

**Clinical trial results:**

A phase II randomised study evaluating the biological and clinical effects of the combination of palbociclib with letrozole as neoadjuvant therapy in post-menopausal women with ER+ primary breast cancer

Summary

EudraCT number	2014-000887-16
Trial protocol	GB
Global end of trial date	03 March 2020

Results information

Result version number	v1 (current)
This version publication date	03 March 2021
First version publication date	03 March 2021

Trial information**Trial identification**

Sponsor protocol code	ICR-CTSU/2014/10044
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Additional study identifiers

ISRCTN number	ISRCTN31243262
ClinicalTrials.gov id (NCT number)	NCT01889680
WHO universal trial number (UTN)	-
Other trial identifiers	sponsor Identification Number: CCR4133, CRUK reference number: CRUK/13/031

Notes:

Sponsors

Sponsor organisation name	Institute of Cancer Research
Sponsor organisation address	123 Old Brompton Road, Lo, United Kingdom, SW7 3RP
Public contact	Michelle Frost, The Institute of Cancer Research, 44 2034376605, pallet-icrctsu@icr.ac.uk
Scientific contact	Michelle Frost, The Institute of Cancer Research, 44 2034376605, pallet-icrctsu@icr.ac.uk
Sponsor organisation name	Royal Marsden NHS Foundation Trust
Sponsor organisation address	Fulham Road, London, United Kingdom, SW3 6JJ
Public contact	Michelle Frost, Institute of Cancer Research, 44 2034376605, pallet-icrctsu@icr.ac.uk
Scientific contact	Michelle Frost, Institute of Cancer Research, 44 2034376605, pallet-icrctsu@icr.ac.uk

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	03 March 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 March 2020
Global end of trial reached?	Yes
Global end of trial date	03 March 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

PALLET has co-primary objectives:

- 1) To compare the changes in the proliferation (cell division) marker Ki67 after 14 weeks treatment with letrozole with or without palbociclib.
- 2) To compare clinical response (i.e. whether the tumour has responded to treatment) after 14 weeks treatment with letrozole with or without palbociclib.

Protection of trial subjects:

Patients were provided with full verbal and written informed consent that included the purpose of the trial, the procedures and treatments involved along with potential risks and side effects. A patient information and consent form were provided and patients were given sufficient time to consider participation.

Full details of the trial treatments and their safety profile were provided in the patient information sheet. Patients had the opportunity to discuss any concerns they had in relation to trial treatment prior to consent and throughout their involvement in the trial.

The collection of core needle biopsies were a mandatory aspect of trial participation and used for the assessment of the co-primary endpoint. The reason for sample collection were clearly described in the patient information sheet as were the potential risks associated with biopsy collection. Every effort was made to minimise discomfort during the biopsy procedure.

Background therapy:

Letrozole: the rationale for the PALLET trial was to assess the effectiveness of the addition of palbociclib, a CDK4/6 inhibitor, when added to letrozole for the neoadjuvant treatment of patients with ER+/HER2-early invasive breast cancer

Evidence for comparator:

Palbociclib is an orally active potent and highly selective reversible inhibitor of CDK4 and CDK6. Preclinical evidence that palbociclib is highly active in ER+ cell lines and encouraging early safety and PK results led to a randomised phase II study evaluating the efficacy and safety of letrozole in combination with palbociclib when compared with letrozole alone in the first-line treatment of postmenopausal patients with ER+/HER2- advanced breast cancer (NCT00721409). A phase II dose of 125mg QD on a schedule of 21/7 (i.e. 21 days continuous treatment followed by 7 days off treatment) was used in combination with letrozole 2.5mg QD continuously. Later patients in the study were prospectively selected taking into account tumour CCND1 amplification and/or p16 loss. 165 patients were enrolled and the study demonstrated an improved clinical benefit rate (CR+PR+SD) of 59% v 36% and a prolongation of PFS from 7.5 to 26.1 months (HR 0.37 95%CI: 0.21, 0.63 P<0.001). The randomised phase II PALOMA-1 trial (palbociclib in combination with letrozole vs. letrozole alone as first-line treatment of ER+/HER2- advanced breast cancer) reported a median PFS of 10.2 months (95% CI 5.7–12.6) for the letrozole group compared to 20.2 months (13.8–27.5) for the palbociclib + letrozole group (HR 0.488, 95% CI 0.319–0.748; one-sided p=0.0004). A recent phase III trial of 521 patients with advanced HR+/HER2-breast cancer that had relapsed or progressed during prior endocrine therapy assessed the efficacy of palbociclib in combination with fulvestrant (NCT01942135, PALOMA-3). The trial reported median PFS of 9.2 months (95% CI, 7.5 to not estimable) with palbociclib-fulvestrant and 3.8 months (95% CI, 3.5 to 5.5) with placebo-fulvestrant (HR for disease progression or death, 0.42; 95% CI, 0.32 to 0.56; P<0.001).

Actual start date of recruitment	01 November 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	United States: 141
Country: Number of subjects enrolled	United Kingdom: 166
Worldwide total number of subjects	307
EEA total number of subjects	0

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)	155
From 65 to 84 years	147
85 years and over	5

Subject disposition

Recruitment

Recruitment details:

A total of 306 patients were recruited between 27 February 2015 and 8 March 2018. 166 patients were randomised in the UK and 141 patients were randomised in North America.

Pre-assignment

Screening details:

Potentially eligible patients screened for PALLET included all postmenopausal women with ER+/HER2-invasive early breast cancer who were suitable for neoadjuvant endocrine therapy. The most common reasons for non-entry to PALLET were tumour size <2cm, patient pre or perimenopausal, patient declined trial or chose surgery over neoadjuvant therapy.

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	Group A: letrozole alone

Arm description:

Group A: letrozole from baseline to week 14

Arm type	Active comparator
Investigational medicinal product name	Letrozole
Investigational medicinal product code	L02BG04
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

2.5mg/day

Arm title	Group B: letrozole for 2 weeks then letrozole + palbociclib
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Arm description:

Group B: letrozole from baseline to week 2 followed by letrozole plus palbociclib to week 14

Arm type	Experimental
Investigational medicinal product name	Letrozole
Investigational medicinal product code	L02BG04
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

2.5mg/day

Investigational medicinal product name	Palbociclib
Investigational medicinal product code	PD-0332991
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

125mg daily on a schedule of 3 weeks on, 1 week off (3/1)

Arm title	Group C: palbociclib for 2 weeks then palbociclib + letrozole
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Arm description:

Group C: palbociclib from baseline to week 2 followed by palbociclib plus letrozole to week 14

Arm type	Experimental
Investigational medicinal product name	Letrozole
Investigational medicinal product code	L02BG04
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

2.5mg/day

Investigational medicinal product name	Palbociclib
Investigational medicinal product code	PD-0332991
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

125mg/day

Arm title	Group D: letrozole plus palbociclib
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Arm description:

Group D: letrozole plus palbociclib from baseline to week 14

Arm type	Experimental
Investigational medicinal product name	Palbociclib
Investigational medicinal product code	PD-0332991
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

125mg/day

Investigational medicinal product name	Letrozole
Investigational medicinal product code	L02BG04
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

2.5mg/day

Number of subjects in period 1	Group A: letrozole alone	Group B: letrozole for 2 weeks then letrozole + palbociclib	Group C: palbociclib for 2 weeks then palbociclib + letrozole
Started	103	68	69
Completed	88	55	57
Not completed	15	13	12
Consent withdrawn by subject	3	1	2
Disease progression	2	-	1
Adverse event, non-fatal	-	2	2
Surgery delayed	2	-	-

Death	-	2	1
Lost to follow-up	5	5	5
Missing data	3	3	1

Number of subjects in period 1	Group D: letrozole plus palbociclib
Started	67
Completed	62
Not completed	5
Consent withdrawn by subject	3
Disease progression	-
Adverse event, non-fatal	-
Surgery delayed	-
Death	-
Lost to follow-up	2
Missing data	-

Baseline characteristics

Reporting groups

Reporting group title	Group A: letrozole alone
Reporting group description: Group A: letrozole from baseline to week 14	
Reporting group title	Group B: letrozole for 2 weeks then letrozole + palbociclib
Reporting group description: Group B: letrozole from baseline to week 2 followed by letrozole plus palbociclib to week 14	
Reporting group title	Group C: palbociclib for 2 weeks then palbociclib + letrozole
Reporting group description: Group C: palbociclib from baseline to week 2 followed by palbociclib plus letrozole to week 14	
Reporting group title	Group D: letrozole plus palbociclib
Reporting group description: Group D: letrozole plus palbociclib from baseline to week 14	

Reporting group values	Group A: letrozole alone	Group B: letrozole for 2 weeks then letrozole + palbociclib	Group C: palbociclib for 2 weeks then palbociclib + letrozole
Number of subjects	103	68	69
Age categorical Units: Subjects			
40-49 years	0	0	1
50-59 years	32	15	19
60-69 years	34	31	29
70-79 years	30	14	17
80 or more years	7	8	3
Age continuous Units: years			
median	65.8	66.3	63.5
inter-quartile range (Q1-Q3)	59.4 to 72.0	60.4 to 72.5	59.3 to 70.5
Gender categorical Units: Subjects			
Female	103	68	69
Male	0	0	0
Tumour grade Units: Subjects			
Low	13	6	4
Intermediate	70	54	52
High	19	7	13
Not known	1	1	0
Histological type Units: Subjects			
Ductal	74	49	46
Lobular	24	14	19
Mixed ductal and lobular	4	1	4
Mucinous	1	4	0
PgR status Units: Subjects			

Positive	74	47	41
Negative	15	10	15
Not done	14	11	13
Surgical intent at baseline			
Type of breast surgery planned at baseline			
Units: Subjects			
Partial mastectomy/lumpectomy	61	45	40
Total or modified radical mastectomy	39	20	25
Missing data	3	3	4

Reporting group values	Group D: letrozole plus palbociclib	Total	
Number of subjects	67	307	
Age categorical			
Units: Subjects			
40-49 years	0	1	
50-59 years	22	88	
60-69 years	30	124	
70-79 years	12	73	
80 or more years	3	21	
Age continuous			
Units: years			
median	63.8		
inter-quartile range (Q1-Q3)	58.5 to 69.1	-	
Gender categorical			
Units: Subjects			
Female	67	307	
Male	0	0	
Tumour grade			
Units: Subjects			
Low	9	32	
Intermediate	51	227	
High	7	46	
Not known	0	2	
Histological type			
Units: Subjects			
Ductal	45	214	
Lobular	18	75	
Mixed ductal and lobular	2	11	
Mucinous	2	7	
PgR status			
Units: Subjects			
Positive	53	215	
Negative	7	47	
Not done	7	45	
Surgical intent at baseline			
Type of breast surgery planned at baseline			
Units: Subjects			
Partial mastectomy/lumpectomy	39	185	
Total or modified radical mastectomy	24	108	

Missing data	4	14	
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Subject analysis sets

Subject analysis set title	Groups B, C and D combined: letrozole with palbociclib
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients treated with letrozole with palbociclib, i.e. in groups B+C+D (Arms 2,3,4) were pooled and compared to those treated with letrozole alone (Group 1/Arm 1)

Reporting group values	Groups B, C and D combined: letrozole with palbociclib		
Number of subjects	204		
Age categorical			
Units: Subjects			
40-49 years	1		
50-59 years	56		
60-69 years	90		
70-79 years	43		
80 or more years	14		
Age continuous			
Units: years			
median			
inter-quartile range (Q1-Q3)			
Gender categorical			
Units: Subjects			
Female			
Male			
Tumour grade			
Units: Subjects			
Low			
Intermediate			
High			
Not known			
Histological type			
Units: Subjects			
Ductal			
Lobular			
Mixed ductal and lobular			
Mucinous			
PgR status			
Units: Subjects			
Positive			
Negative			
Not done			
Surgical intent at baseline			
Type of breast surgery planned at baseline			
Units: Subjects			
Partial mastectomy/lumpectomy			

Total or modified radical mastectomy			
Missing data			

End points

End points reporting groups

Reporting group title	Group A: letrozole alone
Reporting group description:	
Group A: letrozole from baseline to week 14	
Reporting group title	Group B: letrozole for 2 weeks then letrozole + palbociclib
Reporting group description:	
Group B: letrozole from baseline to week 2 followed by letrozole plus palbociclib to week 14	
Reporting group title	Group C: palbociclib for 2 weeks then palbociclib + letrozole
Reporting group description:	
Group C: palbociclib from baseline to week 2 followed by palbociclib plus letrozole to week 14	
Reporting group title	Group D: letrozole plus palbociclib
Reporting group description:	
Group D: letrozole plus palbociclib from baseline to week 14	
Subject analysis set title	Groups B, C and D combined: letrozole with palbociclib
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients treated with letrozole with palbociclib, i.e. in groups B+C+D (Arms 2,3,4) were pooled and compared to those treated with letrozole alone (Group 1/Arm 1)	

Primary: Clinical response as measured by ultrasound according to ECOG criteria after 14 weeks treatment with letrozole with or without palbociclib

End point title	Clinical response as measured by ultrasound according to ECOG criteria after 14 weeks treatment with letrozole with or without palbociclib
End point description:	
End point type	Primary
End point timeframe:	
Assessed after 14 weeks of treatment with letrozole with or without palbociclib	

End point values	Group A: letrozole alone	Group B: letrozole for 2 weeks then letrozole + palbociclib	Group C: palbociclib for 2 weeks then palbociclib + letrozole	Group D: letrozole plus palbociclib
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	93	63	61	62
Units: Number				
Complete response	2	1	2	1
Partial response	44	30	33	34
Stable disease	42	30	25	23
Progressive disease	5	2	1	4

End point values	Groups B, C and D combined:			
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	letrozole with palbociclib			
Subject group type	Subject analysis set			
Number of subjects analysed	186			
Units: Number				
Complete response	4			
Partial response	97			
Stable disease	78			
Progressive disease	7			

Statistical analyses

Statistical analysis title	Comparison of clinical response
Statistical analysis description: A Mann-Whitney test was used to determined if there was evidence of a difference in clinical response between Group A (letrozole alone) and Groups B+C+D (letrozole with palbociclib)	
Comparison groups	Group A: letrozole alone v Groups B, C and D combined: letrozole with palbociclib
Number of subjects included in analysis	279
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.21
Method	Wilcoxon (Mann-Whitney)

Primary: Change in Ki67 (% positive tumour cells) from baseline to after 14 weeks treatment with letrozole with or without palbociclib

End point title	Change in Ki67 (% positive tumour cells) from baseline to after 14 weeks treatment with letrozole with or without palbociclib
End point description: Change in the proliferation marker Ki67 (% positive tumour cells) as tested by IHC from baseline to after 14 weeks treatment with letrozole with or without palbociclib . Paired Ki67 data from baseline and end of treatment at 14 weeks were available for 190 (61.9%) patients. Where pathological complete response was indicated due to no invasive tumour cells present in the surgical specimen and where Ki67 data at week 14 was missing, a value of 0 was imputed.	
End point type	Primary
End point timeframe: Change from baseline to 14 weeks of treatment	

End point values	Group A: letrozole alone	Group B: letrozole for 2 weeks then letrozole + palbociclib	Group C: palbociclib for 2 weeks then palbociclib + letrozole	Group D: letrozole plus palbociclib
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	65	40	47	38
Units: Log-fold change in Ki67				
median (inter-quartile range (Q1-Q3))	-2.2 (-3.4 to -1.0)	-4.1 (-5.1 to -2.7)	-4.0 (-5.1 to -3.0)	-3.9 (-5.0 to -2.9)

End point values	Groups B, C and D combined: letrozole with palbociclib			
Subject group type	Subject analysis set			
Number of subjects analysed	125			
Units: Log-fold change in Ki67				
median (inter-quartile range (Q1-Q3))	-4.1 (-5.0 to -2.8)			

Statistical analyses

Statistical analysis title	Comparison of log-fold change in Ki67
Statistical analysis description:	
Comparison of log-fold change in Ki67 between Group A and Groups B + C + D	
Comparison groups	Group A: letrozole alone v Groups B, C and D combined: letrozole with palbociclib
Number of subjects included in analysis	190
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Wilcoxon (Mann-Whitney)

Secondary: Effect of of randomised treatment on Ki67 after 2 weeks

End point title	Effect of of randomised treatment on Ki67 after 2 weeks
End point description:	
Effect of of randomised treatment on Ki67 after 2 weeks	
End point type	Secondary
End point timeframe:	
From baseline to 2 weeks	

End point values	Group A: letrozole alone	Group B: letrozole for 2 weeks then letrozole + palbociclib	Group C: palbociclib for 2 weeks then palbociclib + letrozole	Group D: letrozole plus palbociclib
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	61	39	44	32
Units: Log fold change in Ki67				
median (inter-quartile range (Q1-Q3))				
From baseline to week 2	-1.3 (-2.9 to -0.6)	-1.3 (-2.5 to -0.8)	-3.1 (-4.1 to -1.5)	-3.9 (-4.7 to -2.7)

End point values	Groups B, C and D combined: letrozole with palbociclib			
Subject group type	Subject analysis set			
Number of subjects analysed	115			
Units: Log fold change in Ki67				
median (inter-quartile range (Q1-Q3))				
From baseline to week 2	-2.8 (-4.1 to -1.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Added effect of additional randomised treatment from weeks 2-14

End point title	Added effect of additional randomised treatment from weeks 2-14
End point description:	
Added effect of additional randomised treatment from weeks 2-14	
End point type	Secondary
End point timeframe:	
From week 2 to week 14	

End point values	Group A: letrozole alone	Group B: letrozole for 2 weeks then letrozole + palbociclib	Group C: palbociclib for 2 weeks then palbociclib + letrozole	Group D: letrozole plus palbociclib
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	61	39	44	32
Units: Log-fold change in Ki67				
median (inter-quartile range (Q1-Q3))				
From week 2 to week 14	-0.1 (-1.1 to 0.4)	-2.1 (-3.5 to -1.3)	-0.4 (-2.1 to 0.0)	0.0 (-0.1 to 0.9)

End point values	Groups B, C and D combined: letrozole with palbociclib			
Subject group type	Subject analysis set			
Number of subjects analysed	115			

Units: Log-fold change in Ki67				
median (inter-quartile range (Q1-Q3))				
From week 2 to week 14	-1.0 (-2.2 to 0.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pathologic complete response rates after letrozole with or without 14 weeks palbociclib

End point title	Pathologic complete response rates after letrozole with or without 14 weeks palbociclib ^[1]
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End point description:

Pathologic complete response in the breast (pCR breast) is defined as no histologic evidence of invasive tumour cells in the surgical breast specimen. Pathologic complete response in breast and axillary lymph nodes as well as non-axillary sentinel node (pCR breast & nodes) is defined as no histologic evidence of invasive tumour cells in the surgical breast specimen, axillary nodes or sentinel nodes identified after neoadjuvant treatment.

End point type	Secondary
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End point timeframe:

14 weeks from baseline

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: This endpoint assessed the effect of addition of palbociclib on change at 14 weeks so arms B, C, D were combined for this end-point analysis as all patients in these arms were on palbociclib at week 14.

End point values	Group A: letrozole alone	Groups B, C and D combined: letrozole with palbociclib		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	91	187		
Units: Number				
pCR breast	1	7		
pCR breast & nodes	0	2		

Statistical analyses

Statistical analysis title	Comparison of pathologic complete response
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Statistical analysis description:

Fisher's exact test to compare rates of pathologic complete response between letrozole alone group (Group A) and letrozole plus palbociclib groups (Groups B+C+D)

Comparison groups	Group A: letrozole alone v Groups B, C and D combined: letrozole with palbociclib
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Number of subjects included in analysis	278
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.28 ^[2]
Method	Fisher exact

Notes:

[2] - pCR breast comparison: p=0.28

pCR breast & nodes comparison: p=1.00

Secondary: PEPI score after letrozole with or without 14 weeks palbociclib

End point title	PEPI score after letrozole with or without 14 weeks
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End point description:

A preoperative endocrine prognostic index (PEPI) for relapse-free survival (PFS) and breast cancer-specific survival (BCSS) was modelled using surgical staging parameters after neoadjuvant treatment (histological grade, pathological tumour size, node status, treatment response), estrogen receptor status, and levels of the proliferation marker Ki67 as described by Ellis MJ et al, J Natl Cancer Inst 2008;100:1380-1388. PEPI risk scores were calculated for RFS and BCSS.

End point type	Secondary
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End point timeframe:

14 weeks from baseline

Notes:

[3] - 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: This endpoint assessed the effect of addition of palbociclib on change at 14 weeks so arms B, C, D were combined for this end-point analysis as all patients in these arms were on palbociclib at week 14.

End point values	Group A: letrozole alone	Groups B, C and D combined: letrozole with palbociclib		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	65	129		
Units: Risk score				
arithmetic mean (standard deviation)				
PEPI Risk score for relapse-free survival	3.7 (± 2.3)	3.6 (± 2.3)		
PEPI risk score - breast cancer specific survival	3.9 (± 2.5)	3.6 (± 2.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes between surgical intent at baseline and surgical intent at 14 weeks

End point title	Changes between surgical intent at baseline and surgical intent at 14 weeks ^[4]
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End point description:

Changes between surgical intent at baseline and surgical intent after 14 weeks after treatment with letrozole with or without palbociclib.

End point type	Secondary
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End point timeframe:

At end of treatment at 14 weeks from baseline

Notes:

[4] - 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: This endpoint assessed the effect of addition of palbociclib on change at 14 weeks so arms B, C, D were combined for this end-point analysis as all patients in these arms were on palbociclib at week 14.

End point values	Group A: letrozole alone	Groups B, C and D combined: letrozole with palbociclib		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	93	177		
Units: Percentage				
Change to breast conservation	14	25		
Breast conservation intended after treatment	62	118		

Statistical analyses

Statistical analysis title	Change in surgical intent at end of treatment
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Statistical analysis description:

Comparison of change in surgical intent from baseline to end of treatment.

Comparison groups	Group A: letrozole alone v Groups B, C and D combined: letrozole with palbociclib
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.86 ^[5]
Method	Wilcoxon (Mann-Whitney)

Notes:

[5] - Change to breast conservation comparison: p=0.86

Breast conservation intended at end of treatment comparison: p=1.00

Secondary: Changes between surgical intent at baseline and actual surgery received

End point title	Changes between surgical intent at baseline and actual surgery received ^[6]
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End point description:

Changes between surgical intent at baseline and actual surgery received after treatment with letrozole with or without palbociclib.

End point type	Secondary
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End point timeframe:

At surgery

Notes:

[6] - 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: This endpoint assessed the effect of addition of palbociclib on change at 14 weeks so arms B, C, D were combined for this end-point analysis as all patients in these arms were on palbociclib at week 14.

End point values	Group A: letrozole alone	Groups B, C and D combined: letrozole with palbociclib		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	90	178		
Units: Percentage				
Change to breast conservation	16	25		
Breast conservation intended at end of treatment	63	123		

Statistical analyses

Statistical analysis title	Change in surgical intent and surgery received
Statistical analysis description:	
Comparison of change from surgical intent to surgery received by treatment group	
Comparison groups	Group A: letrozole alone v Groups B, C and D combined: letrozole with palbociclib
Number of subjects included in analysis	268
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.47 ^[7]
Method	Wilcoxon (Mann-Whitney)

Notes:

[7] - Change to breast conservation comparison: p=0.47

Breast conservation intended at end of treatment comparison: p=1.00

Secondary: Assessment of safety and tolerability

End point title	Assessment of safety and tolerability ^[8]
End point description:	
Summary of worst grade event reported per patient	
End point type	Secondary
End point timeframe:	
From day 1 to 30 days after the last dose of trial treatment	

Notes:

[8] - 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: This endpoint assessed the effect of addition of palbociclib on change at 14 weeks so arms B, C, D were combined for this end-point analysis as all patients in these arms were on palbociclib at week 14.

End point values	Group A: letrozole alone	Groups B, C and D combined: letrozole with palbociclib		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	100	201		
Units: Number				
Any grade	91	199		
Grade 3 or more	17	100		

Statistical analyses

Statistical analysis title	Comparison of worst adverse event grade reported
Statistical analysis description: A Mann-Whitney test was used to determine if there was a difference in worst AE grade between Group A (letrozole only) and Groups B+C+D (letrozole plus palbociclib). Mann Whitney two-sided.	
Comparison groups	Group A: letrozole alone v Groups B, C and D combined: letrozole with palbociclib
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Wilcoxon (Mann-Whitney)

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From day 1 of trial treatment to 30 days after the last administration of trial treatment

Adverse event reporting additional description:

Any toxicity, sign or symptom that occurred after commencement of study treatment and within 30 days of the last administration of study treatment, which was not unequivocally due to progression of disease.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	11.9

Reporting groups

Reporting group title	Group A: letrozole alone
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Reporting group description:

Group A: letrozole from baseline to week 14

Reporting group title	Group B: letrozole for 2 weeks then letrozole + palbociclib
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Reporting group description:

Group B: letrozole from baseline to week 2 followed by letrozole plus palbociclib to week 14

Reporting group title	Group C: palbociclib for 2 weeks then palbociclib + letrozole
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Reporting group description:

Group C: palbociclib from baseline to week 2 followed by palbociclib plus letrozole to week 14

Reporting group title	Group D: letrozole plus palbociclib
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Reporting group description:

Group D: letrozole plus palbociclib from baseline to week 14

Serious adverse events	Group A: letrozole alone	Group B: letrozole for 2 weeks then letrozole + palbociclib	Group C: palbociclib for 2 weeks then palbociclib + letrozole
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 100 (2.00%)	3 / 66 (4.55%)	4 / 69 (5.80%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 100 (0.00%)	0 / 66 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			

subjects affected / exposed	0 / 100 (0.00%)	0 / 66 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 100 (0.00%)	0 / 66 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 100 (0.00%)	0 / 66 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Head injury	Additional description: Minor head injury following a fall		
subjects affected / exposed	0 / 100 (0.00%)	0 / 66 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 100 (0.00%)	0 / 66 (0.00%)	1 / 69 (1.45%)
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			
Hypotension			
subjects affected / exposed	0 / 100 (0.00%)	1 / 66 (1.52%)	0 / 69 (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
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	0 / 100 (0.00%)	0 / 66 (0.00%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea			

subjects affected / exposed	0 / 100 (0.00%)	1 / 66 (1.52%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis	Additional description: Enterocolitis with C-difficile infection		
subjects affected / exposed	0 / 100 (0.00%)	1 / 66 (1.52%)	0 / 69 (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
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 100 (0.00%)	1 / 66 (1.52%)	0 / 69 (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			
Pain in extremity			
subjects affected / exposed	1 / 100 (1.00%)	0 / 66 (0.00%)	0 / 69 (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
Infections and infestations			
Neutropenic sepsis			
subjects affected / exposed	0 / 100 (0.00%)	0 / 66 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Periorbital cellulitis			
subjects affected / exposed	0 / 100 (0.00%)	1 / 66 (1.52%)	0 / 69 (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
Pneumonia			
subjects affected / exposed	0 / 100 (0.00%)	1 / 66 (1.52%)	0 / 69 (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
Skin infection			

subjects affected / exposed	1 / 100 (1.00%)	0 / 66 (0.00%)	0 / 69 (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	0 / 100 (0.00%)	0 / 66 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 100 (0.00%)	1 / 66 (1.52%)	0 / 69 (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
Hyperglycaemia			
subjects affected / exposed	1 / 100 (1.00%)	0 / 66 (0.00%)	0 / 69 (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
Hyponatraemia			
subjects affected / exposed	0 / 100 (0.00%)	0 / 66 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Group D: letrozole plus palbociclib		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 66 (1.52%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 66 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Aspartate aminotransferase increased			

subjects affected / exposed	0 / 66 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 66 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 66 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Head injury	Additional description: Minor head injury following a fall		
subjects affected / exposed	0 / 66 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hip fracture			
subjects affected / exposed	0 / 66 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 66 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			

subjects affected / exposed	0 / 66 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Enterocolitis	Additional description: Enterocolitis with C-difficile infection		
subjects affected / exposed	0 / 66 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 66 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	0 / 66 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Neutropenic sepsis			
subjects affected / exposed	0 / 66 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Periorbital cellulitis			
subjects affected / exposed	0 / 66 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	0 / 66 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin infection			

subjects affected / exposed	0 / 66 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	0 / 66 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 66 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyperglycaemia			
subjects affected / exposed	0 / 66 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	0 / 66 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Group A: letrozole alone	Group B: letrozole for 2 weeks then letrozole + palbociclib	Group C: palbociclib for 2 weeks then palbociclib + letrozole
Total subjects affected by non-serious adverse events			
subjects affected / exposed	91 / 100 (91.00%)	65 / 66 (98.48%)	69 / 69 (100.00%)
Vascular disorders			
Hot flush			
subjects affected / exposed	40 / 100 (40.00%)	19 / 66 (28.79%)	13 / 69 (18.84%)
occurrences (all)	51	26	17
Hypertension			
subjects affected / exposed	11 / 100 (11.00%)	5 / 66 (7.58%)	3 / 69 (4.35%)
occurrences (all)	12	13	3
General disorders and administration			

site conditions			
Chills			
subjects affected / exposed	2 / 100 (2.00%)	2 / 66 (3.03%)	1 / 69 (1.45%)
occurrences (all)	2	2	1
Fatigue			
subjects affected / exposed	41 / 100 (41.00%)	37 / 66 (56.06%)	42 / 69 (60.87%)
occurrences (all)	46	43	53
Mucosal inflammation			
subjects affected / exposed	0 / 100 (0.00%)	3 / 66 (4.55%)	0 / 69 (0.00%)
occurrences (all)	0	4	0
Pain			
subjects affected / exposed	3 / 100 (3.00%)	0 / 66 (0.00%)	4 / 69 (5.80%)
occurrences (all)	5	0	5
Pyrexia			
subjects affected / exposed	0 / 100 (0.00%)	0 / 66 (0.00%)	3 / 69 (4.35%)
occurrences (all)	0	0	3
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	12 / 100 (12.00%)	6 / 66 (9.09%)	5 / 69 (7.25%)
occurrences (all)	12	7	7
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 100 (3.00%)	5 / 66 (7.58%)	8 / 69 (11.59%)
occurrences (all)	4	5	10
Dyspnoea			
subjects affected / exposed	4 / 100 (4.00%)	3 / 66 (4.55%)	4 / 69 (5.80%)
occurrences (all)	4	3	4
Epistaxis			
subjects affected / exposed	2 / 100 (2.00%)	8 / 66 (12.12%)	4 / 69 (5.80%)
occurrences (all)	3	8	4
Oropharyngeal pain			
subjects affected / exposed	2 / 100 (2.00%)	1 / 66 (1.52%)	5 / 69 (7.25%)
occurrences (all)	2	1	7
Productive cough			
subjects affected / exposed	1 / 100 (1.00%)	0 / 66 (0.00%)	5 / 69 (7.25%)
occurrences (all)	1	0	6

Rhinorrhoea			
subjects affected / exposed	0 / 100 (0.00%)	0 / 66 (0.00%)	2 / 69 (2.90%)
occurrences (all)	0	0	2
Upper-airway cough syndrome			
subjects affected / exposed	0 / 100 (0.00%)	0 / 66 (0.00%)	2 / 69 (2.90%)
occurrences (all)	0	0	2
Psychiatric disorders			
Anxiety			
subjects affected / exposed	3 / 100 (3.00%)	1 / 66 (1.52%)	1 / 69 (1.45%)
occurrences (all)	4	1	1
Depression			
subjects affected / exposed	10 / 100 (10.00%)	2 / 66 (3.03%)	3 / 69 (4.35%)
occurrences (all)	10	4	3
Insomnia			
subjects affected / exposed	7 / 100 (7.00%)	4 / 66 (6.06%)	5 / 69 (7.25%)
occurrences (all)	7	4	9
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	7 / 100 (7.00%)	5 / 66 (7.58%)	11 / 69 (15.94%)
occurrences (all)	8	13	19
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 100 (3.00%)	4 / 66 (6.06%)	8 / 69 (11.59%)
occurrences (all)	3	6	8
Blood alkaline phosphatase increased			
subjects affected / exposed	6 / 100 (6.00%)	0 / 66 (0.00%)	5 / 69 (7.25%)
occurrences (all)	8	0	8
Blood creatinine increased			
subjects affected / exposed	0 / 100 (0.00%)	4 / 66 (6.06%)	4 / 69 (5.80%)
occurrences (all)	0	17	4
Neutrophil count decreased			
subjects affected / exposed	2 / 100 (2.00%)	39 / 66 (59.09%)	38 / 69 (55.07%)
occurrences (all)	4	103	125
Platelet count decreased			
subjects affected / exposed	0 / 100 (0.00%)	5 / 66 (7.58%)	18 / 69 (26.09%)
occurrences (all)	0	16	28
White blood cell count decreased			

subjects affected / exposed occurrences (all)	1 / 100 (1.00%) 1	12 / 66 (18.18%) 21	17 / 69 (24.64%) 67
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	7 / 100 (7.00%)	5 / 66 (7.58%)	3 / 69 (4.35%)
occurrences (all)	7	5	4
Fall			
subjects affected / exposed	3 / 100 (3.00%)	1 / 66 (1.52%)	5 / 69 (7.25%)
occurrences (all)	4	1	5
Procedural pain			
subjects affected / exposed	5 / 100 (5.00%)	4 / 66 (6.06%)	3 / 69 (4.35%)
occurrences (all)	5	5	3
Nervous system disorders			
Dizziness			
subjects affected / exposed	8 / 100 (8.00%)	6 / 66 (9.09%)	9 / 69 (13.04%)
occurrences (all)	9	9	10
Dysgeusia			
subjects affected / exposed	1 / 100 (1.00%)	1 / 66 (1.52%)	3 / 69 (4.35%)
occurrences (all)	1	1	3
Headache			
subjects affected / exposed	21 / 100 (21.00%)	12 / 66 (18.18%)	7 / 69 (10.14%)
occurrences (all)	23	15	8
Hypoaesthesia			
subjects affected / exposed	3 / 100 (3.00%)	0 / 66 (0.00%)	0 / 69 (0.00%)
occurrences (all)	3	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 100 (3.00%)	7 / 66 (10.61%)	6 / 69 (8.70%)
occurrences (all)	5	13	13
Eye disorders			
Dry eye			
subjects affected / exposed	2 / 100 (2.00%)	0 / 66 (0.00%)	6 / 69 (8.70%)
occurrences (all)	2	0	6
Gastrointestinal disorders			
Constipation			

subjects affected / exposed	10 / 100 (10.00%)	10 / 66 (15.15%)	7 / 69 (10.14%)
occurrences (all)	11	10	8
Diarrhoea			
subjects affected / exposed	14 / 100 (14.00%)	9 / 66 (13.64%)	11 / 69 (15.94%)
occurrences (all)	18	10	15
Dry mouth			
subjects affected / exposed	4 / 100 (4.00%)	2 / 66 (3.03%)	4 / 69 (5.80%)
occurrences (all)	4	2	4
Dyspepsia			
subjects affected / exposed	7 / 100 (7.00%)	6 / 66 (9.09%)	6 / 69 (8.70%)
occurrences (all)	8	7	8
Flatulence			
subjects affected / exposed	1 / 100 (1.00%)	1 / 66 (1.52%)	0 / 69 (0.00%)
occurrences (all)	1	1	0
Mouth ulceration			
subjects affected / exposed	1 / 100 (1.00%)	3 / 66 (4.55%)	4 / 69 (5.80%)
occurrences (all)	1	4	4
Nausea			
subjects affected / exposed	18 / 100 (18.00%)	16 / 66 (24.24%)	17 / 69 (24.64%)
occurrences (all)	23	20	26
Oral pain			
subjects affected / exposed	1 / 100 (1.00%)	5 / 66 (7.58%)	4 / 69 (5.80%)
occurrences (all)	1	8	4
Stomatitis			
subjects affected / exposed	0 / 100 (0.00%)	5 / 66 (7.58%)	8 / 69 (11.59%)
occurrences (all)	0	5	14
Vomiting			
subjects affected / exposed	4 / 100 (4.00%)	4 / 66 (6.06%)	7 / 69 (10.14%)
occurrences (all)	4	5	8
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	3 / 100 (3.00%)	6 / 66 (9.09%)	8 / 69 (11.59%)
occurrences (all)	3	6	8
Dry skin			
subjects affected / exposed	4 / 100 (4.00%)	4 / 66 (6.06%)	4 / 69 (5.80%)
occurrences (all)	4	4	4

Pruritus			
subjects affected / exposed	2 / 100 (2.00%)	5 / 66 (7.58%)	5 / 69 (7.25%)
occurrences (all)	2	6	5
Rash			
subjects affected / exposed	2 / 100 (2.00%)	4 / 66 (6.06%)	4 / 69 (5.80%)
occurrences (all)	2	5	4
Rash maculo-papular			
subjects affected / exposed	3 / 100 (3.00%)	2 / 66 (3.03%)	4 / 69 (5.80%)
occurrences (all)	3	2	4
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	26 / 100 (26.00%)	12 / 66 (18.18%)	14 / 69 (20.29%)
occurrences (all)	28	14	17
Back pain			
subjects affected / exposed	8 / 100 (8.00%)	5 / 66 (7.58%)	5 / 69 (7.25%)
occurrences (all)	8	5	6
Muscular weakness			
subjects affected / exposed	1 / 100 (1.00%)	0 / 66 (0.00%)	1 / 69 (1.45%)
occurrences (all)	1	0	1
Musculoskeletal pain			
subjects affected / exposed	2 / 100 (2.00%)	4 / 66 (6.06%)	2 / 69 (2.90%)
occurrences (all)	2	5	3
Myalgia			
subjects affected / exposed	11 / 100 (11.00%)	0 / 66 (0.00%)	3 / 69 (4.35%)
occurrences (all)	12	0	3
Osteoporosis			
subjects affected / exposed	2 / 100 (2.00%)	4 / 66 (6.06%)	3 / 69 (4.35%)
occurrences (all)	2	4	3
Pain in extre			
subjects affected / exposed	9 / 100 (9.00%)	4 / 66 (6.06%)	3 / 69 (4.35%)
occurrences (all)	11	4	3
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	1 / 100 (1.00%)	1 / 66 (1.52%)	2 / 69 (2.90%)
occurrences (all)	1	2	2
Oral herpes			

subjects affected / exposed occurrences (all)	1 / 100 (1.00%) 1	0 / 66 (0.00%) 0	6 / 69 (8.70%) 8
Upper respiratory tract infection subjects affected / exposed occurrences (all)	5 / 100 (5.00%) 6	5 / 66 (7.58%) 5	7 / 69 (10.14%) 7
Urinary tract infection subjects affected / exposed occurrences (all)	5 / 100 (5.00%) 6	5 / 66 (7.58%) 5	7 / 69 (10.14%) 7
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	4 / 100 (4.00%) 4	1 / 66 (1.52%) 1	5 / 69 (7.25%) 5
Hyperglycaemia subjects affected / exposed occurrences (all)	1 / 100 (1.00%) 2	0 / 66 (0.00%) 0	1 / 69 (1.45%) 1
Hypokalaemia subjects affected / exposed occurrences (all)	0 / 100 (0.00%) 0	0 / 66 (0.00%) 0	4 / 69 (5.80%) 4

Non-serious adverse events	Group D: letrozole plus palbociclib		
Total subjects affected by non-serious adverse events subjects affected / exposed	65 / 66 (98.48%)		
Vascular disorders			
Hot flush subjects affected / exposed occurrences (all)	22 / 66 (33.33%) 23		
Hypertension subjects affected / exposed occurrences (all)	7 / 66 (10.61%) 9		
General disorders and administration site conditions			
Chills subjects affected / exposed occurrences (all)	3 / 66 (4.55%) 3		
Fatigue subjects affected / exposed occurrences (all)	38 / 66 (57.58%) 52		

Mucosal inflammation subjects affected / exposed occurrences (all)	4 / 66 (6.06%) 5		
Pain subjects affected / exposed occurrences (all)	3 / 66 (4.55%) 4		
Pyrexia subjects affected / exposed occurrences (all)	3 / 66 (4.55%) 3		
Reproductive system and breast disorders Breast pain subjects affected / exposed occurrences (all)	9 / 66 (13.64%) 11		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	8 / 66 (12.12%) 9		
Dyspnoea subjects affected / exposed occurrences (all)	7 / 66 (10.61%) 11		
Epistaxis subjects affected / exposed occurrences (all)	8 / 66 (12.12%) 11		
Oropharyngeal pain subjects affected / exposed occurrences (all)	4 / 66 (6.06%) 4		
Productive cough subjects affected / exposed occurrences (all)	0 / 66 (0.00%) 0		
Rhinorrhoea subjects affected / exposed occurrences (all)	4 / 66 (6.06%) 5		
Upper-airway cough syndrome subjects affected / exposed occurrences (all)	4 / 66 (6.06%) 5		
Psychiatric disorders			

Anxiety subjects affected / exposed occurrences (all)	3 / 66 (4.55%) 4		
Depression subjects affected / exposed occurrences (all)	4 / 66 (6.06%) 4		
Insomnia subjects affected / exposed occurrences (all)	7 / 66 (10.61%) 7		
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all)	7 / 66 (10.61%) 8		
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	3 / 66 (4.55%) 5		
Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	2 / 66 (3.03%) 2		
Blood creatinine increased subjects affected / exposed occurrences (all)	2 / 66 (3.03%) 2		
Neutrophil count decreased subjects affected / exposed occurrences (all)	33 / 66 (50.00%) 94		
Platelet count decreased subjects affected / exposed occurrences (all)	8 / 66 (12.12%) 20		
White blood cell count decreased subjects affected / exposed occurrences (all)	20 / 66 (30.30%) 53		
Injury, poisoning and procedural complications Contusion subjects affected / exposed occurrences (all)	1 / 66 (1.52%) 1		
Fall			

subjects affected / exposed occurrences (all)	0 / 66 (0.00%) 0		
Procedural pain subjects affected / exposed occurrences (all)	2 / 66 (3.03%) 5		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	9 / 66 (13.64%) 12		
Dysgeusia subjects affected / exposed occurrences (all)	5 / 66 (7.58%) 6		
Headache subjects affected / exposed occurrences (all)	19 / 66 (28.79%) 34		
Hypoaesthesia subjects affected / exposed occurrences (all)	3 / 66 (4.55%) 3		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	7 / 66 (10.61%) 10		
Eye disorders Dry eye subjects affected / exposed occurrences (all)	1 / 66 (1.52%) 1		
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all)	9 / 66 (13.64%) 12		
Diarrhoea subjects affected / exposed occurrences (all)	13 / 66 (19.70%) 16		
Dry mouth subjects affected / exposed occurrences (all)	1 / 66 (1.52%) 1		
Dyspepsia			

subjects affected / exposed	7 / 66 (10.61%)		
occurrences (all)	7		
Flatulence			
subjects affected / exposed	3 / 66 (4.55%)		
occurrences (all)	3		
Mouth ulceration			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	17 / 66 (25.76%)		
occurrences (all)	26		
Oral pain			
subjects affected / exposed	3 / 66 (4.55%)		
occurrences (all)	3		
Stomatitis			
subjects affected / exposed	7 / 66 (10.61%)		
occurrences (all)	9		
Vomiting			
subjects affected / exposed	3 / 66 (4.55%)		
occurrences (all)	3		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	12 / 66 (18.18%)		
occurrences (all)	14		
Dry skin			
subjects affected / exposed	6 / 66 (9.09%)		
occurrences (all)	7		
Pruritus			
subjects affected / exposed	7 / 66 (10.61%)		
occurrences (all)	8		
Rash			
subjects affected / exposed	4 / 66 (6.06%)		
occurrences (all)	4		
Rash maculo-papular			
subjects affected / exposed	3 / 66 (4.55%)		
occurrences (all)	3		

Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	13 / 66 (19.70%)		
occurrences (all)	19		
Back pain			
subjects affected / exposed	4 / 66 (6.06%)		
occurrences (all)	5		
Muscular weakness			
subjects affected / exposed	3 / 66 (4.55%)		
occurrences (all)	6		
Musculoskeletal pain			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	5 / 66 (7.58%)		
occurrences (all)	5		
Osteoporosis			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences (all)	1		
Pain in extre			
subjects affected / exposed	2 / 66 (3.03%)		
occurrences (all)	3		
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	4 / 66 (6.06%)		
occurrences (all)	4		
Oral herpes			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	3 / 66 (4.55%)		
occurrences (all)	4		
Urinary tract infection			
subjects affected / exposed	3 / 66 (4.55%)		
occurrences (all)	4		
Metabolism and nutrition disorders			

Decreased appetite subjects affected / exposed occurrences (all)	7 / 66 (10.61%) 9		
Hyperglycaemia subjects affected / exposed occurrences (all)	6 / 66 (9.09%) 7		
Hypokalaemia subjects affected / exposed occurrences (all)	1 / 66 (1.52%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 November 2015	Addition of secondary endpoint and associated secondary objective: Changes between surgical intent at baseline, surgical intent after 14 weeks and actual surgery received after treatment with letrozole with or without palbociclib. Background and trial rationale section of protocol updated to reflect new information following publication of data from a Phase III trial of palbociclib. Eligibility criteria updated in UK protocol for clarity and to ensure alignment with North American protocol. Minor revisions and clarification to screening assessment section. Prohibition of PPIs as a concomitant medication with palbociclib treatment removed.
18 March 2016	Update to palbociclib Investigator Brochure. No change to protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/30523750>