Clinical trial results:
PERtuzumab-trastuzumab plus lEetrozoLe In endocrine Sensitive breast cancer: a phase II neoAdjuvant study

Summary

EudraCT number	2013-002662-40
Trial protocol	IT
Global end of trial date	12 January 2018

Results information

Result version number	v1 (current)
This version publication date	01 November 2022
First version publication date	01 November 2022
Summary attachment (see zip file)	Medica Journal article (1-s2.0-S0923753419311937-main.pdf)

Trial information

Trial identification

Sponsor protocol code	AS.T.R.O.BC01-13

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	ASTRO Association for Translational research in Oncology.
Sponsor organisation address	Via G. Mameli 3/1, Genova, Italy, 16122
Public contact	Gian Luca De Salvo, Istituto Oncologico Veneto, 0039 0498215704, clinical.trial@ioveneto.it
Scientific contact	Gian Luca De Salvo, Istituto Oncologico Veneto, 0039 0498215704, clinical.trial@ioveneto.it

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 July 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 January 2018
Global end of trial reached?	Yes
Global end of trial date	12 January 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

to evaluate the rate of pathologic complete response (pCR), as defined as complete disappearance of invasive tumor in breast and axillary nodes

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Council for Harmonisation (ICH) guideline E6: Good Clinical Practice (GCP).

As applicable according to local regulations, the protocol and all protocol amendments were reviewed and approved by Italian Competent Authority AIFA.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 September 2013
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: 44
Worldwide total number of subjects	44
EEA total number of subjects	44

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)	22
From 65 to 84 years	22

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

From January 2014 to July 2017, 64 patients from 8 Institutions were enrolled, and 61 were evaluable for molecular response after 2 weeks of letrozole treatment; after the molecular evaluation 44 patients were considered for the analysis.

Pre-assignment

Screening details:

Patients were included in the study only if they met all the following criteria
- female patients with primary diagnosis of infiltrating breast cancer
- HR positivity (ER ≥ 10% and/or PgR ≥10%) and HER2 positivity (IHC 3+ or FISH/CISH amplification) as assessed by local laboratory
- Stage II-IIIA
- age >18 yrs
- ECOG Performance Status 0-1

Period 1

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

Arms

Arm title	Trastuzumab+Pertuzumab

Arm description:

Trastuzumab+Pertuzumab for the molecular responders should be administered for five 21-day cycles prior to surgery, that should be performed within 3 weeks from the last iv therapy infusion.

Arm type	single arm
Investigational medicinal product name	Pertuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Pertuzumab was administered as an intravenous infusion on Day 1 of the first treatment cycle as a loading dose of 840 mg. The following 4 courses were administered at the dose of 420 mg on Day 1 every 3 weeks.
Initial infusions of pertuzumab was administered over 60 (± 10) minutes and patients observed for 60 minutes from the end of infusion for infusion-related symptoms such as fever, chills, hypotension, shortness of breath, skin rash, headache, nausea and/or vomiting.
Interruption or slowing of the infusion could be made to reduce such symptoms. If the infusion was well tolerated, subsequent infusions could be administered over 30 to 60 (± 10) minutes, with patients observed for a further 30 minutes.

Number of subjects in period 1	Trastuzumab+Pertuzumab
Started	44
Completed	44

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	44	44	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	22	22	
From 65-84 years	22	22	
Age continuous Units: years			
median	64.1		
full range (min-max)	49.5 to 83.8	-	
Gender categorical Units: Subjects			
Female	44	44	
Male	0	0	
molecular responders patients Units: Subjects			
molecular responders	44	44	
KI67 Units: percent			
median	30		
full range (min-max)	7 to 90	-	

Subject analysis sets

Subject analysis set title	Pertuzumab+Trastuzumab
Subject analysis set type	Full analysis

Subject analysis set description:
Molecular responders

Reporting group values	Pertuzumab+Trastuzumab		
Number of subjects	44		
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)	22		
From 65-84 years	22		
Age continuous			
Units: years			
median	64.1		
full range (min-max)	49.5 to 83.8		
Gender categorical			
Units: Subjects			
Female	44		
Male	44		
molecular responders patients			
Units: Subjects			
molecular responders	44		
KI67			
Units: percent			
median	30		
full range (min-max)	7 to 90		

End points

End points reporting groups

Reporting group title	Trastuzumab+Pertuzumab
Reporting group description:	
Trastuzumab+Pertuzumab for the molecular responders should be administered for five 21-day cycles prior to surgery, that should be performed within 3 weeks from the last iv therapy infusion.	
Subject analysis set title	Pertuzumab+Trastuzumab
Subject analysis set type	Full analysis
Subject analysis set description:	
Molecular responders	

Primary: Number of pCR in responder patients

End point title	Number of pCR in responder patients
End point description:	
Pathologic response: A pathologic complete response (pCR) was defined the complete absence of infiltrating tumor cells in the breast and in the lymph nodes. Residual in situ disease (DCIS) was included in the pCR category.	
End point type	Primary
End point timeframe:	
From the end of Screening to Surgery	

End point values	Trastuzumab+ Pertuzumab	Pertuzumab+Tr astuzumab		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	44	44[1]		
Units: number	9	9		

Notes:

[1] - workaround for single arm submission

Statistical analyses

Statistical analysis title	Efficacy results
Statistical analysis description:	
Sixty-four patients were enrolled, 44 were classified as molecular responders. All these patients completed the assigned treatment with letrozole-trastuzumab-pertuzumab and underwent surgery. A pCR was observed in 9/44 cases (20.5%, 95%CI 11.1%-34.5%).	
Comparison groups	Trastuzumab+Pertuzumab v Pertuzumab+Trastuzumab
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	≤ 0.05
Method	Wilson score method

Notes:

[2] - A phase II study in order to estimate the rate of pCR after use of Trastuzumab +Pertuzumab

Adverse events

Adverse events information	
Timeframe for reporting adverse events: from 1st dose of Pertuzumab to withdrawal of therapy/Study conclusion	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22

Reporting groups	
Reporting group title	safety evaluable population
Reporting group description: all subjects enrolled in the study who received at least 1 dose of the investigational study treatment (ie, pertuzumab).	

Serious adverse events	safety evaluable population		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 44 (6.82%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary oedema			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Urinary tract infection			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	safety evaluable population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	29 / 44 (65.91%)		
General disorders and administration site conditions			
fever			
subjects affected / exposed	4 / 44 (9.09%)		
occurrences (all)	4		
Fatigue			
subjects affected / exposed	11 / 44 (25.00%)		
occurrences (all)	11		
Eye disorders			
Conjunctivitis			
subjects affected / exposed	2 / 44 (4.55%)		
occurrences (all)	2		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	11 / 44 (25.00%)		
occurrences (all)	11		
Abdominal pain			
subjects affected / exposed	2 / 44 (4.55%)		
occurrences (all)	2		
Nausea			
subjects affected / exposed	2 / 44 (4.55%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	2 / 44 (4.55%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 44 (6.82%)		
occurrences (all)	3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 January 2014	Amendment 1, dated 15 Jan 2014, was implemented due to administrative reasons (adding of one clinical centre and change of one local PI) and to accomplish with the Competent Authority suggestions. This amendement specified the following modifications: In the paragraph 5.6 Pre-study, concomitant, and post-study treatment(s), the text: "Any oral, injected or implanted hormonal methods of contraception" was changed with "Hormonal replacement therapy" - In the paragraph 6.3 "LVEF ≤ 50%" was changed with "LVEF ≤ 45%" - Pertuzumab and trastuzumab could be administered on the same day (day 1) if no reactions at cycle 1 for the following 4 cycles. - The centre of Vicenza was added and the PI of the Milan INT centre was changed from prof. De Braud to dr Giulia Bianchi
01 July 2016	Amendment 2, dated 01 July 2016, was implemented to prolong the recruitment period of the study due to the trend registered until then that was slower than expected. Moreover, there were some changes in the participating centres. A new version of the pertuzumab IB was implemented. This amendement specified the following modifications: - Recruitment period prolonged from 24 to 44 months - Estimated date of last subject completed from March 2016 to October 2017 - Changes in the number and list of participating centres: from 12 to 10 clinical centres. Aviano and Trento were added, Pisa and Candiolo were excluded. - Investigator's Brochure of Perejeta Ed. 14_02/2015 was implemented
01 June 2017	Amendment 3, dated 01 June 2017, was implemented to further prolong the recruitment period of the study. Moreover, there was an update in the translational section of the study, with some changes in the planned analyses. A new version of the pertuzumab IB was implemented. Finally, some administrative changes were implemented, change of the sponsor legal representative amd changes in the participating centres. This amendement specified the following modifications: - Change of legal representative of the sponsor from prof. Conte to dr Bengala - Recruitment period prolonged from 44 to 52 months - Change of the estimated date of last subject completed from October 2017 to May 2018 - Changes in the translational biomarker analyses eliminating the analysis of pAKT and adding a panel of other relevant cancer-realted genes, pTEN, tumor infiltrating lymphocytes - Changes in the list of the participating centres: Verona e Vicenza were excluded. Change of the PI of Udine from dr Puglisi to dr Russo - Investigator's Brochure of Perejeta Ed. 16_02/2017 was implemented

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported