Clinical trial results:
A randomized, double-blind, placebo-controlled, phase II trial of Palbociclib in combination with Letrozole versus Placebo in combination with Letrozole for patients with Estrogen Receptor Positive advanced or recurrent Endometrial cancer.
ENGOT-EN3-NSGO/PALEO

Summary

EudraCT number	2016-001848-20
Trial protocol	DK FI DE ES
Global end of trial date	29 April 2022

Results information

Result version number	v1 (current)
This version publication date	08 December 2024
First version publication date	08 December 2024

Trial information

Trial identification

Sponsor protocol code	ENGOT-EN3-NSGO/PALEO

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02730429
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Nordic Society of Gynaecological Oncology - Clinical Trial Unit (NSGO-CTU)
Sponsor organisation address	Blegdamsvej 9, Copenhagen OE, Denmark, 2100
Public contact	Mansoor Raza Mirza, Nordic Society of Gynaecological Oncology - Clinical Trial Unit (NSGO-CTU), 45 35459624, Mansoor.Raza.Mirza@Regionh.dk
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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	01 November 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 November 2020
Global end of trial reached?	Yes
Global end of trial date	29 April 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The overall objective is to obtain preliminary evidence of efficacy of palbociclib-letrozole combination vs. placebo-letrozole combination therapy in the treatment of ER+ advanced or relapsed endometrial cancer.
The primary objective is evaulation of Progression-Free Survival (PFS) in patient cohorts receiving either palbociclib-letrozole vs. placebo-letrozole for treatment of ER+ advanced or relapsed endometrial cancer.

Protection of trial subjects:

All study subjects were required to read and sign the informed consent form.

The IDMC was established to provide independent review and assessment of the efficacy and safety data in a systematic manner and to safeguard the interest and safety of the participating patients in the study. The IDMC consisted of 3 independent individuals, and made recommendations to the sponsor, based on
their review, to continue or stop the trial based on their assessment of safety information.

The trial was conducted in accordance with the ethical principles of the Declaration of Helsinki and the ICH-GCP guidelines. The local principal investigators were responsible for ensuring that the trial was conducted in accordance with the protocol, the ethical principles of the Declaration of Helsinki, current ICH guidelines on GCP and applicable local regulatory requirements.

Background therapy:

Patients are randomized to one of the two treatment arms:

• Arm A: (comparator arm) letrozole 2.5mg orally once daily on days 1-28 and placebo orally once daily on days 1-21 in a 28 days cycle until progression.
• Arm B (experimental arm): Patients receive letrozole 2.5mg orally once daily on days 1-28 and palbociclib 125 mg orally once daily on days 1-21 in a 28 days cycle until progression.

Evidence for comparator: -	
Actual start date of recruitment	16 February 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	42 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Norway: 6
Country: Number of subjects enrolled	Spain: 20
Country: Number of subjects enrolled	Finland: 3

Country: Number of subjects enrolled	Germany: 22
Country: Number of subjects enrolled	Denmark: 22
Worldwide total number of subjects	73
EEA total number of subjects	73

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)	29
From 65 to 84 years	44
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Potential candidates for the trial were identified by a member of the treatment team, by referrals from other departments/hospitals/GP. The investigator screened patients' medical records for suitability for enrollment in the trial. Enrollment occured only after the patient had given written informed consent. Recruitment from Q1 2017 to Q4 2018.

Pre-assignment

Screening details:

All patients had to commence treatment within 7 days after randomization. Patients who failed screening, could be rescreened later, at the Investigators discretion and upon discussion with and approval by sponsor.

Period 1

Period 1 title	Overall period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer

Blinding implementation details:

Palbociclib and placebo treatment was blinded. The trial medication was labeled using a unique Lot-ID, which was linked to the randomization scheme. The active and placebo capsules were identical and presented in the same packaging to ensure blinding of the study medication.

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A

Arm description:

Comparator Arm A: Patients receive tablet letrozole 2.5mg orally once daily on days 1-28 and tablet placebo for palbociclib orally once daily on days 1-21 in a 28 days cycle until progression.

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

Dosage and administration details:

Tablet Letrozole 2,5 mg taken orally once daily on days 1-28 in each 28 day cycle.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

One placebo capsule orally once daily on days 1-21 in a 28 days cycle.

Arm title	Arm B

Arm description:

Experimental Arm B: Patients receive tablet letrozole 2.5mg orally once daily on days 1-28 and tablet palbociclib orally once daily on days 1-21 in a 28 days cycle until progression.

Arm type	Experimental

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

Dosage and administration details:

One palbociclib capsule (125 mg/capsule) orally once daily on days 1-21 in a 28 days cycle.

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

Dosage and administration details:

Patients receive tablet letrozole 2.5 mg orally once daily on days 1-28 in a 28 days cycle.

Number of subjects in period 1	Arm A	Arm B
Started	37	36
Completed	3	3
Not completed	34	33
Disease progression	31	27
Death	-	1
Other reason - performance status deteriorated	-	1
Patient request	1	1
Adverse event	1	3
Other reason - Investigator decision	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Arm A
Reporting group description:	
Comparator Arm A: Patients receive tablet letrozole 2.5mg orally once daily on days 1-28 and tablet placebo for palbociclib orally once daily on days 1-21 in a 28 days cycle until progression.	
Reporting group title	Arm B
Reporting group description:	
Experimental Arm B: Patients receive tablet letrozole 2.5mg orally once daily on days 1-28 and tablet palbociclib orally once daily on days 1-21 in a 28 days cycle until progression.	

Reporting group values	Arm A	Arm B	Total
Number of subjects	37	36	73
Age categorical Units: Subjects			
Adults (18-64 years)	16	13	29
From 65-84 years	21	23	44
Gender categorical Units: Subjects			
Female	37	36	73
Male	0	0	0
Race Units: Subjects			
White	37	36	73
Previous cancer Units: Subjects			
Yes	3	1	4
No	34	35	69
Previous Diabetes Units: Subjects			
Yes	3	6	9
No	34	30	64
Previous Hypertension Units: Subjects			
Yes	18	19	37
No	19	17	36
Previous Ischaemic heart disease Units: Subjects			
Yes	0	2	2
No	37	34	71
ECOG performance status Units: Subjects			
Grade 0	23	18	41
Grade 1	10	15	25
Missing	4	3	7
RECIST status Units: Subjects			
Measurable	31	32	63

Evaluable	6	4	10
FIGO stage Units: Subjects			
Stage I	14	10	24
Stage II	7	7	14
Stage III	7	9	16
Stage IVA	2	0	2
Stage IVB	5	5	10
Unknown	2	5	7
Prior vaginal brachytherapy Units: Subjects			
Yes	7	12	19
No	30	24	54
Prior external beam therapy Units: Subjects			
Yes	15	13	28
No	22	23	45
Prior megestrol acetate/MPA Units: Subjects			
Yes	7	5	12
No	30	31	61
Prior Chemotherapy Units: Subjects			
Adjuvant	6	14	20
First line	19	7	26
Second line	1	6	7
Third line	1	0	1
Other	2	3	5
Missing	8	6	14
Prior lines of therapy Units: Subjects			
None	4	5	9
One	17	19	36
≥2	16	12	28

End points

End points reporting groups

Reporting group title	Arm A
Reporting group description:	
Comparator Arm A: Patients receive tablet letrozole 2.5mg orally once daily on days 1-28 and tablet placebo for palbociclib orally once daily on days 1-21 in a 28 days cycle until progression.	
Reporting group title	Arm B
Reporting group description:	
Experimental Arm B: Patients receive tablet letrozole 2.5mg orally once daily on days 1-28 and tablet palbociclib orally once daily on days 1-21 in a 28 days cycle until progression.	

Primary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)
End point description:	
The progression events are defined by well-documented and verifiable imaging data. PFS was censored if the patient was lost to follow-up or refused to continue in the trial (i.e. withdraws consent). For patients alive and without progression at the time of analysis, PFS was censored. In any case of censoring, the date of censoring was the last time point documenting survival status.	
End point type	Primary
End point timeframe:	
The PFS is calculated as time elapsed from date of randomization to date of progression or death of disease, whichever is the first registered event.	

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	36		
Units: month				
median (confidence interval 95%)	3 (2.7 to 6.8)	8.3 (4.6 to 11.2)		

Statistical analyses

Statistical analysis title	Comparison of PFS between arms
Statistical analysis description:	
PFS between arms was compared using the log rank test, the hazard ratio was estimated using cox-regression including the stratification factors: Number of prior chemotherapy lines, measurable versus evaluable disease, and prior medroxyprogesterone/megestrol acetate treatment	
Comparison groups	Arm A v Arm B
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.191
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.71

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.43
upper limit	1.19
Variability estimate	Standard error of the mean
Dispersion value	0.189

Secondary: Objective Response Rate (ORR) according to RECIST 1.1

End point title	Objective Response Rate (ORR) according to RECIST 1.1

End point description:

ORR according to Response Evaluation Criteria in Solid Tumours 1.1 (RECIST 1.1). ORR is determined as the rate of patients with an observed tumour response. Best overall response is the best response (CR, PR, SD, PD) recorded from the start of treatment until disease progression taking as reference for progressive disease the smallest measurements recorded since the treatment started.

End point type	Secondary

End point timeframe:

ORR is recorded from the start of treatment until disease progression.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	33		
Units: patients				
CR	3	0		
PR	3	3		
SD	12	21		
PD	19	9		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR) (CR+PR+SD)

End point title	Disease Control Rate (DCR) (CR+PR+SD)

End point description:

The percentage of patients in the treatment arm, which achieve complete response (CR) or partial response (PR) or stable disease (SD) for at least 12 weeks, assessed according to RECIST 1.1 criteria.

End point type	Secondary

End point timeframe:

From start of treatment until end of follow-up.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	33		
Units: Patients				
Yes	18	24		
No	19	9		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Subsequent Therapy (TFST)

End point title	Time to First Subsequent Therapy (TFST)

End point description:

TFST is defined as the time from start of treatment until initiation of subsequent-line of anti-cancer treatment or death. TFST was censored if the patient was lost to follow-up or refused to continue in the trial (i.e. withdraws consent). For patients alive and without initiation of third-line treatment at the time of analysis, TFST was censored. In any case of censoring, the date of censoring was the last time point documenting survival status.

End point type	Secondary

End point timeframe:

Time from randomization to first subsequent treatment or death of disease, whichever is the first registered event.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	36		
Units: month				
median (confidence interval 95%)	8.3 (4.0 to 12.1)	9.2 (6.5 to 13.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival 2 (PFS2)

End point title	Progression Free Survival 2 (PFS2)

End point description:

PFS2 is defined as the time elapsed from date of randomization to date of 2nd progression or death of disease, whichever is the first registered event. PFS2 was censored if the patient was lost to follow-up or refused to continue in the trial (i.e. withdraws consent). For patients alive and without progression at the time of analysis, PFS2 was censored. In any case of censoring, the date of censoring was the last time point documenting survival status.

End point type	Secondary

End point timeframe:

Time from randomization to second subsequent disease progression or death.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	36		
Units: month				
median (confidence interval 95%)	14.1 (11.0 to 28.1)	16.3 (9.0 to 25.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Second Subsequent Therapy (TSST)

End point title	Time to Second Subsequent Therapy (TSST)

End point description:

TSST is defined as the time from start of treatment until initiation of anti-cancer treatment for second subsequent progression of disease or death. TSST was censored if the patient was lost to follow-up or refused to continue in the trial (i.e. withdraws consent). For patients alive and without initiation of fourth-line treatment at the time of analysis, TSST was censored. In any case of censoring, the date of censoring was the last time point documenting survival status.

End point type	Secondary

End point timeframe:

Time from randomization to second subsequent therapy or death.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	36		
Units: month				
median (confidence interval 95%)	16.0 (11.6 to 28.7)	16.3 (9.0 to 27.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Reported Outcome (PRO); EORTC’s QLQ-C30 (Overall QoL)

End point title	Patient Reported Outcome (PRO); EORTC’s QLQ-C30 (Overall QoL)

End point description:

Quality of Life (QoL) scores, assessed by the "European Organisation for Research and Treatment of Cancer- Quality of Life Questionnaire - C30" (EORTC-QLQ-C30), calculated using the EORTC scoring manual. Scores were calculated for each individual patient at selected visits.
First part: 28 questions on difficulties in everyday life. Scores from 1 to 4; 1 = "Not at all", 2 = "A little",

3 = "Quite a bit", 4 = "Very much".
Second part: 2 questions on general health and QoL self-assessment: scores from 1 to 7; 1 = "Very poor", 7 = "Excellent".
Reported values for Time 1-10 are mean overall QoL measures normalised to a number from 0-100, where a high score indicates high QoL.
The unit for Time 1-10 is 'months'.

End point type	Secondary

End point timeframe:

QoL scores assessed before treatment until 6 months after end of treatment.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	35		
Units: Score				
arithmetic mean (standard deviation)				
Time 1	61 (± 23)	64 (± 24)		
Time 2	57 (± 27)	64 (± 26)		
Time 3	65 (± 25)	61 (± 22)		
Time 4	63 (± 26)	64 (± 16)		
Time 5	68 (± 18)	63 (± 23)		
Time 6	59 (± 29)	66 (± 18)		
Time 7	73 (± 20)	71 (± 18)		
Time 8	76 (± 19)	65 (± 16)		
Time 9	60 (± 19)	65 (± 22)		
Time 10	58 (± 22)	67 (± 12)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS)

End point title	Overall survival (OS)

End point description:

The percentage of people in each of the two treatment arms, who are still alive 3,5 years after randomization. OS is defined as the time from the date of randomization to the date of death, regardless of the cause of death. Patients who were alive at the time of the analysis were censored at the date of their last follow-up assessment. Patients without follow-up assessment were censored at the day of their last dose and patients with no post baseline information were censored at the time of their first administration of treatment drugs.

End point type	Secondary

End point timeframe:

OS was assessed from end of treatment until death or 42 months after randomization.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37[1]	36[2]		
Units: month				
number (not applicable)	21.2	22.4		

Notes:

[1] - The median in months is indicated as 'number' (95% CI 16.7-NE). NE = No estimate.

[2] - The median in months is indicated as 'number' (95% CI 13.1-NE). NE = No estimate.

Statistical analyses

No statistical analyses for this end point

Secondary: PFS; number of prior lines (primary advanced disease)

End point title	PFS; number of prior lines (primary advanced disease)

End point description:

Progression-free survival in the subgroup of patients with primary advanced disease.

End point type	Secondary

End point timeframe:

Time from date of randomization to date of progression or death.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4[3]	5[4]		
Units: month				
number (not applicable)	0.19	1.1		

Notes:

[3] - The median in months is indicated as 'number' (95% CI 0.16-NE). NE = No estimate.

[4] - The median in months is indicated as 'number' (95% CI 0.24-NE). NE = No estimate.

Statistical analyses

No statistical analyses for this end point

Secondary: PFS; number of prior lines (1st relapse)

End point title	PFS; number of prior lines (1st relapse)

End point description:

Progression-free survival in the subgroup of patients with 1st relapse of disease.

End point type	Secondary

End point timeframe:

Time from date of randomization to date of progression or death.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	19		
Units: month				
median (confidence interval 95%)	0.5 (0.2 to 0.9)	0.6 (0.4 to 0.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: PFS; number of prior lines (≥2 relapses)

End point title	PFS; number of prior lines (≥2 relapses)

End point description:

Progression-free survival in the subgroup of patients with 2nd or more relapses of disease.

End point type	Secondary

End point timeframe:

Time from date of randomization to date of progression or death.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	12		
Units: month				
median (confidence interval 95%)	0.22 (0.16 to 0.46)	0.23 (0.20 to 0.92)		

Statistical analyses

No statistical analyses for this end point

Secondary: PFS; RECIST 1.1 (Measurable disease)

End point title	PFS; RECIST 1.1 (Measurable disease)

End point description:

PFS in the subgroup of patients with measurable disease according to RECIST 1.1.

End point type	Secondary

End point timeframe:

Time from date of randomization to date of progression or death.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	32		
Units: month				
median (confidence interval 95%)	0.25 (0.22 to 0.47)	0.67 (0.29 to 0.93)		

Statistical analyses

No statistical analyses for this end point

Secondary: PFS; RECIST 1.1 (Evaluable disease)

End point title	PFS; RECIST 1.1 (Evaluable disease)

End point description:

PFS in the subgroup of patients with evaluable disease according to RECIST 1.1.

End point type	Secondary

End point timeframe:

Time from date of randomization to date of progression or death.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6[5]	4[6]		
Units: month				
number (not applicable)	0.92	0.69		

Notes:

[5] - The median in months is indicated as 'number' (95% CI 0.14-NE). NE = No estimate.

[6] - The median in months is indicated as 'number' (95% CI 0.21-NE). NE = No estimate.

Statistical analyses

No statistical analyses for this end point

Secondary: PFS; prior use of endocrine therapy (no prior treatment)

End point title	PFS; prior use of endocrine therapy (no prior treatment)

End point description:

PFS in the subgroup of patients that recieved no prior endocrine treatment.

End point type	Secondary

End point timeframe:

Time from date of randomization to date of progression or death.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7[7]	4[8]		
Units: month				
number (not applicable)	0.23	0.23		

Notes:

[7] - The median in months is indicated as 'number' (95% CI 0.16-0.46).

[8] - The median in months is indicated as 'number' (95% CI 0.20-NE). NE = No estimate.

Statistical analyses

No statistical analyses for this end point

Secondary: PFS; prior use of endocrine therapy (one line of MPA/Megace treatment)

End point title	PFS; prior use of endocrine therapy (one line of MPA/Megace treatment)

End point description:

PFS in the subgroup of patients that recieved one line of prior endocrine treatment. Patient may have received maximum one line of endocrine therapy containing MPA/Megace.

End point type	Secondary

End point timeframe:

Time from date of randomization to date of progression or death.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	32		
Units: month				
median (confidence interval 95%)	0.46 (0.22 to 0.87)	0.80 (0.40 to 1.08)		

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Reported Outcome (PRO); EORTC’s QLQ-EN24 (gastrointestinal symptoms)

End point title	Patient Reported Outcome (PRO); EORTC’s QLQ-EN24 (gastrointestinal symptoms)

End point description:

Quality of Life (QoL) scores, assessed by the "European Organisation for Research and Treatment of Cancer- Quality of Life Questionnaire – EN24" (EORTC-QLQ-EN24), calculated using the EORTC scoring manual. This questionnaire is designed for patients with endometrial cancer. Scores were calculated for each patient at selected visits.
QLQ-EN24 incorporates 5 multi-item scales to assess lymphoedema, urological symptoms, gastrointestinal symptoms, body image and sexual/vaginal problems. In addition, 8 single items assess pain in back and pelvis, tingling/numbness, muscular pain, hair loss, taste change, sexual interest, sexual activity and sexual enjoyment.
Scores from 1 to 4; 1 = "Not at all", 2 = "A little", 3 = "Quite a bit", 4 = "Very much".
Reported values for Time 1-10 are mean scores for gastrointestinal symptoms normalized to a number from 0-100, where a high score represents a high level of symptomatology.

The unit for Time 1-10 is 'months'.

End point type	Secondary

End point timeframe:

QoL scores assessed before treatment until 6 months after end of treatment.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	32		
Units: Score				
arithmetic mean (standard deviation)				
Time 1	13 (± 13)	17 (± 18)		
Time 2	13 (± 11)	16 (± 20)		
Time 3	12 (± 12)	15 (± 14)		
Time 4	17 (± 20)	16 (± 14)		
Time 5	13 (± 19)	20 (± 22)		
Time 6	11 (± 13)	14 (± 15)		
Time 7	8 (± 14)	16 (± 16)		
Time 8	8 (± 17)	19 (± 13)		
Time 9	11 (± 14)	18 (± 14)		
Time 10	7 (± 12)	29 (± 21)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The investigator must report all adverse events from first dose until 28 days after the last dose of treatment drugs. The AEs must be documented in the eCRFs.
Concomitant illnesses, which existed before entry into the trial, will not be considered AEs.

Adverse event reporting additional description:

Concomitant illnesses, which existed before entry into the trial, will not be considered AEs unless they worsen during the treatment period. Pre-existing conditions will be recorded in the eCRF on the Medical History or appropriate page.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.0

Reporting groups

Reporting group title	Arm A

Reporting group description:

Comparator Arm A: Patients receive tablet letrozole 2.5mg orally once daily on days 1-28 and tablet placebo for palbociclib orally once daily on days 1-21 in a 28 days cycle until progression.

Reporting group title	Arm B

Reporting group description:

Experimental Arm B: Patients receive tablet letrozole 2.5mg orally once daily on days 1-28 and tablet palbociclib orally once daily on days 1-21 in a 28 days cycle until progression.

Serious adverse events	Arm A	Arm B	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 37 (18.92%)	17 / 36 (47.22%)	
number of deaths (all causes)	17	17	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Brain metastasis			
subjects affected / exposed	1 / 37 (2.70%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumor - former vaginal bleeding			
subjects affected / exposed	0 / 37 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Broken leg			

subjects affected / exposed	0 / 37 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Cerebral ischemia			
subjects affected / exposed	1 / 37 (2.70%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral stroke			
subjects affected / exposed	1 / 37 (2.70%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	0 / 37 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
pulmonary embolism			
subjects affected / exposed	1 / 37 (2.70%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			
subjects affected / exposed	0 / 37 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 37 (0.00%)	2 / 36 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve disease			
subjects affected / exposed	1 / 37 (2.70%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			

Acute confusional syndrome			
subjects affected / exposed	0 / 37 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusion			
subjects affected / exposed	0 / 37 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 37 (2.70%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Mailaise			
subjects affected / exposed	1 / 37 (2.70%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	3 / 37 (8.11%)	2 / 36 (5.56%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reduced general condition			
subjects affected / exposed	1 / 37 (2.70%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Ileus			
subjects affected / exposed	0 / 37 (0.00%)	2 / 36 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal bleeding			

subjects affected / exposed	1 / 37 (2.70%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
progression former abdominal pain			
subjects affected / exposed	0 / 37 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Bloody cough			
subjects affected / exposed	0 / 37 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 37 (2.70%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
tumor progression, renal failure			
subjects affected / exposed	1 / 37 (2.70%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infection			
subjects affected / exposed	0 / 37 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
pneumonia			
subjects affected / exposed	0 / 37 (0.00%)	2 / 36 (5.56%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 37 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Urinary tract infection			
subjects affected / exposed	0 / 37 (0.00%)	2 / 36 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 37 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Arm A	Arm B	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 37 (81.08%)	34 / 36 (94.44%)	
Vascular disorders			
Epistaxis			
subjects affected / exposed	0 / 37 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	2	
Hot flashes			
subjects affected / exposed	4 / 37 (10.81%)	5 / 36 (13.89%)	
occurrences (all)	4	6	
Hypertension			
subjects affected / exposed	1 / 37 (2.70%)	5 / 36 (13.89%)	
occurrences (all)	1	7	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	6 / 37 (16.22%)	8 / 36 (22.22%)	
occurrences (all)	14	13	
Edema			
subjects affected / exposed	5 / 37 (13.51%)	3 / 36 (8.33%)	
occurrences (all)	7	3	
Fatigue			
subjects affected / exposed	9 / 37 (24.32%)	5 / 36 (13.89%)	
occurrences (all)	11	7	
Fever			

subjects affected / exposed	3 / 37 (8.11%)	6 / 36 (16.67%)	
occurrences (all)	10	6	
Pain			
subjects affected / exposed	14 / 37 (37.84%)	14 / 36 (38.89%)	
occurrences (all)	29	25	
Reproductive system and breast disorders			
Vaginal bleeding			
subjects affected / exposed	1 / 37 (2.70%)	2 / 36 (5.56%)	
occurrences (all)	1	2	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 37 (8.11%)	3 / 36 (8.33%)	
occurrences (all)	3	3	
Dyspnoea			
subjects affected / exposed	3 / 37 (8.11%)	1 / 36 (2.78%)	
occurrences (all)	3	1	
Pulmonary embolism			
subjects affected / exposed	2 / 37 (5.41%)	0 / 36 (0.00%)	
occurrences (all)	4	0	
Pneumonia			
subjects affected / exposed	0 / 37 (0.00%)	5 / 36 (13.89%)	
occurrences (all)	0	5	
Investigations			
blood alanine aminotransferase increased			
subjects affected / exposed	2 / 37 (5.41%)	2 / 36 (5.56%)	
occurrences (all)	3	5	
Blood alkaline phosphatase increased			
subjects affected / exposed	5 / 37 (13.51%)	0 / 36 (0.00%)	
occurrences (all)	6	0	
blood aspartate aminotransferase increased			
subjects affected / exposed	1 / 37 (2.70%)	3 / 36 (8.33%)	
occurrences (all)	1	6	
Blood creatine increased			

subjects affected / exposed	2 / 37 (5.41%)	4 / 36 (11.11%)	
occurrences (all)	2	4	
ldh increased			
subjects affected / exposed	0 / 37 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	4	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 37 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	3	
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 37 (8.11%)	1 / 36 (2.78%)	
occurrences (all)	7	1	
Insomnia			
subjects affected / exposed	2 / 37 (5.41%)	1 / 36 (2.78%)	
occurrences (all)	2	1	
Peripheral motor neuropathy			
subjects affected / exposed	2 / 37 (5.41%)	4 / 36 (11.11%)	
occurrences (all)	2	6	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 37 (8.11%)	13 / 36 (36.11%)	
occurrences (all)	7	19	
Leukopenia			
subjects affected / exposed	0 / 37 (0.00%)	9 / 36 (25.00%)	
occurrences (all)	0	18	
Neutropenia			
subjects affected / exposed	1 / 37 (2.70%)	24 / 36 (66.67%)	
occurrences (all)	1	135	
Thrombocytopenia			
subjects affected / exposed	0 / 37 (0.00%)	4 / 36 (11.11%)	
occurrences (all)	0	8	
Eye disorders			
Dry eyes			
subjects affected / exposed	0 / 37 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	2	
Gastrointestinal disorders			

Constipation			
subjects affected / exposed	9 / 37 (24.32%)	8 / 36 (22.22%)	
occurrences (all)	14	8	
Diarrhoea			
subjects affected / exposed	9 / 37 (24.32%)	7 / 36 (19.44%)	
occurrences (all)	12	8	
Dry mouth			
subjects affected / exposed	3 / 37 (8.11%)	0 / 36 (0.00%)	
occurrences (all)	5	0	
Dyspepsia			
subjects affected / exposed	1 / 37 (2.70%)	2 / 36 (5.56%)	
occurrences (all)	1	2	
Mucositis oral			
subjects affected / exposed	3 / 37 (8.11%)	6 / 36 (16.67%)	
occurrences (all)	4	6	
Nausea			
subjects affected / exposed	11 / 37 (29.73%)	8 / 36 (22.22%)	
occurrences (all)	12	9	
Stomatitis			
subjects affected / exposed	2 / 37 (5.41%)	1 / 36 (2.78%)	
occurrences (all)	3	1	
Vomiting			
subjects affected / exposed	2 / 37 (5.41%)	6 / 36 (16.67%)	
occurrences (all)	4	6	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	3 / 37 (8.11%)	6 / 36 (16.67%)	
occurrences (all)	4	6	
Itching			
subjects affected / exposed	2 / 37 (5.41%)	0 / 36 (0.00%)	
occurrences (all)	2	0	
Rash			
subjects affected / exposed	2 / 37 (5.41%)	2 / 36 (5.56%)	
occurrences (all)	2	3	
Renal and urinary disorders			

Dysuria			
subjects affected / exposed	0 / 37 (0.00%)	3 / 36 (8.33%)	
occurrences (all)	0	3	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	9 / 37 (24.32%)	4 / 36 (11.11%)	
occurrences (all)	12	4	
Myalgia			
subjects affected / exposed	2 / 37 (5.41%)	1 / 36 (2.78%)	
occurrences (all)	2	1	
Infections and infestations			
Infection			
subjects affected / exposed	0 / 37 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	2	
Upper respiratory infection			
subjects affected / exposed	3 / 37 (8.11%)	0 / 36 (0.00%)	
occurrences (all)	3	0	
Urinary tract infection			
subjects affected / exposed	5 / 37 (13.51%)	6 / 36 (16.67%)	
occurrences (all)	7	7	
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	4 / 37 (10.81%)	5 / 36 (13.89%)	
occurrences (all)	5	7	
Decreased appetite			
subjects affected / exposed	1 / 37 (2.70%)	2 / 36 (5.56%)	
occurrences (all)	2	3	
Hypomagnesaemia			
subjects affected / exposed	2 / 37 (5.41%)	3 / 36 (8.33%)	
occurrences (all)	2	11	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 March 2017	Amendment (Protocol version 3.0) submitted for Danish EC and CA: The following was corrected in the amendment: - Palbociclib has received marketing authorization in breast cancer - Safety document updated to latest SmPC for Palbociclib - Safety update in relation to blood samples on day 14 in first and second series - Timeline adjustments - Smaller general updates
29 October 2019	Amendment (Protocol version 4.0) submitted for Danish EC and CA: The following was corrected in the amendment: - Error in cycle 2, day 1 activities from protocol V3.0 corrected - Timeline adjustments - Clarification regarding dose levels. - Clarification to emphasize that death caused by progression of disease, or the cancer is NOT seen as an AE in the PALEO trial. - Clarification to let sites know, that whether tumour slides should be sent, will first be decided after primary endpoint has been reached. And there has been a change in the procedure of where to store/handle the TR samples. - New IB for Palbociclib added. - Examples of which patients may be included in the PALEO trial added. - Smaller general updates

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.

N/A

Notes: