Clinical trial results:
A Phase II Study of Palbociclib plus Fulvestrant versus Placebo plus Fulvestrant for pretreated patients with ER+/HER2- Metastatic Breast Cancer.

Summary

EudraCT number	2014-005387-15
Trial protocol	BE GB IT
Global end of trial date	22 December 2022

Results information

Result version number	v1 (current)
This version publication date	27 March 2024
First version publication date	27 March 2024

Trial information

Trial identification

Sponsor protocol code	IBCSG 53-14

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02536742
WHO universal trial number (UTN)	-
Other trial identifiers	Breast International Group: BIG_14-04, Pfizer Inc.: WI198393

Notes:

Sponsors

Sponsor organisation name	ETOP IBCSG Partners Foundation
Sponsor organisation address	Effingerstrasse 33, Bern, Switzerland, 3008
Public contact	ETOP IBCSG Partners Regulatory Office, ETOP IBCSG Partners Foundation, +41 31 511 94 00, ibcsg-regulatory@etop.ibcsg.org
Scientific contact	ETOP IBCSG Partners Regulatory Office, ETOP IBCSG Partners Foundation, +41 31 511 94 00, ibcsg-regulatory@etop.ibcsg.org

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	28 August 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 August 2020
Global end of trial reached?	Yes
Global end of trial date	22 December 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This is a single-arm phase II trial for postmenopausal patients receiving fulvestrant and palbociclib for ER+ / HER2-negative metastatic or locally advanced breast cancer who have progressed under previous endocrine therapy. The primary objective is to interrogate in a prospective manner a series of potential biomarkers, which will be assessed for their association with progression-free survival (PFS).

Protection of trial subjects:

Participating institutions' ethics committees or Institutional Review Boards approved the trial according to local laws and regulations. All patients gave written informed consent, and the trial was performed in compliance with the Helsinki Declaration. The Data Safety and Monitoring Board reviewed the data from this research throughout the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 January 2016
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 Kingdom: 3
Country: Number of subjects enrolled	Belgium: 75
Country: Number of subjects enrolled	Italy: 46
Worldwide total number of subjects	124
EEA total number of subjects	121

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)	79

From 65 to 84 years	45
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The first patient was registered on 29 August 2016 (randomized on 30 August 2016). The last patient was registered on 14 June 2019. The final accrual was 124 patients.

Pre-assignment

Screening details:

1 patient was registered but not enrolled under the original protocol and is not included.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

no blinding

Arms

Arm title	Fulvestrant + palbociclib

Arm description:

Patients are treated with fulvestrant (500mg im administered on days 1 and 15 of cycle 1, then on day 1 of every 28 days cycle) plus palbociclib (125mg po per day, continuously for 3 weeks followed by 1 week off; repeated at each subsequent cycle of 28 days). Patients will receive the treatment until progression, lack of tolerability, or patient declines further protocol treatment.

Fulvestrant is used in accordance with the currently approved SPC and regarded as non-investigational medicinal product (NIMPs), in accordance with the applicable EU legislation.

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 at a dose of 125 mg per day continuously for 3 weeks followed by 1 week off; repeated at each subsequent cycle of 28 days.

Number of subjects in period 1	Fulvestrant + palbociclib
Started	124
Completed	122
Not completed	2
Patient determined to have triple-negative breast	1
Never started treatment because of persistent base	1

Baseline characteristics

Reporting groups

Reporting group title	Overall Study

Reporting group description: -

Reporting group values	Overall Study	Total	
Number of subjects	124	124	
Age categorical Units: Subjects			
Adults (18-64 years)	79	79	
From 65-84 years	45	45	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	124	124	
Male	0	0	

Subject analysis sets

Subject analysis set title	Analysis Population
Subject analysis set type	Per protocol

Subject analysis set description:

There were 2 patients excluded who did not start protocol therapy or did not have the target disease, thus 122 patients in the clinical population.

Reporting group values	Analysis Population		
Number of subjects	122		
Age categorical Units: Subjects			
Adults (18-64 years)	78		
From 65-84 years	44		
85 years and over	0		
Gender categorical Units: Subjects			
Female	122		
Male	0		

End points

End points reporting groups

Reporting group title	Fulvestrant + palbociclib

Reporting group description:

Patients are treated with fulvestrant (500mg im administered on days 1 and 15 of cycle 1, then on day 1 of every 28 days cycle) plus palbociclib (125mg po per day, continuously for 3 weeks followed by 1 week off; repeated at each subsequent cycle of 28 days). Patients will receive the treatment until progression, lack of tolerability, or patient declines further protocol treatment.

