Clinical trial results:
“Neo-Adjuvant Treatment with the CDK4,6 inhibitor Palbociclib in HER2-positive and ER-positive breast cancer: effect on Ki67 and apoptosis before, during and after treatment“

Summary

EudraCT number	2014-001984-11
Trial protocol	IT
Global end of trial date	10 January 2019

Results information

Result version number	v1 (current)
This version publication date	06 July 2022
First version publication date	06 July 2022
Summary attachment (see zip file)	Napher2 Synopsis (Study Synopsis NA-PHER2_vers. 3.0_22Mar16.pdf)

Trial information

Trial identification

Sponsor protocol code	FM-14-B01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02530424
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	FONDAZIONE MICHELANGELO
Sponsor organisation address	Via Agostino Bertani 14, milano, Italy,
Public contact	Clinical Operation, Michelangelo Tech S.r.l, +39 0287086420, clinical.operation@fondazionemichelangelo.org
Scientific contact	Clinical Operation, Michelangelo Tech S.r.l, +39 0287086420, clinical.operation@fondazionemichelangelo.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	07 May 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 February 2018
Global end of trial reached?	Yes
Global end of trial date	10 January 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

. Characterize changes of Ki67 from baseline before therapy and at 2 weeks and at surgery (approximately 22 weeks after start of neoadjuvant therapy with HPPF).
. Characterize changes in apoptosis from baseline before therapy and at surgery (approximately 22 weeks after start of neoadjuvant therapy with HPPF).
. Study the tolerability profile of the combination

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Council on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed. Also, all participants gave written informed consent before data collection began.

Background therapy:

-

Evidence for comparator:

-

Actual start date of recruitment	14 May 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 103
Worldwide total number of subjects	103
EEA total number of subjects	103

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)	90
From 65 to 84 years	13
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First Patient Enrolled: 14 May 2015; Last Patient Enrolled: 16 Feb 2018; Country: Italy.

Pre-assignment

Screening details:

Female patients aged 18 years or older with histologically confirmed invasive unilateral breast cancer ER+, PgR known (positive for cohort C) suitable for neoadjuvant treatment. HER2 status centrally confirmed (HER2 3+ or neu amplified for cohorts A and B; HER2 1+/2+ without amplification for cohort C); Ki67 > 20% for cohort C; ECOG 0 or 1.

Period 1

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

Blinding implementation details:

Not applicable

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort A

Arm description:

Patients with ER positive tumors (> 10%) and HER2 3+ or neu amplified receive Trastuzumab+Pertuzumab+Palbociclib+Fulvestrant (HPPF)

Arm type	Experimental
Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

8 mg/kg loading dose IV, then 6 mg/kg IV q.3 wks (repeat for a total of 6 administrations)

Investigational medicinal product name	Pertuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

840 mg loading dose IV, then 420 mg IV q. 3 wks (repeat for a total of 6 administrations)

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

Dosage and administration details:

125 mg po q.d. x 21 q. 4 wks (= 1 cycle; repeat for a total of 5 cycles)

Investigational medicinal product name	Fulvestrant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for injection

Routes of administration	Intramuscular use

Dosage and administration details:

dose of 500 mg every 4 weeks (repeat for 5 times) with an additional 500 mg dose given two weeks after the initial dose (total administrations including the additional one = 6)

Arm title	Cohort B

Arm description:

Patients with ER positive tumors (> 10%) and HER2 3+ or neu amplified receive Trastuzumab+Pertuzumab+Palbociclib (HPP)

Arm type	Experimental
Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

8 mg/kg loading dose IV, then 6 mg/kg IV q.3 wks (repeat for a total of 6 administrations)

Investigational medicinal product name	Pertuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

840 mg loading dose IV, then 420 mg IV q. 3 wks (repeat for a total of 6 administrations)

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

Dosage and administration details:

125 mg po q.d. x 21 q. 4 wks (= 1 cycle; repeat for a total of 5 cycles)

Arm title	Cohort C

Arm description:

Patients with ER positive tumors (> 10%), PgR positive, HER2 1+/2+ (without amplification) and Ki67 > 20% receive Trastuzumab+Pertuzumab+Palbociclib+Fulvestrant (HPPF)

Arm type	Experimental
Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

8 mg/kg loading dose IV, then 6 mg/kg IV q.3 wks (repeat for a total of 6 administrations)

Investigational medicinal product name	Pertuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

840 mg loading dose IV, then 420 mg IV q. 3 wks (repeat for a total of 6 administrations)

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

Dosage and administration details:

125 mg po q.d. x 21 q. 4 wks (= 1 cycle; repeat for a total of 5 cycles)

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

Dosage and administration details:

dose of 500 mg every 4 weeks (repeat for 5 times) with an additional 500 mg dose given two weeks after the initial dose (total administrations including the additional one = 6)

Number of subjects in period 1	Cohort A	Cohort B	Cohort C
Started	36	39	28
Completed	30	26	23
Not completed	6	13	5
Not eligible	6	13	5

Baseline characteristics

Reporting groups	
Reporting group title	Cohort A
Reporting group description:	
Patients with ER positive tumors (> 10%) and HER2 3+ or neu amplified receive Trastuzumab+Pertuzumab+Palbociclib+Fulvestrant (HPPF)	
Reporting group title	Cohort B
Reporting group description:	
Patients with ER positive tumors (> 10%) and HER2 3+ or neu amplified receive Trastuzumab+Pertuzumab+Palbociclib (HPP)	
Reporting group title	Cohort C
Reporting group description:	
Patients with ER positive tumors (> 10%), PgR positive, HER2 1+/2+ (without amplification) and Ki67 > 20% receive Trastuzumab+Pertuzumab+Palbociclib+Fulvestrant (HPPF)	

Reporting group values	Cohort A	Cohort B	Cohort C
Number of subjects	36	39	28
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	50.3	48.5	51.2
standard deviation	± 10.3	± 11.8	± 12.3
Gender categorical Units: Subjects			
Women	36	39	28
Race Units: Subjects			
caucasian	36	39	28
T stage Units: Subjects			
T1c	2	2	2
T2	24	28	21
T3	7	8	4
T4d	3	1	1
Axillary lymph nodes status Units: Subjects			
N0	17	14	11

N1	15	24	15
N2	3	1	2
Missing	1	0	0
Histology Units: Subjects			
Ductal invasive	34	35	25
Lobular invasive	1	0	2
Other	1	4	1
Tumour grade Units: Subjects			
G2	12	18	13
G3	19	20	10
GX	4	1	5
Missing	1	0	0
Weight Units: kilogram(s)			
arithmetic mean	63.2	67.7	64.4
standard deviation	± 14.2	± 14.8	± 10.9
Largest Breast Lesion diameter by palpation Units: centimetre			
arithmetic mean	4.3	4.1	4.1
standard deviation	± 1.6	± 1.7	± 2.0
Axillary largest diameter by palpation Units: centimetre			
arithmetic mean	2.0	1.9	1.7
standard deviation	± 0.7	± 0.9	± 0.7

Reporting group values	Total		
Number of subjects	103		
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)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Women	103		

Race Units: Subjects			
caucasian	103		
T stage Units: Subjects			
T1c	6		
T2	73		
T3	19		
T4d	5		
Axillary lymph nodes status Units: Subjects			
N0	42		
N1	54		
N2	6		
Missing	1		
Histology Units: Subjects			
Ductal invasive	94		
Lobular invasive	3		
Other	6		
Tumour grade Units: Subjects			
G2	43		
G3	49		
GX	10		
Missing	1		
Weight Units: kilogram(s) arithmetic mean standard deviation	- -		
Largest Breast Lesion diameter by palpation Units: centimetre arithmetic mean standard deviation	- -		
Axillary largest diameter by palpation Units: centimetre arithmetic mean standard deviation	- -		

End points

End points reporting groups

Reporting group title	Cohort A
Reporting group description:	
Patients with ER positive tumors (> 10%) and HER2 3+ or neu amplified receive Trastuzumab+Pertuzumab+Palbociclib+Fulvestrant (HPPF)	
Reporting group title	Cohort B
Reporting group description:	
Patients with ER positive tumors (> 10%) and HER2 3+ or neu amplified receive Trastuzumab+Pertuzumab+Palbociclib (HPP)	
Reporting group title	Cohort C
Reporting group description:	
Patients with ER positive tumors (> 10%), PgR positive, HER2 1+/2+ (without amplification) and Ki67 > 20% receive Trastuzumab+Pertuzumab+Palbociclib+Fulvestrant (HPPF)	

Primary: Ki67 values

End point title	Ki67 values[1]
End point description:	
Changes of Ki67 from baseline before therapy and at 2 weeks	
End point type	Primary
End point timeframe:	
At week 2	

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: All objectives for efficacy and safety were assessed separately for each study cohort. No comparative analyses were planned

End point values	Cohort A	Cohort B	Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25	25	23	
Units: percent				
median (confidence interval 95%)	-24.0 (-31.0 to -17.1)	-25.7 (-31.7 to -19.6)	-29.5 (-35.5 to -23.5)	

Statistical analyses

No statistical analyses for this end point

Primary: Ki67 values

End point title	Ki67 values[2]
End point description:	
Changes of Ki67 from baseline before therapy and at surgery	
End point type	Primary
End point timeframe:	
At surgery (approximately 22 weeks after start of neoadjuvant therapy)	

Notes:

[2] - 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: All objectives for efficacy and safety were assessed separately for each study cohort. No comparative analyses were planned

End point values	Cohort A	Cohort B	Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25	25	23	
Units: percent				
median (confidence interval 95%)	-10.9 (-19.3 to -2.6)	-9.5 (-18.2 to -0.9)	-19.3 (-24.5 to 14.0)	

Statistical analyses

No statistical analyses for this end point

Primary: Apoptosis

End point title	Apoptosis[3]

End point description:

Changes from baseline before therapy and at 2 weeks

End point type	Primary

End point timeframe:

At baseline and at 2 weeks

Notes:

[3] - 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: All objectives for efficacy and safety were assessed separately for each study cohort. No comparative analyses were planned

End point values	Cohort A	Cohort B	Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25	25	23	
Units: percent				
median (confidence interval 95%)	-0.5 (-0.9 to -0.1)	-0.0 (-0.7 to 0.7)	-0.6 (-1.3 to -0.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Pathological Complete Response

End point title	Pathological Complete Response

End point description:

Absence of invasive cells in breast and axilla (ypT0-ypTis ypN0) at surgery

End point type	Secondary

End point timeframe:

At surgery

End point values	Cohort A	Cohort B	Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	30	23	26	
Units: subject				
Yes	8	0	5	
No	22	23	21	

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical response

End point title	Clinical response
End point description: Clinical objective response rate	
End point type	Secondary
End point timeframe: At surgery	

End point values	Cohort A	Cohort B	Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	30	26	23	
Units: Subject				
Complete response	15	9	3	
Partial response	14	14	15	
Stable disease	1	2	4	
Progressive disease	0	1	1	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Overall study	
Adverse event reporting additional description:	
Treatment Emergent Adverse Events	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups	
Reporting group title	Cohort A
Reporting group description:	
Patients with ER positive tumors (> 10%) and HER2 3+ or neu amplified receive Trastuzumab+Pertuzumab+Palbociclib+Fulvestrant (HPPF)	
Reporting group title	Cohort B
Reporting group description:	
Patients with ER positive tumors (> 10%) and HER2 3+ or neu amplified receive Trastuzumab+Pertuzumab+Palbociclib (HPP)	
Reporting group title	Cohort C
Reporting group description:	
Patients with ER positive tumors (> 10%), PgR positive, HER2 1+/2+ (without amplification) and Ki67 > 20% receive Trastuzumab+Pertuzumab+Palbociclib+Fulvestrant (HPPF)	

Serious adverse events	Cohort A	Cohort B	Cohort C
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 35 (0.00%)	0 / 39 (0.00%)	0 / 28 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

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

Non-serious adverse events	Cohort A	Cohort B	Cohort C
Total subjects affected by non-serious adverse events			
subjects affected / exposed	35 / 35 (100.00%)	38 / 39 (97.44%)	27 / 28 (96.43%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 35 (2.86%)	3 / 39 (7.69%)	2 / 28 (7.14%)
occurrences (all)	1	3	2
Aspartate aminotransferase increased			

subjects affected / exposed	1 / 35 (2.86%)	3 / 39 (7.69%)	2 / 28 (7.14%)
occurrences (all)	1	3	2
Vascular disorders			
Hot flush			
subjects affected / exposed	5 / 35 (14.29%)	0 / 39 (0.00%)	3 / 28 (10.71%)
occurrences (all)	5	0	3
Hypertension			
subjects affected / exposed	2 / 35 (5.71%)	4 / 39 (10.26%)	3 / 28 (10.71%)
occurrences (all)	2	4	3
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 35 (8.57%)	3 / 39 (7.69%)	4 / 28 (14.29%)
occurrences (all)	3	3	4
Dysgeusia			
subjects affected / exposed	3 / 35 (8.57%)	2 / 39 (5.13%)	2 / 28 (7.14%)
occurrences (all)	3	2	2
General disorders and administration site conditions			
Mucosal inflammation			
subjects affected / exposed	11 / 35 (31.43%)	13 / 39 (33.33%)	7 / 28 (25.00%)
occurrences (all)	11	13	7
Pyrexia			
subjects affected / exposed	4 / 35 (11.43%)	11 / 39 (28.21%)	7 / 28 (25.00%)
occurrences (all)	4	11	7
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	24 / 35 (68.57%)	25 / 39 (64.10%)	14 / 28 (50.00%)
occurrences (all)	24	25	14
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	26 / 35 (74.29%)	23 / 39 (58.97%)	15 / 28 (53.57%)
occurrences (all)	26	23	15
Stomatitis			
subjects affected / exposed	5 / 35 (14.29%)	11 / 39 (28.21%)	8 / 28 (28.57%)
occurrences (all)	5	11	8
Respiratory, thoracic and mediastinal disorders			

Epistaxis			
subjects affected / exposed	8 / 35 (22.86%)	7 / 39 (17.95%)	2 / 28 (7.14%)
occurrences (all)	8	7	2
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	2 / 35 (5.71%)	7 / 39 (17.95%)	2 / 28 (7.14%)
occurrences (all)	2	7	2
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 35 (2.86%)	2 / 39 (5.13%)	2 / 28 (7.14%)
occurrences (all)	1	2	2
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 35 (2.86%)	1 / 39 (2.56%)	3 / 28 (10.71%)
occurrences (all)	1	1	3
Infections and infestations			
Cystitis			
subjects affected / exposed	1 / 35 (2.86%)	2 / 39 (5.13%)	2 / 28 (7.14%)
occurrences (all)	1	2	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 July 2015	The protocol was first amended (Protocol Version 2, amendment 1, July 6, 2015) because accumulating data on safety and tolerability of palbociclib in combination with other antineoplastic agents allowed to better clarify intervention with palbociclib in the presence of defined types and grades of adverse events. In addition, patients who experience grade and frequency of adverse events requiring decrease of the palbociclib dose level to 75 mg, if clinically stable and fully recovered from the adverse event, were allowed to re-escalate to 100 mg per investigator's discretion.
22 March 2016	A second amendment (amendment 2, Protocol Version 3, March 22, 2016) was activated to allow inclusion of new study cohorts based on available preclinical and clinical literature data. The two new cohorts were Cohort B: Patients with ER positive tumors (> 10%) and HER2 3+ or neu amplified who were planned to receive Trastuzumab+Pertuzumab+Palbociclib (HPP) without fulvestrant. Allocation to Cohort B had to be started after completion of recruitment to Cohort A. Cohort C: Patients with ER positive tumors (> 10%), PgR positive, HER2 1+/2+ and Ki67 > 20% who were planned to receive Trastuzumab+Pertuzumab+Palbociclib+Fulvestrant (HPPF).

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.

Due to the somehow slower rate of accrual in Cohort C, the registration of patients in this cohort was discontinued on February 2018 although less than 32 patients were registered.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/29326029

http://www.ncbi.nlm.nih.gov/pubmed/29326028

http://www.ncbi.nlm.nih.gov/pubmed/35013314