Clinical trial results:
Open-label, randomized, multicenter, international, parallel exploratory phase II study, comparing 3 FEC-3 Docetaxel chemotherapy to letrozole + palbociclib combination as neoadjuvant treatment of stage II-IIIA PAM 50 ROR-defined low or intermediate risk Luminal breast cancer, in postmenopausal women.

Summary

EudraCT number	2014-002560-33
Trial protocol	FR BE
Global end of trial date	25 May 2020

Results information

Result version number	v1 (current)
This version publication date	05 November 2021
First version publication date	05 November 2021

Trial information

Trial identification

Sponsor protocol code	UC-0140/1404_CARMINA04

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02400567
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	UNICANCER
Sponsor organisation address	101 rue de Tolbiac, Paris, France, 75013
Public contact	Nourredine AIT-RAHMOUNE, UNICANCER, 33 1 71 93 67 04, n.ait-rahmoune@unicancer.fr
Scientific contact	Nourredine AIT-RAHMOUNE, UNICANCER, 33 1 71 93 67 04, n.ait-rahmoune@unicancer.fr

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	17 June 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 May 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this trial was to evaluate the ability of each treatment strategy to provide residual cancer burden (RCB) 0-I histological tumor response at surgery (local assessment) in luminal A node-positive (N+) and luminal B patients subgroup.

Protection of trial subjects:

In order to ensure the protection of the rights, safety and well-being of trial subjects, this clinical trial was conducted in accordance with the Declaration of Helsinki (1964) and subsequent amendments, ICH Good Clinical Practice Guidelines (CPMP/ICH/135/95), the European Directive (2001/20/CE) and the applicable local regulatory requirements and laws.
Furthermore, independent Ethics Committees in France and Belgium reviewed and gave a favorable opinion to the study documents, including the initial protocol and all subsequent amendments, and all information and documents provided to subjects/patients.

Background therapy: -
Evidence for comparator: -

Actual start date of recruitment	02 February 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 12
Country: Number of subjects enrolled	France: 174
Worldwide total number of subjects	186
EEA total number of subjects	186

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	110
From 65 to 84 years	76
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

NEOPAL was an international multicentric phase II trial comparing two neoadjuvant treatments, the sequential standard chemotherapy (3 FEC 100-3 Docetaxel 100) with the combination of letrozole plus palbociclib in stage II-IIIA Luminal A N+/Luminal B breast cancer patients.

Pre-assignment

Screening details:

The study consisted of a screening phase before randomization to establish eligibility, a treatment phase (21-day treatment cycles; 19 weeks), and a long-term follow-up to monitor the residual cancer burden, clinical response, relapse-free survival, invasive disease-free survival, breast conservation therapy, and safety.

Pre-assignment period milestones

Number of subjects started	186
Number of subjects completed	106

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Not meeting inclusion criteria: 13
Reason: Number of subjects	Consent withdrawn by subject: 2
Reason: Number of subjects	Prosigma technical failure: 15
Reason: Number of subjects	Non-luminal breast cancer: 15
Reason: Number of subjects	Unknown lymph node status: 16
Reason: Number of subjects	Node-negative: 19

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	Palbociclib + letrozole

Arm description:

Patients received palbociclib (125 mg oral) once daily on a discontinuous 3/4 weeks schedule (i.e 21 days of palbociclib followed by 7 days off) up to the day prior to surgery plus letrozole (2.5 mg, oral) daily up to the day prior to surgery.

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:

Palbociclib was administered orally (125mg) once a day for 21 days of every 28-day cycle followed by 7 days off treatment until the day prior to surgery, for about 19 weeks. The medication should have been taken orally with a glass of water, approximately at the same time each day, during a meal, preferably in the morning.

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

Dosage and administration details:

Letrozole was administered orally (2.5 mg) once a day until the day prior to surgery, for about 19 weeks.

Arm title	FEC100-Docetaxel

Arm description:

Patients received the standard chemotherapy consisting of 3 cycles of 5-FU, epirubicin, and cyclophosphamide (FEC100) followed by 3 cycles of Docetaxel:
FEC100 (cycles 1 to 3) ddministrated every 3 weeks (5-FU: 500 mg/m2, 30 minutes IV infusion; Epirubicin: 100 mg/m2, 10 minutes IV infusion, Cyclophosphamide: 500 mg/m2, 30 minutes IV infusion
Docetaxel (cycles 4 to 6) administered every 3 weeks, beginning 3 weeks after the last administration of FEC100 (Docetaxel : 100 mg/m2, 60 minutes IV infusion)

Arm type	Active comparator
Investigational medicinal product name	5-FU
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

500 mg/m2, 30 minutes intravenous infusion at weeks 1, 4, and 7

Investigational medicinal product name	Epirubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

100 mg/m2, 10 minutes intravenous infusion at weeks 1, 4, and 7

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

500 mg/m2, 30 minutes intravenous infusion at weeks 1, 4, and 7

Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

100 mg/m2, 60 minutes intravenous infusion at weeks 10, 13, and 16

Number of subjects in period 1[1]	Palbociclib + letrozole	FEC100-Docetaxel
Started	53	53
Completed	42	42
Not completed	11	11
Consent withdrawn by subject	-	1
Disease progression	5	8
Death	6	1
Protocol deviation	-	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 186 patients were enrolled in this study were screened to determine their breast cancer subtype using the genomic PAM50 test. 106 out of the 186 screened patients were eligible to randomization. The baseline period correspond to these 106 randomized patients.

Baseline characteristics

Reporting groups	
Reporting group title	Palbociclib + letrozole
Reporting group description:	
Patients received palbociclib (125 mg oral) once daily on a discontinuous 3/4 weeks schedule (i.e 21 days of palbociclib followed by 7 days off) up to the day prior to surgery plus letrozole (2.5 mg, oral) daily up to the day prior to surgery.	
Reporting group title	FEC100-Docetaxel
Reporting group description:	
Patients received the standard chemotherapy consisting of 3 cycles of 5-FU, epirubicin, and cyclophosphamide (FEC100) followed by 3 cycles of Docetaxel: FEC100 (cycles 1 to 3) ddministrated every 3 weeks (5-FU: 500 mg/m2, 30 minutes IV infusion; Epirubicin: 100 mg/m2, 10 minutes IV infusion, Cyclophosphamide: 500 mg/m2, 30 minutes IV infusion Docetaxel (cycles 4 to 6) administered every 3 weeks, beginning 3 weeks after the last administration of FEC100 (Docetaxel : 100 mg/m2, 60 minutes IV infusion)	

Reporting group values	Palbociclib + letrozole	FEC100-Docetaxel	Total
Number of subjects	53	53	106
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	26	30	56
From 65-84 years	27	23	50
85 years and over	0	0	0
Age continuous Units: years			
median	65	63	
full range (min-max)	49 to 78	48 to 80	-
Gender categorical Units: Subjects			
Female	53	53	106
Male	0	0	0
Body mass index Units: Subjects			
<18	2	1	3
18-24	16	17	33
25-30	19	21	40
>30	15	13	28
Missing	1	1	2
Eastern Cooperative Oncology Group Units: Subjects			
ECOG 0	44	47	91

ECOG 1	9	6	15
Molecular subtype			
Molecular subtype defined by the PAM 50 test			
Units: Subjects			
Luminal A	6	6	12
Luminal B	47	47	94
Risk of recurrence			
The risk of recurrence status was defined using the PAM50 test			
Units: Subjects			
Intermediate	7	9	16
High	46	44	90

Subject analysis sets

Subject analysis set title	ITT population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All randomized patients were included in the intent-to-treat population, whether or not any study medication was administered after randomization, and regardless of the eligibility status. As far as statistical inferences were concerned, patients were analyzed in the treatment group and in the stratum to which they were assigned by the randomization.

Reporting group values	ITT population		
Number of subjects	106		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	56		
From 65-84 years	50		
85 years and over	0		
Age continuous Units: years			
median	63		
full range (min-max)	48 to 80		
Gender categorical Units: Subjects			
Female	106		
Male	0		
Body mass index Units: Subjects			
<18	3		
18-24	33		
25-30	40		
>30	28		
Missing	2		
Eastern Cooperative Oncology Group			

Units: Subjects			
ECOG 0	91		
ECOG 1	15		
Molecular subtype			
Molecular subtype defined by the PAM 50 test			
Units: Subjects			
Luminal A	12		
Luminal B	94		
Risk of recurrence			
The risk of recurrence status was defined using the PAM50 test			
Units: Subjects			
Intermediate	16		
High	90		

End points

End points reporting groups

Reporting group title	Palbociclib + letrozole

Reporting group description:

Patients received palbociclib (125 mg oral) once daily on a discontinuous 3/4 weeks schedule (i.e 21 days of palbociclib followed by 7 days off) up to the day prior to surgery plus letrozole (2.5 mg, oral) daily up to the day prior to surgery.

Reporting group title	FEC100-Docetaxel

Reporting group description:

Patients received the standard chemotherapy consisting of 3 cycles of 5-FU, epirubicin, and cyclophosphamide (FEC100) followed by 3 cycles of Docetaxel:
FEC100 (cycles 1 to 3) ddministrated every 3 weeks (5-FU: 500 mg/m2, 30 minutes IV infusion; Epirubicin: 100 mg/m2, 10 minutes IV infusion, Cyclophosphamide: 500 mg/m2, 30 minutes IV infusion
Docetaxel (cycles 4 to 6) administered every 3 weeks, beginning 3 weeks after the last administration of FEC100 (Docetaxel : 100 mg/m2, 60 minutes IV infusion)

Subject analysis set title	ITT population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All randomized patients were included in the intent-to-treat population, whether or not any study medication was administered after randomization, and regardless of the eligibility status. As far as statistical inferences were concerned, patients were analyzed in the treatment group and in the stratum to which they were assigned by the randomization.

Primary: Residual cancer burden

End point title	Residual cancer burden[1]

End point description:

End point type	Primary

End point timeframe:

The main objective of this trial was to evaluate the ability of each treatment strategy to provide residual cancer burden (RCB) 0-I after the completion of neoadjuvant therapy (19 weeks from randomization)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The primary endpoint was residual cancer burden in breast and axillary lymph nodes after neoadjuvant treatment. The decision rule was that if fewer than 20% RCB 0-I were seen, the palbociclib + letrozole regimen would be regarded as insufficiently active.

End point values	Palbociclib + letrozole	FEC100-Docetaxel	ITT population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	53	53	106	
Units: percent				
number (not applicable)	7.7	15.7	11.7	

Statistical analyses

No statistical analyses for this end point

Secondary: Best clinical response

End point title	Best clinical response

End point description:

"Not applicable" refers to 3 patients who did not undergo surgery (1 in the palbociclib + letrozole arm, 2 in the FEC100-Docetaxel arm) and 1 patient with missing data in the FEC100-Docetaxel arm.

End point type	Secondary

End point timeframe:

At surgery, after 8 weeks of treatment

End point values	Palbociclib + letrozole	FEC100-Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	53		
Units: percent				
number (not applicable)				
Complete response	16	15		
Partial response	22	23		
Stable disease	13	12		
Not applicable	1	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of breast cancer surgery

End point title	Rate of breast cancer surgery

End point description:

Rates of breast conservation therapy in both arms, with regard to the initially planned surgery.

End point type	Secondary

End point timeframe:

At surgery (Week 8)

End point values	Palbociclib + letrozole	FEC100-Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52[2]	51[3]		
Units: percent				
number (confidence interval 95%)	69.2 (56.6 to 81.9)	68.6 (55.9 to 81.4)		

Notes:

[2] - 1 patient did not undergo surgery

[3] - 2 patients did not undergo surgery

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival

End point title	Progression-free survival

End point description:

Progression-free survival was defined as the time from the date of randomization to the date of tumor progression, relapse (local, regional, or distant), or death from any cause, whichever occurs first.

End point type	Secondary

End point timeframe:

3 years

End point values	Palbociclib + letrozole	FEC100-Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	53		
Units: percent				
number (confidence interval 95%)	86.7 (78 to 96.4)	92 (84.7 to 99.8)		

Statistical analyses

Statistical analysis title	PFS analysis
Comparison groups	Palbociclib + letrozole v FEC100-Docetaxel
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	Logrank
Dispersion value	0.979

Secondary: Invasive disease-free survival

End point title	Invasive disease-free survival

End point description:

Invasive disease-free survival was defined as the interval between the date of randomization and the date of invasive breast cancer relapse (local, regional, or distant) or the date of invasive contralateral breast cancer or second invasive cancer or death from any cause, whichever occurs first.

End point type	Secondary

End point timeframe:

3 years

End point values	Palbociclib + letrozole	FEC100-Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	53		
Units: percent				
number (confidence interval 95%)	86.7 (78 to 96.4)	92 (84.7 to 99.8)		

Statistical analyses

Statistical analysis title	iDFS analysis
Comparison groups	Palbociclib + letrozole v FEC100-Docetaxel
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	Logrank
Dispersion value	0.707

Secondary: Cnetral RCB 0-I rate

End point title	Cnetral RCB 0-I rate

End point description:

End point type	Secondary

End point timeframe:

After the completion of neoadjuvant therapy (19 weeks from randomization)

End point values	Palbociclib + letrozole	FEC100-Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	53		
Units: percent				
number (confidence interval 95%)	5.8 (0 to 12.1)	13.7 (4.1 to 23.2)		

Statistical analyses

No statistical analyses for this end point

Post-hoc: Overall survival

End point title	Overall survival

End point description:

End point type	Post-hoc
End point timeframe: 3 years	

End point values	Palbociclib + letrozole	FEC100-Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	53		
Units: percent				
number (confidence interval 95%)	90.5 (82.9 to 98.8)	98.0 (94.1 to 100.0)		

Statistical analyses

Statistical analysis title	OS analysis
Comparison groups	Palbociclib + letrozole v FEC100-Docetaxel
Number of subjects included in analysis	106
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	< 0.05
Method	Logrank
Dispersion value	0.047

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Overall period of the study (up to 3 years after first study intake)

Adverse event reporting additional description:

For non-serious adverse events, the number of patient affected were the only value available, the number of occurrences were not recorded. Thus, the number of patient affected was entered in both "Subjects affected number" and "Occurrence all number" fields.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	Palbociclib + letrozole

Reporting group description:

Patients received palbociclib (125 mg oral) once daily on a discontinuous 3/4 weeks schedule (i.e 21 days of palbociclib followed by 7 days off) up to the day prior to surgery plus letrozole (2.5 mg, oral) daily up to the day prior to surgery.

Reporting group title	FEC100-Docetaxel

Reporting group description:

Patients received the standard chemotherapy consisting of 3 cycles of 5-FU, epirubicin, and cyclophosphamide (FEC100) followed by 3 cycles of Docetaxel:
FEC100 (cycles 1 to 3) ddministrated every 3 weeks (5-FU: 500 mg/m2, 30 minutes IV infusion; Epirubicin: 100 mg/m2, 10 minutes IV infusion, Cyclophosphamide: 500 mg/m2, 30 minutes IV infusion
Docetaxel (cycles 4 to 6) administered every 3 weeks, beginning 3 weeks after the last administration of FEC100 (Docetaxel : 100 mg/m2, 60 minutes IV infusion)

Serious adverse events	Palbociclib + letrozole	FEC100-Docetaxel	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 52 (15.38%)	16 / 52 (30.77%)	
number of deaths (all causes)	6	1	
number of deaths resulting from adverse events	1	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma endometrial			
subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ileocecal valve carcinoma			
subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Low grade lymphoma			

subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Infusion site extravasation			
subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Chronic subdural hematoma			
subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Transient ischemic attack			
subjects affected / exposed	0 / 52 (0.00%)	1 / 52 (1.92%)	
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			
Febrile aplasia			
subjects affected / exposed	0 / 52 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	1 / 52 (1.92%)	8 / 52 (15.38%)	
occurrences causally related to treatment / all	1 / 1	8 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 52 (1.92%)	3 / 52 (5.77%)	
occurrences causally related to treatment / all	1 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			

subjects affected / exposed	0 / 52 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucositis Oral			
subjects affected / exposed	0 / 52 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suicide			
subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Infections and infestations			
Bilateral pneumonia			
subjects affected / exposed	0 / 52 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial infection			
subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colonic abscess			
subjects affected / exposed	0 / 52 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kidney infection			
subjects affected / exposed	0 / 52 (0.00%)	1 / 52 (1.92%)	
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	Palbociclib + letrozole	FEC100-Docetaxel	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	52 / 52 (100.00%)	52 / 52 (100.00%)	
Vascular disorders			
Hot Flashes			
subjects affected / exposed	20 / 52 (38.46%)	1 / 52 (1.92%)	
occurrences (all)	20	1	
Hypertension			
subjects affected / exposed	3 / 52 (5.77%)	2 / 52 (3.85%)	
occurrences (all)	3	2	
Lymphocele			
subjects affected / exposed	3 / 52 (5.77%)	5 / 52 (9.62%)	
occurrences (all)	3	5	
General disorders and administration site conditions			
Decrease appetite			
subjects affected / exposed	2 / 52 (3.85%)	17 / 52 (32.69%)	
occurrences (all)	2	17	
Asthenia			
subjects affected / exposed	21 / 52 (40.38%)	33 / 52 (63.46%)	
occurrences (all)	21	33	
Pain			
subjects affected / exposed	3 / 52 (5.77%)	5 / 52 (9.62%)	
occurrences (all)	3	5	
Fatigue			
subjects affected / exposed	11 / 52 (21.15%)	14 / 52 (26.92%)	
occurrences (all)	11	14	
Fever			
subjects affected / exposed	1 / 52 (1.92%)	7 / 52 (13.46%)	
occurrences (all)	1	7	
Hyperthermia			
subjects affected / exposed	2 / 52 (3.85%)	5 / 52 (9.62%)	
occurrences (all)	2	5	
Illness			
subjects affected / exposed	0 / 52 (0.00%)	3 / 52 (5.77%)	
occurrences (all)	0	3	
Xerosis			

subjects affected / exposed	1 / 52 (1.92%)	6 / 52 (11.54%)	
occurrences (all)	1	6	
Reproductive system and breast disorders			
Vulvovaginal dryness			
subjects affected / exposed	3 / 52 (5.77%)	1 / 52 (1.92%)	
occurrences (all)	3	1	
Respiratory, thoracic and mediastinal disorders			
Dyspnea			
subjects affected / exposed	2 / 52 (3.85%)	10 / 52 (19.23%)	
occurrences (all)	2	10	
Epistaxis			
subjects affected / exposed	3 / 52 (5.77%)	6 / 52 (11.54%)	
occurrences (all)	3	6	
Nasopharyngitis			
subjects affected / exposed	1 / 52 (1.92%)	5 / 52 (9.62%)	
occurrences (all)	1	5	
Rhinitis			
subjects affected / exposed	1 / 52 (1.92%)	6 / 52 (11.54%)	
occurrences (all)	1	6	
Cough			
subjects affected / exposed	2 / 52 (3.85%)	3 / 52 (5.77%)	
occurrences (all)	2	3	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	3 / 52 (5.77%)	6 / 52 (11.54%)	
occurrences (all)	3	6	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	5 / 52 (9.62%)	14 / 52 (26.92%)	
occurrences (all)	5	14	
Aspartate aminotransferase increased			
subjects affected / exposed	6 / 52 (11.54%)	12 / 52 (23.08%)	
occurrences (all)	6	12	
Hyperchloraemia			

subjects affected / exposed	0 / 52 (0.00%)	3 / 52 (5.77%)	
occurrences (all)	0	3	
Creatinine increased			
subjects affected / exposed	7 / 52 (13.46%)	3 / 52 (5.77%)	
occurrences (all)	7	3	
Gamma-glutamyltransferase increased			
subjects affected / exposed	9 / 52 (17.31%)	19 / 52 (36.54%)	
occurrences (all)	9	19	
Hypercalcaemia			
subjects affected / exposed	3 / 52 (5.77%)	1 / 52 (1.92%)	
occurrences (all)	3	1	
Blood alkaline phosphatase increased			
subjects affected / exposed	7 / 52 (13.46%)	3 / 52 (5.77%)	
occurrences (all)	7	3	
Weight decreased			
subjects affected / exposed	1 / 52 (1.92%)	8 / 52 (15.38%)	
occurrences (all)	1	8	
Cardiac disorders			
Oedema peripheral			
subjects affected / exposed	2 / 52 (3.85%)	10 / 52 (19.23%)	
occurrences (all)	2	10	
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 52 (11.54%)	10 / 52 (19.23%)	
occurrences (all)	6	10	
Dysgeusia			
subjects affected / exposed	1 / 52 (1.92%)	17 / 52 (32.69%)	
occurrences (all)	1	17	
Neuropathy peripheral			
subjects affected / exposed	0 / 52 (0.00%)	9 / 52 (17.31%)	
occurrences (all)	0	9	
Paraesthesia			
subjects affected / exposed	2 / 52 (3.85%)	8 / 52 (15.38%)	
occurrences (all)	2	8	
Blood and lymphatic system disorders			

Anemia			
subjects affected / exposed	22 / 52 (42.31%)	38 / 52 (73.08%)	
occurrences (all)	22	38	
Leukopenia			
subjects affected / exposed	38 / 52 (73.08%)	17 / 52 (32.69%)	
occurrences (all)	38	17	
Lymphopenia			
subjects affected / exposed	9 / 52 (17.31%)	25 / 52 (48.08%)	
occurrences (all)	9	25	
Neutropenia			
subjects affected / exposed	42 / 52 (80.77%)	26 / 52 (50.00%)	
occurrences (all)	42	26	
Thrombocytopenia			
subjects affected / exposed	15 / 52 (28.85%)	6 / 52 (11.54%)	
occurrences (all)	15	6	
Eye disorders			
Increased tear secretion			
subjects affected / exposed	1 / 52 (1.92%)	10 / 52 (19.23%)	
occurrences (all)	1	10	
Conjunctivitis			
subjects affected / exposed	0 / 52 (0.00%)	3 / 52 (5.77%)	
occurrences (all)	0	3	
Dry eye			
subjects affected / exposed	1 / 52 (1.92%)	4 / 52 (7.69%)	
occurrences (all)	1	4	
Gastrointestinal disorders			
Dry mouth			
subjects affected / exposed	2 / 52 (3.85%)	6 / 52 (11.54%)	
occurrences (all)	2	6	
Constipation			
subjects affected / exposed	5 / 52 (9.62%)	13 / 52 (25.00%)	
occurrences (all)	5	13	
Diarrhoea			
subjects affected / exposed	3 / 52 (5.77%)	17 / 52 (32.69%)	
occurrences (all)	3	17	
Abdominal pain			

subjects affected / exposed	0 / 52 (0.00%)	4 / 52 (7.69%)	
occurrences (all)	0	4	
Upper abdominal pain			
subjects affected / exposed	4 / 52 (7.69%)	7 / 52 (13.46%)	
occurrences (all)	4	7	
Stomatitis			
subjects affected / exposed	6 / 52 (11.54%)	19 / 52 (36.54%)	
occurrences (all)	6	19	
Nausea			
subjects affected / exposed	5 / 52 (9.62%)	37 / 52 (71.15%)	
occurrences (all)	5	37	
Gastrooesophageal reflux disease			
subjects affected / exposed	3 / 52 (5.77%)	1 / 52 (1.92%)	
occurrences (all)	3	1	
Aphthous ulcer			
subjects affected / exposed	7 / 52 (13.46%)	7 / 52 (13.46%)	
occurrences (all)	7	7	
Vomiting			
subjects affected / exposed	1 / 52 (1.92%)	10 / 52 (19.23%)	
occurrences (all)	1	10	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	2 / 52 (3.85%)	26 / 52 (50.00%)	
occurrences (all)	2	26	
Erythema			
subjects affected / exposed	1 / 52 (1.92%)	4 / 52 (7.69%)	
occurrences (all)	1	4	
Pruritus			
subjects affected / exposed	5 / 52 (9.62%)	2 / 52 (3.85%)	
occurrences (all)	5	2	
Dry skin			
subjects affected / exposed	5 / 52 (9.62%)	4 / 52 (7.69%)	
occurrences (all)	5	4	
Acral peeling skin syndrome			
subjects affected / exposed	0 / 52 (0.00%)	16 / 52 (30.77%)	
occurrences (all)	0	16	

Nail disorder			
subjects affected / exposed	0 / 52 (0.00%)	13 / 52 (25.00%)	
occurrences (all)	0	13	
Renal and urinary disorders			
Urinary tract infection			
subjects affected / exposed	1 / 52 (1.92%)	3 / 52 (5.77%)	
occurrences (all)	1	3	
Blood urea increased			
subjects affected / exposed	2 / 52 (3.85%)	4 / 52 (7.69%)	
occurrences (all)	2	4	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	9 / 52 (17.31%)	20 / 52 (38.46%)	
occurrences (all)	9	20	
Muscle spasms			
subjects affected / exposed	3 / 52 (5.77%)	3 / 52 (5.77%)	
occurrences (all)	3	3	
Back pain			
subjects affected / exposed	2 / 52 (3.85%)	3 / 52 (5.77%)	
occurrences (all)	2	3	
Musculoskeletal pain			
subjects affected / exposed	3 / 52 (5.77%)	1 / 52 (1.92%)	
occurrences (all)	3	1	
Pain in extremity			
subjects affected / exposed	3 / 52 (5.77%)	1 / 52 (1.92%)	
occurrences (all)	3	1	
Myalgia			
subjects affected / exposed	3 / 52 (5.77%)	18 / 52 (34.62%)	
occurrences (all)	3	18	
Infections and infestations			
Vulvovaginal mycotic infection			
subjects affected / exposed	0 / 52 (0.00%)	4 / 52 (7.69%)	
occurrences (all)	0	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 January 2015	- In 2014, preclinical and clinical data demonstrated that the anti-proliferation effect of palbociclib was reversible shortly after the end of treatment. To avoid relapse and disease progression between the end of palbociclib treatment and surgery, the treatment schedule was modified in Arm A to stop the palbociclib treatment 1 day instead of 14 days before surgery. - The primary objective was modified to include only the local evaluation (at the investigator sites) of the RCB. The central RCB evaluation was then evaluated as secondary objective. - The secondary objective disease-free survival was clarified to be evaluate as the invasive disease-free survival.
15 December 2015	In 2015, the results of the PALOMA-1 and PALOMA-3 studies showed that palbocilib increased hormonal therapy-incuded PFS in the metastatic setting. Based on these results, the investigators decided to include luminal A N- patients in the NEOPAL study to receive a neoadjuvant treatment of palbociclib plus letrozole. These patients were then followed in an open cohort.

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.

Recruited patients were mostly luminal B breast cancer with very limited number of luminal A.
RCB might not be the most suitable primary Endpoint for the evaluation of neoadjuvant adjuvant therapy.
53 patients were recruited by arm, 60 were planned

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/30307466