Fulvestrant is used in accordance with the currently approved SPC and regarded as non-investigational medicinal product (NIMPs), in accordance with the applicable EU legislation.

Subject analysis set title	Analysis Population
Subject analysis set type	Per protocol

Subject analysis set description:

There were 2 patients excluded who did not start protocol therapy or did not have the target disease, thus 122 patients in the clinical population.

Primary: Number of Participants With and Without Progression Free Survival (PFS) Events

End point title	Number of Participants With and Without Progression Free Survival (PFS) Events[1]

End point description:

Time from treatment initiation until documented disease progression according to RECIST 1.1 or death, whichever occurs first

End point type	Primary

End point timeframe:

Maximum 36 months

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: No statistical analysis done

End point values	Analysis Population			
Subject group type	Subject analysis set			
Number of subjects analysed	122			
Units: Participants				
PFS event, Yes	92			
PFS event, No	30			

Statistical analyses

No statistical analyses for this end point

Secondary: Best Overall Response

End point title	Best Overall Response

End point description:

Best overall response is based on RECIST (Response evaluation criteria in solid tumors) 1.1 criteria and is defined as best response recorded from enrollment across all time points until disease progression. Confirmation of partial response (PR) or complete response (CR) by an additional scan was not requested in this trial (rationale: initially because of randomized placebo-controlled design;

subsequently because no hypothesis testing of progression-free survival, PFS, distribution relative to an historical control).

End point type	Secondary

End point timeframe:

From date of enrolment until patient's end of treatment visit (or a maximum of 12 months after EoT in the absence of tumor progression), assessed up to 48 months.

End point values	Analysis Population			
Subject group type	Subject analysis set			
Number of subjects analysed	122			
Units: Participants				
Complete response (CR)	6			
Partial response (PR)	20			
Stable disease (SD)	80			
Progressive disease (PD)	16			

Statistical analyses

No statistical analyses for this end point

Secondary: Best Overall Response of Complete Response (CR) or Partial Response (PR) or Stable Disease (SD)

End point title	Best Overall Response of Complete Response (CR) or Partial Response (PR) or Stable Disease (SD)

End point description:

Disease control is defined as best overall response of complete response (CR) or partial response (PR), or stable disease (SD) (or non-CR/non-PD, progressive disease, in the case of non-measurable disease only) lasting for at least 24 weeks, measured from enrollment until first documentation of progressive disease

End point type	Secondary

End point timeframe:

From date of enrolment until patient's end of treatment visit (or a maximum of 12 months after EoT in the absence of tumor progression), assessed up to 48 months.

End point values	Analysis Population			
Subject group type	Subject analysis set			
Number of subjects analysed	122			
Units: Participants				
Disease control not observed	33			
Disease control observed (CR or PR or SD)	89			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Maximum 36 months

Adverse event reporting additional description:

AEs were collected using Common Terminology Criteria for Adverse Events (CTCAE) v4.0. AEs were collected at the end of each cycle, from first dose of trial treatment until 28 days after all treatment discontinuation.

Assessment type	Systematic

Dictionary used

Dictionary name	NCI CTCAE
Dictionary version	4.0

Reporting groups

Reporting group title	Analysis Population

Reporting group description:

Palbociclib plus Fulvestrant
Palbociclib: 125 mg, orally, daily for 3 weeks followed by 1 week off; repeated at every 28 days cycle until progression, lack of tolerability, or patient declines further protocol treatment.
Fulvestrant: 500mg, intramuscularly on days 1 and 15 of cycle 1, then on day 1 (+/- 3 days) of every 28 days cycle until progression, lack of tolerability, or patient declines further protocol treatment.

Serious adverse events	Analysis Population		
Total subjects affected by serious adverse events			
subjects affected / exposed	89 / 122 (72.95%)		
number of deaths (all causes)	30		
number of deaths resulting from adverse events	0		
Investigations			
Neutrophil count decreased			
subjects affected / exposed	87 / 122 (71.31%)		
occurrences causally related to treatment / all	124 / 124		
deaths causally related to treatment / all	0 / 0		
Weight gain			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
White blood cell decreased			
subjects affected / exposed	5 / 122 (4.10%)		
occurrences causally related to treatment / all	5 / 5		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			

Depressed level of consciousness			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 122 (1.64%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Conjunctivitis			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	3 / 122 (2.46%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Mucositis oral			
subjects affected / exposed	3 / 122 (2.46%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Anorexia			

subjects affected / exposed	1 / 122 (0.82%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Analysis Population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	122 / 122 (100.00%)		
Vascular disorders			
Thromboembolic event			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences (all)	1		
Vascular disorders - Other			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences (all)	1		
Surgical and medical procedures			
Surgical and medical procedures - Other			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences (all)	1		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	4 / 122 (3.28%)		
occurrences (all)	4		
General disorders and administration site conditions - Other			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences (all)	1		
Pneumothorax			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences (all)	1		

Investigations			
GGT increased			
subjects affected / exposed	2 / 122 (1.64%)		
occurrences (all)	2		
Neutrophil count decreased			
subjects affected / exposed	39 / 122 (31.97%)		
occurrences (all)	56		
Platelet count decreased			
subjects affected / exposed	24 / 122 (19.67%)		
occurrences (all)	37		
Injury, poisoning and procedural complications			
Fracture			
subjects affected / exposed	2 / 122 (1.64%)		
occurrences (all)	2		
Cardiac disorders			
Sick sinus syndrome			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences (all)	1		
Nervous system disorders - Other			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences (all)	1		
Paresthesia			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences (all)	1		
Syncope			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	51 / 122 (41.80%)		
occurrences (all)	61		
Gastrointestinal disorders			

Ascites subjects affected / exposed occurrences (all)	1 / 122 (0.82%) 1		
Diarrhoea subjects affected / exposed occurrences (all)	17 / 122 (13.93%) 20		
Dysphagia subjects affected / exposed occurrences (all)	1 / 122 (0.82%) 1		
Mucositis management oral subjects affected / exposed occurrences (all)	1 / 122 (0.82%) 1		
Nausea subjects affected / exposed occurrences (all)	29 / 122 (23.77%) 32		
Skin and subcutaneous tissue disorders Skin and subcutaneous tissue disorders - Other subjects affected / exposed occurrences (all)	 1 / 122 (0.82%) 1		
Endocrine disorders Endocrine disorders - Other subjects affected / exposed occurrences (all)	 1 / 122 (0.82%) 1		
Musculoskeletal and connective tissue disorders Musculoskeletal and connective tissue disorder - Other subjects affected / exposed occurrences (all)	 1 / 122 (0.82%) 1		
Myalgia subjects affected / exposed occurrences (all)	1 / 122 (0.82%) 1		
Osteonecrosis of jaw subjects affected / exposed occurrences (all)	2 / 122 (1.64%) 2		
Infections and infestations			

Bronchial infection subjects affected / exposed occurrences (all) Infections and infestations - Other subjects affected / exposed occurrences (all) Upper respiratory infection subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all)	1 / 122 (0.82%) 1 1 / 122 (0.82%) 1 1 / 122 (0.82%) 1 1 / 122 (0.82%) 1		
Metabolism and nutrition disorders Hyperglycaemia subjects affected / exposed occurrences (all) Hyperuricemia subjects affected / exposed occurrences (all)	9 / 122 (7.38%) 9 3 / 122 (2.46%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 January 2017	Based on recommendations from the IBCSG DSMC, IBCSG decided to close the placebo arm of the PYTHIA study on 23 November 2016. The decision was taken after reviewing the current accrual (1 patient randomized since activation of the first center on 04 May 2016) and following the recent announcement by Pfizer that palbociclib received approval in the EU for the treatment of women with HR+/HER2- locally advanced or metastatic breast cancer. The approval also covers the use of palbociclib in combination with fulvestrant in women who have received prior endocrine therapy. The DSMC recommended to unblind the treatment of the one patient randomized, to inform the patient about her treatment assignment, and to offer her palbociclib if she has been randomized to placebo (n.b., per the code break form in the database, she had been assigned to palbociclib). Patients already consented and all future patients were to be informed of the closing of the placebo arm and that they would receive palbociclib and fulvestrant. The PYTHIA trial remained open for patient enrollment in Belgium but not in Italy. Amendment 1, which was distributed on 20 February 2017, implemented the design change to single-arm trial of 120 patients, with revised primary objective.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported