
Number of subjects included in analysis	393
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.421
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	1.36

Secondary: Overall Survival (OS) ESR1 Wild Type	
End point title	Overall Survival (OS) ESR1 Wild Type
End point description:	
OS is defined as the time from the date of randomization to the date of death from any cause.	
End point type	Secondary
End point timeframe:	
From randomization until death (up to approximately 34 months)	

End point values	Exemestane or Fulvestrant + Palbo ESR1 wild type population	Capecitabine ESR1 Wild Type Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	206	187		
Units: months				
median (confidence interval 95%)	33.7 (27.6 to 45.1)	32 (28 to 46.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR) ESR1 Wild Type

End point title	Objective Response Rate (ORR) ESR1 Wild Type

End point description:

Complete Response (CR) plus Partial Response (PR) based on the investigator’s assessment according to the RECIST version 1.1 in patients randomized with measurable disease.
Tumor assessment will be performed at baseline, the same method of measurement used at baseline will be used for further evaluations, that will be conducted every 8 weeks (±7days). The best response across treatment will be recorded. OR is defined as the complete plus partial responses out of the patients who had measurable disease at baseline.

End point type	Secondary

End point timeframe:

Through study treatment, and average of 8 months

End point values	Exemestane or Fulvestrant + Palbo ESR1 wild type population	Capecitabine ESR1 Wild Type Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	206	187		
Units: participants	47	55		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Benefit Rate (CBR) ESR1 Wild Type

End point title	Clinical Benefit Rate (CBR) ESR1 Wild Type

End point description:

CB is defined as complete response (CR), partial response (PR), or stable disease (SD) based on the investigator´s assessment lasting more than 24 weeks according to the RECIST version 1.1 in all randomized patients (ITT population). Per RECIST, CR is defined as the disappearance of all target lesions; PR is defined as an >=30% decrease in the sum of the longest diameter of target lesions; SD is defined as a failure to meet criteria for CR or PR in the absence of progressive disease. Overall Response

(OR) = CR + PR.

End point type	Secondary

End point timeframe:

Through study treatment, and average of 8 months

End point values	Exemestane or Fulvestrant + Palbo ESR1 wild type population	Capecitabine ESR1 Wild Type Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	206	187		
Units: participants	157	154		

Statistical analyses

No statistical analyses for this end point

Secondary: Response Duration (RD) ESR1 Wild Type

End point title	Response Duration (RD) ESR1 Wild Type

End point description:

Tumor response was assessed using Response Evaluation Criteria In Solid Tumors Criteria (RECIST 1.1) criteria. RD was defined as the time from the first documentation of objective tumor response (complete response (CR) or partial response (PR)) to the first documented progressive disease (PD), or to death due to any cause, whichever occurs first.
Per RECIST, CR is defined as the disappearance of all target lesions; PR is defined as an >=30% decrease in the sum of the longest diameter of target lesions; PD is defined as a 20% increase in the sum of the longest diameter of target lesions, or a measurable increase in a non-target lesion, or the appearance of new lesions

End point type	Secondary

End point timeframe:

Through study treatment, and average of 8 months

End point values	Exemestane or Fulvestrant + Palbo ESR1 wild type population	Capecitabine ESR1 Wild Type Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	47	55		
Units: months				
median (confidence interval 95%)	9.7 (8.7 to 21.7)	11.2 (7.2 to 17.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline Between Treatment Comparison in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) Functional Scale Scores

End point title	Change From Baseline Between Treatment Comparison in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) Functional Scale Scores

End point description:

The EORTC QLQ C30 is a 30 item questionnaire composed of 5 multi item functional subscales (physical, role, cognitive emotional, and social functioning), 3 multi item symptom scales (fatigue, nausea/vomiting, pain), a global health/quality of life (QOL) subscale, and 6 items cancer related symptoms (dyspnea, sleep disturbance, appetite, diarrhea, constipation, financial impact of cancer). The questionnaire employs 28 4 point Likert scales with responses from "not at all" to "very much" and 2 7 point Likert scales for global health and overall QOL. For functional and global QOL scales, higher scores represent a better level of functioning and are converted to a 0 to 100 scale. For symptom oriented scales, a higher score represents more severe symptoms.
Patients completed EORTC QLQ-C30 (v3.0) at baseline, at every two cycles for the first seven cycles, then at every three cycles until the end of treatment, and once again at the visit after treatment.

End point type	Secondary

End point timeframe:

Baseline, cycles 3, 5, 7, then at every three cycles until the end of treatment, and at the visit after treatment

End point values	Cohort 1 and 2: (Exemestane or Fulvestrant) Plus Palbociclib	Cohort 1 and 2: Capecitabine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	268	269		
Units: units on a scale				
arithmetic mean (confidence interval 95%)				
Global health status / QoL	3.28 (1.06 to 5.49)	1.97 (-0.33 to 4.29)		
Physical functioning	-1.73 (-3.94 to 0.48)	-2.94 (-5.07 to -0.81)		
Role functioning	-1.09 (-4.45 to 2.27)	-4.97 (-7.82 to -2.12)		
Emotional functioning	6.78 (3.67 to 9.88)	8.67 (6.04 to 11.29)		
Cognitive functioning	-2.18 (-4.91 to 0.54)	-2.42 (-4.66 to -0.18)		
Social functioning	-0.67 (-3.43 to 2.07)	-3.01 (-5.45 to -0.56)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline Between Treatment Comparison in EORTC QLQ-C30 Symptom Scale Scores

End point title	Change From Baseline Between Treatment Comparison in EORTC QLQ-C30 Symptom Scale Scores

End point description:

The EORTC QLQ C30 is a 30 item questionnaire composed of 5 multi item functional subscales (physical, role, cognitive emotional, and social functioning), 3 multi item symptom scales (fatigue, nausea/vomiting, pain), a global health/quality of life (QOL) subscale, and 6 items cancer related symptoms (dyspnea, sleep disturbance, appetite, diarrhea, constipation, financial impact of cancer). The questionnaire employs 28 4 point Likert scales with responses from "not at all" to "very much" and 2 7 point Likert scales for global health and overall QOL. For functional and global QOL scales, higher scores represent a better level of functioning and are converted to a 0 to 100 scale. For symptom oriented scales, a higher score represents more severe symptoms.
Patients completed EORTC QLQ-C30 (v3.0) at baseline, at every two cycles for the first seven cycles, then at every three cycles until the end of treatment, and once again at the visit after treatment.

End point type	Secondary

End point timeframe:

Baseline, cycles 3, 5, 7, then at every three cycles until the end of treatment, and at the visit after treatment

End point values	Cohort 1 and 2: (Exemestane or Fulvestrant) Plus Palbociclib	Cohort 1 and 2: Capecitabine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	268	269		
Units: units on a scale				
arithmetic mean (confidence interval 95%)				
Fatigue	3.85 (0.82 to 6.88)	5.79 (3.14 to 8.43)		
Nausea and vomiting	1.65 (-0.02 to 3.33)	1.45 (-0.07 to 2.98)		
Pain	-1.79 (-4.86 to 1.27)	-1.9 (-4.7 to 0.91)		
Dyspnoea	2.73 (-0.64 to 6.11)	-0.05 (-2.44 to 2.34)		
Insomnia	-3.04 (-6.63 to 0.54)	-5.94 (-8.92 to -2.97)		
Appetite loss	2.99 (-0.3 to 6.3)	1.04 (-1.57 to 3.65)		
Constipation	3.91 (0.56 to 7.27)	-1.45 (-4.10 to 1.19)		
Diarrhoea	3.67 (1.06 to 6.29)	6.73 (4.61 to 8.85)		
Financial difficulties	-1.31 (-4.74 to 2.10)	1.73 (-1.11 to 4.59)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline Between Treatment Comparison in European Organization for Research and Treatment of Cancer Breast Cancer Module (EORTC QLQ BR23) Functional Scale Scores

End point title	Change From Baseline Between Treatment Comparison in European Organization for Research and Treatment of Cancer Breast Cancer Module (EORTC QLQ BR23) Functional Scale Scores

End point description:

Patient reported outcomes of health related quality of life will be assessed using the breast modules (QLQ-BR23) instruments The EORTC QLQ BR23 is a 23 item breast cancer specific companion module to the EORTC QLQ C30 and consists of two functional scales (body image and sexuality); 3 symptom subscales (arm/hand, breast, and systemic side effects) and single items covering sexual enjoyment, distress at hair loss, and future perspective.
Patients completed BC-specific EORTC QLQ-BR23 (v1.0) at baseline, at every two cycles for the first seven cycles, then at every three cycles until the end of treatment, and once again at the visit after treatment.

End point type	Secondary

End point timeframe:

Baseline, cycles 3, 5, 7, then at every three cycles until the end of treatment, and at the visit after treatment

End point values	Cohort 1 and 2: (Exemestane or Fulvestrant) Plus Palbociclib	Cohort 1 and 2: Capecitabine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	268	269		
Units: units on a scale				
arithmetic mean (confidence interval 95%)				
Body image	-1.83 (-4.73 to 1.06)	0.14 (-2.16 to 2.44)		
Sexual functioning	2.94 (0.56 to 5.31)	1.72 (-0.37 to 3.81)		
Sexual enjoyment	-6.32 (-11.86 to -0.78)	-4.32 (-9.25 to 0.6)		
Future perspective	13.8 (9.61 to 17.99)	15.22 (11.66 to 18.78)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline Between Treatment Comparison in EORTC QLQ BR23 Symptom Scale Scores

End point title	Change From Baseline Between Treatment Comparison in EORTC QLQ BR23 Symptom Scale Scores

End point description:

Patient reported outcomes of health related quality of life will be assessed using the breast modules

(QLQ-BR23)
instruments The EORTC QLQ BR23 is a 23 item breast cancer specific companion module to the EORTC QLQ
C30 and consists of two functional scales (body image and sexuality); 3 symptom subscales (arm/hand, breast, and
systemic side effects) and single items covering sexual enjoyment, distress at hair loss, and future perspective.
Patients completed BC-specific EORTC QLQ-BR23 (v1.0) at baseline, at every two cycles for the first seven cycles,
then at every three cycles until the end of treatment, and once again at the visit after treatment.

End point type	Secondary

End point timeframe:

Baseline, cycles 3, 5, 7, then at every three cycles until the end of treatment, and at the visit after treatment

End point values	Cohort 1 and 2: (Exemestane or Fulvestrant) Plus Palbociclib	Cohort 1 and 2: Capecitabine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	268	269		
Units: units on a scale				
arithmetic mean (confidence interval 95%)				
Systemic therapy side effects	5.61 (3.29 to 7.94)	4.49 (2.88 to 6.10)		
Breast symptoms	-0.42 (-2.31 to 1.46)	-2.0 (-3.46 to -0.53)		
Arm symptoms	-2.26 (-4.44 to -0.08)	-2.09 (-4.02 to -0.15)		
Upset by hair loss	8.35 (2.25 to 14.45)	-1.96 (-7.53 to 3.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline Between Treatment Comparison in EuroQoL 5D (EQ-5D) Health Index Scores

End point title	Change From Baseline Between Treatment Comparison in EuroQoL 5D (EQ-5D) Health Index Scores

End point description:

EQ 5D (version 3L) is a 6 item instrument which assess health status in terms of a single index value. It consists of 5 descriptors of current health state (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression); a patient is asked to rate each state on a 3 level scale (1=no problem, 2=some problem, and 3=extreme problem) with higher levels indicating greater severity/impairment. It also includes a visual analogue scale, EQ VAS, which records patient's self-rated health on a scale from 0 (worst imaginable) to 100 (best imaginable). Published weights are available that allow for the creation of a single summary score. Overall scores range from 0 to 1, with low scores representing a higher level of dysfunction and 1 as perfect health.
EQ 5D questionnaires were completed at baseline, at every two cycles for the first seven cycles, then at every three cycles until the end of treatment, and once again at the visit after treatment.

End point type	Secondary

End point timeframe:

Baseline, cycles 3, 5, 7, then at every three cycles until the end of treatment, and at the visit after treatment

End point values	Cohort 1 and 2: (Exemestane or Fulvestrant) Plus Palbociclib	Cohort 1 and 2: Capecitabine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	268	269		
Units: units on a scale				
arithmetic mean (confidence interval 95%)	0.72 (0.69 to 0.74)	0.71 (0.69 to 0.73)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline Between Treatment Comparison in EQ-5D Visual Analog Scale (VAS) Scores Scale

End point title	Change From Baseline Between Treatment Comparison in EQ-5D Visual Analog Scale (VAS) Scores Scale

End point description:

The EuroQol-5D (version 3L) is a brief self-administered, validated instrument consisting of 2 parts. The second part
consists of the EQ-5D general health status as measured by a visual analog scale (EQ-5D VAS). EQ-5D VAS measures
the participant's self-rated health status on a scale from 0 (worst imaginable health state) to 100 (best imaginable health
state).

End point type	Secondary

End point timeframe:

Baseline, cycles 3, 5, 7, then at every three cycles until the end of treatment, and at the visit after treatment

End point values	Cohort 1 and 2: (Exemestane or Fulvestrant) Plus Palbociclib	Cohort 1 and 2: Capecitabine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	268	269		
Units: units on a scale				
arithmetic mean (confidence interval 95%)	67.1 (65.3 to 69)	66.6 (64.9 to 68.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Deterioration (TTD) in EORTC QLQ-C30 Functional Scale

End point title	Time to Deterioration (TTD) in EORTC QLQ-C30 Functional Scale

End point description:

Time to deterioration is defined as the time from the date of randomization to the date of first detection of deterioration for each EORTC QLQ-C30 subscales, the global health status/QOL score, and for each QLQ-BR23 score [(date of first detection of deterioration – date of randomization + 1). Deterioration is defined as a change from baseline ≥ minimally important difference (MID) for EORTC QLQ-C30 symptom scores and QLQ-BR23 score and as a change from baseline ≤ -MID for EORTC QLQ-C30 functional scales, global health status/QOL score. Patients without deterioration have been censored at their last quality of life assessment. For patients with no post-baseline assessment time to deterioration have been censored at Day 1.

End point type	Secondary

End point timeframe:

Baseline, cycles 3, 5, 7, then at every three cycles until the end of treatment, and at the visit after treatment

End point values	Cohort 1 & 2: (Exemestane or Fulvestrant) + Palbo & Cape			
Subject group type	Subject analysis set			
Number of subjects analysed	537			
Units: Hazard ratio				
number (confidence interval 95%)				
Physical functioning	0.62 (0.5 to 0.7)			
Role functioning	0.63 (0.51 to 0.79)			
Emotional functioning	0.97 (0.76 to 1.25)			
Cognitive functioning	0.7 (0.54 to 0.89)			
Social functioning	0.62 (0.49 to 0.78)			
Global health status/quality of life	0.7 (0.55 to 0.89)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Deterioration (TTD) in EORTC QLQ-C30 Symptom Scale

End point title	Time to Deterioration (TTD) in EORTC QLQ-C30 Symptom Scale

End point description:

Time to deterioration is defined as the time from the date of randomization to the date of first detection of deterioration for each EORTC QLQ-C30 subscales, the global health status/QOL score, and for each QLQ-BR23 score [(date of first detection of deterioration – date of randomization + 1). Deterioration is defined as a change from baseline ≥ minimally important difference (MID) for EORTC QLQ-C30 symptom

scores and QLQ-BR23 score and as a change from baseline ≤ -MID for EORTC QLQ-C30 functional scales, global health status/QOL score. Patients without deterioration have been censored at their last quality of life assessment. For patients with no post-baseline assessment time to deterioration have been censored at Day 1.

End point type	Secondary

End point timeframe:

Baseline, cycles 3, 5, 7, then at every three cycles until the end of treatment, and at the visit after treatment

End point values	Cohort 1 & 2: (Exemestane or Fulvestrant) + Palbo & Cape			
Subject group type	Subject analysis set			
Number of subjects analysed	537			
Units: Hazard ratio				
number (confidence interval 95%)				
Fatigue	0.7 (0.57 to 0.86)			
Nausea and vomiting	0.58 (0.45 to 0.76)			
Pain	0.78 (0.62 to 0.99)			
Dyspnea	1.08 (0.81 to 1.44)			
Insomnia	0.84 (0.64 to 1.1)			
Appetite loss	0.71 (0.54 to 0.92)			
Constipation	1.08 (0.83 to 1.41)			
Diarrhea	0.42 (0.32 to 0.55)			
Financial difficulties	0.78 (0.56 to 1.07)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Deterioration (TTD) in EORTC QLQ-BR23 Functional Scale

End point title	Time to Deterioration (TTD) in EORTC QLQ-BR23 Functional Scale

End point description:

Time to deterioration is defined as the time from the date of randomization to the date of first detection of deterioration for each EORTC QLQ-C30 subscales, the global health status/QOL score, and for each QLQ-BR23 score [(date of first detection of deterioration – date of randomization + 1). Deterioration is defined as a change from baseline ≥ minimally important difference (MID) for EORTC QLQ-C30 symptom scores and QLQ-BR23 score and as a change from baseline ≤ -MID for EORTC QLQ-C30 functional scales, global health status/QOL score. Patients without deterioration have been censored at their last quality of life assessment. For patients with no post-baseline assessment time to deterioration have been censored at Day 1.

End point type	Secondary

End point timeframe:

Baseline, cycles 3, 5, 7, then at every three cycles until the end of treatment, and at the visit after treatment

End point values	Cohort 1 & 2: (Exemestane or Fulvestrant) + Palbo & Cape			
Subject group type	Subject analysis set			
Number of subjects analysed	537			
Units: Hazard ratio				
number (confidence interval 95%)				
Body image	0.95 (0.74 to 1.21)			
Sexual functioning	0.8 (0.54 to 1.18)			
Sexual enjoyment	1.53 (0.91 to 2.55)			
Future perspective	1.01 (0.74 to 1.39)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Deterioration (TTD) in EORTC QLQ-BR23 Symptom Scale

End point title	Time to Deterioration (TTD) in EORTC QLQ-BR23 Symptom Scale

End point description:

Time to deterioration is defined as the time from the date of randomization to the date of first detection of deterioration for each EORTC QLQ-C30 subscales, the global health status/QOL score, and for each QLQ-BR23 score [(date of first detection of deterioration – date of randomization + 1). Deterioration is defined as a change from baseline ≥ minimally important difference (MID) for EORTC QLQ-C30 symptom scores and QLQ-BR23 score and as a change from baseline ≤ -MID for EORTC QLQ-C30 functional scales, global health status/QOL score. Patients without deterioration have been censored at their last quality of life assessment. For patients with no post-baseline assessment time to deterioration have been censored at Day 1

End point type	Secondary

End point timeframe:

Baseline, cycles 3, 5, 7, then at every three cycles until the end of treatment, and at the visit after treatment

End point values	Cohort 1 & 2: (Exemestane or Fulvestrant) + Palbo & Cape			
Subject group type	Subject analysis set			
Number of subjects analysed	537			
Units: Hazard ratio				

number (confidence interval 95%)				
Upset by hair loss	1.33 (0.83 to 2.15)			
Systemic side-effects	0.79 (0.64 to 0.98)			
Breast symptoms	0.93 (0.71 to 1.21)			
Arm symptoms	0.84 (0.66 to 1.09)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Through study treatment, an average of 8 months

Adverse event reporting additional description:

AE were reported after Informed Consent Document (ICD) and before study drugs until approximately 30 days following the discontinuation of study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	NCI CTCAE
Dictionary version	4.0

Reporting groups

Reporting group title	Cohort 1: Palbociclib Plus Exemestane
Reporting group description: -	
Reporting group title	Cohort 2: Palbociclib Plus Fulvestrant
Reporting group description: -	
Reporting group title	Cohort 1 and 2: Capecitabine
Reporting group description: -	

Serious adverse events	Cohort 1: Palbociclib Plus Exemestane	Cohort 2: Palbociclib Plus Fulvestrant	Cohort 1 and 2: Capecitabine
Total subjects affected by serious adverse events			
subjects affected / exposed	40 / 150 (26.67%)	31 / 149 (20.81%)	104 / 289 (35.99%)
number of deaths (all causes)	85	43	116
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder cancer			
subjects affected / exposed	1 / 150 (0.67%)	0 / 149 (0.00%)	0 / 289 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic myeloid leukaemia			
subjects affected / exposed	0 / 150 (0.00%)	0 / 149 (0.00%)	1 / 289 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disease Progression			
subjects affected / exposed	5 / 150 (3.33%)	3 / 149 (2.01%)	3 / 289 (1.04%)
occurrences causally related to treatment / all	0 / 5	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 5	0 / 3	0 / 3

Malignant melanoma			
subjects affected / exposed	0 / 150 (0.00%)	0 / 149 (0.00%)	1 / 289 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal carcinoma			
subjects affected / exposed	0 / 150 (0.00%)	0 / 149 (0.00%)	1 / 289 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 150 (0.00%)	0 / 149 (0.00%)	2 / 289 (0.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Venous thrombosis			
subjects affected / exposed	0 / 150 (0.00%)	1 / 149 (0.67%)	1 / 289 (0.35%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	1 / 150 (0.67%)	0 / 149 (0.00%)	0 / 289 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 150 (0.67%)	0 / 149 (0.00%)	0 / 289 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	1 / 150 (0.67%)	1 / 149 (0.67%)	3 / 289 (1.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Embolism			
subjects affected / exposed	0 / 150 (0.00%)	0 / 149 (0.00%)	1 / 289 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Fatigue			
subjects affected / exposed	0 / 150 (0.00%)	0 / 149 (0.00%)	2 / 289 (0.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 150 (0.00%)	0 / 149 (0.00%)	1 / 289 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 150 (0.00%)	0 / 149 (0.00%)	1 / 289 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphoedema			
subjects affected / exposed	1 / 150 (0.67%)	0 / 149 (0.00%)	0 / 289 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaise			
subjects affected / exposed	0 / 150 (0.00%)	0 / 149 (0.00%)	1 / 289 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Mastitis			
subjects affected / exposed	0 / 150 (0.00%)	1 / 149 (0.67%)	0 / 289 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Salpingo-oophorectomy bilateral			
subjects affected / exposed	0 / 150 (0.00%)	0 / 149 (0.00%)	1 / 289 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			

subjects affected / exposed	0 / 150 (0.00%)	0 / 149 (0.00%)	1 / 289 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	1 / 150 (0.67%)	0 / 149 (0.00%)	0 / 289 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	3 / 150 (2.00%)	1 / 149 (0.67%)	6 / 289 (2.08%)
occurrences causally related to treatment / all	0 / 3	0 / 1	2 / 5
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 150 (0.00%)	0 / 149 (0.00%)	6 / 289 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Dyspnoea			
subjects affected / exposed	0 / 150 (0.00%)	1 / 149 (0.67%)	1 / 289 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	0 / 150 (0.00%)	0 / 149 (0.00%)	1 / 289 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	1 / 150 (0.67%)	1 / 149 (0.67%)	0 / 289 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 150 (0.00%)	1 / 149 (0.67%)	1 / 289 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			

subjects affected / exposed	1 / 150 (0.67%)	0 / 149 (0.00%)	0 / 289 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	1 / 150 (0.67%)	0 / 149 (0.00%)	0 / 289 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Hypokalaemia			
subjects affected / exposed	0 / 150 (0.00%)	0 / 149 (0.00%)	1 / 289 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelet count decreased			
subjects affected / exposed	0 / 150 (0.00%)	0 / 149 (0.00%)	1 / 289 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	1 / 150 (0.67%)	0 / 149 (0.00%)	0 / 289 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose			
subjects affected / exposed	0 / 150 (0.00%)	0 / 149 (0.00%)	1 / 289 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seroma			
subjects affected / exposed	0 / 150 (0.00%)	0 / 149 (0.00%)	1 / 289 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thermal burn			
subjects affected / exposed	0 / 150 (0.00%)	0 / 149 (0.00%)	1 / 289 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cardiac disorders			
Cardiac failure			
subjects affected / exposed	1 / 150 (0.67%)	1 / 149 (0.67%)	2 / 289 (0.69%)
occurrences causally related to treatment / all	0 / 1	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral ischaemia			
subjects affected / exposed	0 / 150 (0.00%)	0 / 149 (0.00%)	1 / 289 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	1 / 150 (0.67%)	0 / 149 (0.00%)	1 / 289 (0.35%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	0 / 150 (0.00%)	0 / 149 (0.00%)	1 / 289 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression			
subjects affected / exposed	0 / 150 (0.00%)	1 / 149 (0.67%)	2 / 289 (0.69%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subarachnoid haematoma			
subjects affected / exposed	1 / 150 (0.67%)	0 / 149 (0.00%)	0 / 289 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	1 / 150 (0.67%)	0 / 149 (0.00%)	0 / 289 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anemia			

subjects affected / exposed	1 / 150 (0.67%)	0 / 149 (0.00%)	1 / 289 (0.35%)
occurrences causally related to treatment / all	2 / 2	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	2 / 150 (1.33%)	0 / 149 (0.00%)	3 / 289 (1.04%)
occurrences causally related to treatment / all	2 / 2	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	0 / 150 (0.00%)	0 / 149 (0.00%)	1 / 289 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Uveitis			
subjects affected / exposed	1 / 150 (0.67%)	0 / 149 (0.00%)	0 / 289 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 150 (0.00%)	0 / 149 (0.00%)	1 / 289 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	0 / 150 (0.00%)	1 / 149 (0.67%)	0 / 289 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Colitis			
subjects affected / exposed	0 / 150 (0.00%)	0 / 149 (0.00%)	3 / 289 (1.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Diarrhoea			
subjects affected / exposed	1 / 150 (0.67%)	1 / 149 (0.67%)	17 / 289 (5.88%)
occurrences causally related to treatment / all	1 / 1	0 / 1	18 / 19
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1

Diverticulitis			
subjects affected / exposed	0 / 150 (0.00%)	0 / 149 (0.00%)	1 / 289 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 150 (0.00%)	1 / 149 (0.67%)	2 / 289 (0.69%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 150 (0.67%)	1 / 149 (0.67%)	4 / 289 (1.38%)
occurrences causally related to treatment / all	1 / 1	1 / 1	3 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enteritis			
subjects affected / exposed	0 / 150 (0.00%)	0 / 149 (0.00%)	1 / 289 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 150 (0.00%)	0 / 149 (0.00%)	2 / 289 (0.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 150 (0.00%)	1 / 149 (0.67%)	1 / 289 (0.35%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	0 / 150 (0.00%)	0 / 149 (0.00%)	1 / 289 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct stenosis			
subjects affected / exposed	0 / 150 (0.00%)	0 / 149 (0.00%)	1 / 289 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Biliary colic			

subjects affected / exposed	0 / 150 (0.00%)	0 / 149 (0.00%)	1 / 289 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	2 / 150 (1.33%)	0 / 149 (0.00%)	0 / 289 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 150 (0.00%)	1 / 149 (0.67%)	0 / 289 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydronephrosis			
subjects affected / exposed	0 / 150 (0.00%)	0 / 149 (0.00%)	1 / 289 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Cellulitis			
subjects affected / exposed	0 / 150 (0.00%)	0 / 149 (0.00%)	1 / 289 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	0 / 150 (0.00%)	0 / 149 (0.00%)	1 / 289 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 150 (0.00%)	0 / 149 (0.00%)	1 / 289 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 150 (0.00%)	1 / 149 (0.67%)	0 / 289 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0

Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 150 (0.67%)	0 / 149 (0.00%)	0 / 289 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone pain			
subjects affected / exposed	1 / 150 (0.67%)	0 / 149 (0.00%)	0 / 289 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 150 (0.00%)	0 / 149 (0.00%)	2 / 289 (0.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip arthroplasty			
subjects affected / exposed	1 / 150 (0.67%)	0 / 149 (0.00%)	1 / 289 (0.35%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 150 (0.00%)	0 / 149 (0.00%)	1 / 289 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	0 / 150 (0.00%)	0 / 149 (0.00%)	1 / 289 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint dislocation			
subjects affected / exposed	0 / 150 (0.00%)	1 / 149 (0.67%)	0 / 289 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar spinal stenosis			
subjects affected / exposed	0 / 150 (0.00%)	1 / 149 (0.67%)	0 / 289 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Lumbar vertebral fracture			
subjects affected / exposed	1 / 150 (0.67%)	0 / 149 (0.00%)	0 / 289 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteonecrosis of jaw			
subjects affected / exposed	0 / 150 (0.00%)	1 / 149 (0.67%)	0 / 289 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 150 (0.00%)	0 / 149 (0.00%)	1 / 289 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	0 / 150 (0.00%)	0 / 149 (0.00%)	1 / 289 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bacteraemia			
subjects affected / exposed	1 / 150 (0.67%)	0 / 149 (0.00%)	0 / 289 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	1 / 150 (0.67%)	0 / 149 (0.00%)	0 / 289 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 150 (0.67%)	2 / 149 (1.34%)	1 / 289 (0.35%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 150 (0.00%)	1 / 149 (0.67%)	0 / 289 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			

subjects affected / exposed	2 / 150 (1.33%)	1 / 149 (0.67%)	0 / 289 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Respiratory tract infection			
subjects affected / exposed	2 / 150 (1.33%)	2 / 149 (1.34%)	0 / 289 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tooth infection			
subjects affected / exposed	1 / 150 (0.67%)	0 / 149 (0.00%)	0 / 289 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Cohort 1: Palbociclib Plus Exemestane	Cohort 2: Palbociclib Plus Fulvestrant	Cohort 1 and 2: Capecitabine
Total subjects affected by non-serious adverse events			
subjects affected / exposed	149 / 150 (99.33%)	149 / 149 (100.00%)	283 / 289 (97.92%)
Vascular disorders			
Hypertension			
subjects affected / exposed	52 / 150 (34.67%)	58 / 149 (38.93%)	114 / 289 (39.45%)
occurrences (all)	123	145	299
Hot flashes			
subjects affected / exposed	15 / 150 (10.00%)	10 / 149 (6.71%)	2 / 289 (0.69%)
occurrences (all)	16	16	2
Thromboembolic event			
subjects affected / exposed	0 / 150 (0.00%)	0 / 149 (0.00%)	17 / 289 (5.88%)
occurrences (all)	0	0	19
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	84 / 150 (56.00%)	80 / 149 (53.69%)	170 / 289 (58.82%)
occurrences (all)	143	168	414
Hypothermia			
subjects affected / exposed	28 / 150 (18.67%)	22 / 149 (14.77%)	46 / 289 (15.92%)
occurrences (all)	47	72	86

Fever			
subjects affected / exposed	15 / 150 (10.00%)	12 / 149 (8.05%)	30 / 289 (10.38%)
occurrences (all)	22	16	37
Flu like symptoms			
subjects affected / exposed	15 / 150 (10.00%)	16 / 149 (10.74%)	22 / 289 (7.61%)
occurrences (all)	21	18	29
Pain			
subjects affected / exposed	15 / 150 (10.00%)	10 / 149 (6.71%)	18 / 289 (6.23%)
occurrences (all)	19	10	22
Edema limbs			
subjects affected / exposed	10 / 150 (6.67%)	9 / 149 (6.04%)	13 / 289 (4.50%)
occurrences (all)	12	11	14
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	21 / 150 (14.00%)	17 / 149 (11.41%)	26 / 289 (9.00%)
occurrences (all)	32	19	35
Dyspnea			
subjects affected / exposed	8 / 150 (5.33%)	16 / 149 (10.74%)	24 / 289 (8.30%)
occurrences (all)	9	17	34
Epistaxis			
subjects affected / exposed	9 / 150 (6.00%)	3 / 149 (2.01%)	12 / 289 (4.15%)
occurrences (all)	10	3	14
Psychiatric disorders			
Insomnia			
subjects affected / exposed	14 / 150 (9.33%)	8 / 149 (5.37%)	23 / 289 (7.96%)
occurrences (all)	16	8	25
Anxiety			
subjects affected / exposed	13 / 150 (8.67%)	8 / 149 (5.37%)	15 / 289 (5.19%)
occurrences (all)	18	10	20
Investigations			
Weight loss			
subjects affected / exposed	31 / 150 (20.67%)	38 / 149 (25.50%)	79 / 289 (27.34%)
occurrences (all)	52	65	145
Weight gain			
subjects affected / exposed	33 / 150 (22.00%)	28 / 149 (18.79%)	78 / 289 (26.99%)
occurrences (all)	70	61	161

White blood cell decreased			
subjects affected / exposed	146 / 150 (97.33%)	141 / 149 (94.63%)	129 / 289 (44.64%)
occurrences (all)	2001	1951	772
Neutrophil count decreased			
subjects affected / exposed	142 / 150 (94.67%)	140 / 149 (93.96%)	102 / 289 (35.29%)
occurrences (all)	1899	1878	692
Aspartate aminotransferase increased			
subjects affected / exposed	65 / 150 (43.33%)	84 / 149 (56.38%)	174 / 289 (60.21%)
occurrences (all)	210	281	820
Alkaline phosphatase increased			
subjects affected / exposed	45 / 150 (30.00%)	65 / 149 (43.62%)	185 / 289 (64.01%)
occurrences (all)	190	391	1359
Alanine aminotransferase increased			
subjects affected / exposed	54 / 150 (36.00%)	58 / 149 (38.93%)	140 / 289 (48.44%)
occurrences (all)	15	166	580
Platelet count decreased			
subjects affected / exposed	72 / 150 (48.00%)	80 / 149 (53.69%)	87 / 289 (30.10%)
occurrences (all)	427	466	415
Creatinine increased			
subjects affected / exposed	37 / 150 (24.67%)	42 / 149 (28.19%)	57 / 289 (19.72%)
occurrences (all)	162	245	345
Blood bilirubin increased			
subjects affected / exposed	10 / 150 (6.67%)	14 / 149 (9.40%)	84 / 289 (29.07%)
occurrences (all)	38	33	497
Nervous system disorders			
Headache			
subjects affected / exposed	25 / 150 (16.67%)	29 / 149 (19.46%)	39 / 289 (13.49%)
occurrences (all)	35	45	70
Dizziness			
subjects affected / exposed	12 / 150 (8.00%)	12 / 149 (8.05%)	42 / 289 (14.53%)
occurrences (all)	17	12	58
Dysgeusia			
subjects affected / exposed	9 / 150 (6.00%)	7 / 149 (4.70%)	29 / 289 (10.03%)
occurrences (all)	10	7	33
Blood and lymphatic system disorders			

Anemia			
subjects affected / exposed	112 / 150 (74.67%)	123 / 149 (82.55%)	178 / 289 (61.59%)
occurrences (all)	1149	1355	1289
Eye disorders			
Conjunctivitis			
subjects affected / exposed	17 / 150 (11.33%)	12 / 149 (8.05%)	59 / 289 (20.42%)
occurrences (all)	30	19	84
Watering eyes			
subjects affected / exposed	8 / 150 (5.33%)	5 / 149 (3.36%)	22 / 289 (7.61%)
occurrences (all)	11	7	30
Dry eye			
subjects affected / exposed	5 / 150 (3.33%)	4 / 149 (2.68%)	20 / 289 (6.92%)
occurrences (all)	8	6	22
Gastrointestinal disorders			
Diarrhea			
subjects affected / exposed	30 / 150 (20.00%)	31 / 149 (20.81%)	161 / 289 (55.71%)
occurrences (all)	58	62	416
Nausea			
subjects affected / exposed	35 / 150 (23.33%)	39 / 149 (26.17%)	112 / 289 (38.75%)
occurrences (all)	53	62	186
Mucositis oral			
subjects affected / exposed	39 / 150 (26.00%)	24 / 149 (16.11%)	85 / 289 (29.41%)
occurrences (all)	82	50	133
Vomiting			
subjects affected / exposed	27 / 150 (18.00%)	23 / 149 (15.44%)	85 / 289 (29.41%)
occurrences (all)	49	30	130
Constipation			
subjects affected / exposed	23 / 150 (15.33%)	17 / 149 (11.41%)	42 / 289 (14.53%)
occurrences (all)	27	19	56
Abdominal pain			
subjects affected / exposed	19 / 150 (12.67%)	6 / 149 (4.03%)	44 / 289 (15.22%)
occurrences (all)	22	8	74
Dyspepsia			
subjects affected / exposed	18 / 150 (12.00%)	11 / 149 (7.38%)	32 / 289 (11.07%)
occurrences (all)	21	18	38
Dry mouth			

subjects affected / exposed	8 / 150 (5.33%)	7 / 149 (4.70%)	23 / 289 (7.96%)
occurrences (all)	14	9	28
Gastrointestinal pain			
subjects affected / exposed	8 / 150 (5.33%)	7 / 149 (4.70%)	19 / 289 (6.57%)
occurrences (all)	12	8	28
Sore throat			
subjects affected / exposed	8 / 150 (5.33%)	4 / 149 (2.68%)	7 / 289 (2.42%)
occurrences (all)	10	5	7
Skin and subcutaneous tissue disorders			
Palmar-plantar erythrodysesthesia syndrome			
subjects affected / exposed	8 / 150 (5.33%)	2 / 149 (1.34%)	211 / 289 (73.01%)
occurrences (all)	13	2	939
Pruritus			
subjects affected / exposed	23 / 150 (15.33%)	12 / 149 (8.05%)	25 / 289 (8.65%)
occurrences (all)	31	25	30
Alopecia			
subjects affected / exposed	15 / 150 (10.00%)	21 / 149 (14.09%)	11 / 289 (3.81%)
occurrences (all)	16	29	11
Dry skin			
subjects affected / exposed	9 / 150 (6.00%)	8 / 149 (5.37%)	20 / 289 (6.92%)
occurrences (all)	11	8	25
Nail disorder			
subjects affected / exposed	4 / 150 (2.67%)	3 / 149 (2.01%)	24 / 289 (8.30%)
occurrences (all)	4	4	54
Rash and other skin disorders			
subjects affected / exposed	8 / 150 (5.33%)	5 / 149 (3.36%)	5 / 289 (1.73%)
occurrences (all)	13	8	8
Skin hyperpigmentation			
subjects affected / exposed	0 / 150 (0.00%)	0 / 149 (0.00%)	16 / 289 (5.54%)
occurrences (all)	0	0	21
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	25 / 150 (16.67%)	31 / 149 (20.81%)	51 / 289 (17.65%)
occurrences (all)	32	46	69
Arthralgia			

subjects affected / exposed	31 / 150 (20.67%)	22 / 149 (14.77%)	34 / 289 (11.76%)
occurrences (all)	49	30	44
Bone pain			
subjects affected / exposed	18 / 150 (12.00%)	13 / 149 (8.72%)	28 / 289 (9.69%)
occurrences (all)	27	14	37
Pain in extremity			
subjects affected / exposed	12 / 150 (8.00%)	15 / 149 (10.07%)	29 / 289 (10.03%)
occurrences (all)	22	17	38
Myalgia			
subjects affected / exposed	12 / 150 (8.00%)	7 / 149 (4.70%)	12 / 289 (4.15%)
occurrences (all)	15	10	13
Infections and infestations			
Upper respiratory infection			
subjects affected / exposed	28 / 150 (18.67%)	20 / 149 (13.42%)	41 / 289 (14.19%)
occurrences (all)	44	25	52
Chills			
subjects affected / exposed	10 / 150 (6.67%)	14 / 149 (9.40%)	17 / 289 (5.88%)
occurrences (all)	13	15	19
Urinary tract infection			
subjects affected / exposed	10 / 150 (6.67%)	7 / 149 (4.70%)	10 / 289 (3.46%)
occurrences (all)	11	8	13
Paronychia			
subjects affected / exposed	0 / 150 (0.00%)	0 / 149 (0.00%)	17 / 289 (5.88%)
occurrences (all)	0	0	39
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	23 / 150 (15.33%)	19 / 149 (12.75%)	68 / 289 (23.53%)
occurrences (all)	34	27	86
Obesity			
subjects affected / exposed	14 / 150 (9.33%)	16 / 149 (10.74%)	28 / 289 (9.69%)
occurrences (all)	24	22	43
Hyperglycemia			
subjects affected / exposed	71 / 150 (47.33%)	81 / 149 (54.36%)	158 / 289 (54.67%)
occurrences (all)	575	522	1092
Hyperkalemia			

subjects affected / exposed	29 / 150 (19.33%)	29 / 149 (19.46%)	55 / 289 (19.03%)
occurrences (all)	68	62	117
Hypercalcemia			
subjects affected / exposed	22 / 150 (14.67%)	27 / 149 (18.12%)	59 / 289 (20.42%)
occurrences (all)	38	86	229
Hypocalcemia			
subjects affected / exposed	20 / 150 (13.33%)	30 / 149 (20.13%)	52 / 289 (17.99%)
occurrences (all)	49	101	187
Hypomagnesemia			
subjects affected / exposed	25 / 150 (16.67%)	28 / 149 (18.79%)	43 / 289 (14.88%)
occurrences (all)	88	160	181
Hyponatremia			
subjects affected / exposed	15 / 150 (10.00%)	26 / 149 (17.45%)	49 / 289 (16.96%)
occurrences (all)	19	125	95
Hypokalemia			
subjects affected / exposed	17 / 150 (11.33%)	14 / 149 (9.40%)	49 / 289 (16.96%)
occurrences (all)	57	20	176
Hypoalbuminemia			
subjects affected / exposed	8 / 150 (5.33%)	29 / 149 (19.46%)	40 / 289 (13.84%)
occurrences (all)	13	97	146
Hypernatremia			
subjects affected / exposed	20 / 150 (13.33%)	14 / 149 (9.40%)	34 / 289 (11.76%)
occurrences (all)	39	34	92
Hypermagnesemia			
subjects affected / exposed	7 / 150 (4.67%)	14 / 149 (9.40%)	33 / 289 (11.42%)
occurrences (all)	28	20	85
Hypoglycemia			
subjects affected / exposed	11 / 150 (7.33%)	10 / 149 (6.71%)	20 / 289 (6.92%)
occurrences (all)	29	14	50

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 December 2013	Update on the number of plasma samples needed for exploratory analyses
19 February 2014	Modify the eligibility criteria. New instructions about palbociclib administration and change information about the prohibited concomitant medication
02 March 2014	Clarify the eligiblity criteria and the stratification factors.
09 March 2016	The design of the study is modified to include a new Cohort in order to provide the opportunity to confirm the clinical benefit of PAL in combination with ET in relation to ESR1 mutational status. The study objectives, the eligibility criteria and the sample size were changed according to the new study design.
12 July 2017	Modify the eligibility criteria. Add the collection of the new biological samples. Clarify the dose modification of capecitabine in case of non-haematologic toxicities. Update the list of "List of Drugs Known to Predispose to Torsade de Pointes".
24 August 2018	Clarify palbociclib and capecitabine dose modifications. Modify the mandatory assessments. Modify the eligibility criteria.
05 November 2019	Include the guidance for the clinical management of Interstitial Lung Disease (ILD)/ pneumonitis according to palbociclib IB v Jun2019

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

1. capecitabine outcome was better than initially anticipated
2. open-label study design may lead to biased interpretations
3. subtype classification for exploratory objective was carried out in 70% of patients in the primary tumour

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/33385521

http://www.ncbi.nlm.nih.gov/pubmed/34425406