Clinical trial results:
PAM50 HER2-enriched phenotype as a predictor of early response to neoadjuvant lapatinib plus trastuzumab in Stage I to IIIA HER2-positive breast cancer

Summary

EudraCT number	2013-001036-22
Trial protocol	ES
Global end of trial date	26 November 2018

Results information

Result version number	v1 (current)
This version publication date	05 May 2022
First version publication date	05 May 2022
Summary attachment (see zip file)	SOLTI-1114_Sinopsys_CSR_ENG (PAMELA_Sinopsys_CSR_V1.0_10SEP2018_ENG-final.pdf)

Trial information

Trial identification

Sponsor protocol code	SOLTI-1114

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01973660
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	SOLTI
Sponsor organisation address	C/Balmes 89 3-7, Barcelona, Spain, 08008
Public contact	Investigación Clínica, SOLTI, 34 933436302, regsolti@gruposolti.org
Scientific contact	Investigación Clinica, SOLTI, 34 933436302, regsolti@gruposolti.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	10 September 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 September 2018
Global end of trial reached?	Yes
Global end of trial date	26 November 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the ability of the PAM50 HER2-enriched (HER2-E) subtype to predict pathological complete response in the breast (pCRB) to dual HER2 blockade with lapatinib and trastuzumab, with or without endocrine therapy, at the time of surgery.

Protection of trial subjects:

All patients received written and verbal information regarding the study. The given information emphasised that participation in the study was voluntary and that the patient could withdraw from the study at any time and for any reason. All patients were given the opportunity to ask questions about the study and were given sufficient time to decide whether to participate in the study.
Before any study-related procedures, the informed consent form was signed and personally dated by the patient (or their legally acceptable representative and/or witness, as applicable) and by the person who conducted the informed consent discussion. The consent included information that data was recorded, collected, processed and could be transferred to European Economic Area (EEA) or non-EEA countries. In accordance with the European Union Data Protection Directive (95/46/EC), the data did not identify any person taking part in the study.

Background therapy:

At present, HER2 status is defined in the clinical setting with the IHC/ISH technique; however, in recent studies it has been seen that the clinically defined HER+ population is not biologically homogeneous and that determining gene expression profiles can identify the different intrinsic molecular subtypes53,58, that are predominantly of the HER2-E subtype in HER2+/ER- disease (50-60%) and of the luminal A/B subtype in HER2+/ER+ disease (50-60%). Thus, gene expression profiling may likely provide additional information apart from the HR status. In fact, in the XENA study, a recent, small retrospective trial, it was shown that the HER2-E subtype determined using the PAM50 platform predicts the response to the trastuzumab-based neoadjuvant chemotherapy regardless of HR status59. Moreover, the NOAH study verified that the HER2-E subtype determined by the PAM50 platform and the PAM50 ROR groups predict pCR and disease-free survival after trastuzumab-based chemotherapy58.

Based on the above, we present the hypothesis that the PAM50-determined HER2-E subtype predicts the response to the neoadjuvant dual HER2 blockade, with or without endocrine therapy, in early stage HER2+ breast cancer (stage I-IIIA).

Evidence for comparator: -

Actual start date of recruitment	15 July 2013
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	Spain: 151
Worldwide total number of subjects	151
EEA total number of subjects	151

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)	151
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between October 2013 and December 2015, a total number of 216 patients were screened and signed the informed consent. Of these, 151 patients were Enrolled into the study. For the remaining 65 patients, the reasons for non-enrolment are listed in the table below, as documented in the CRF End of Selection form.

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	151
Number of subjects completed	151

Period 1

Period 1 title	Treatment period
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Total sample
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Lapatinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 1000 mg; administered once daily	
Investigational medicinal product name	Transtuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details: Loading dose of 8 mg followed by 6 mg/kg, administered every 3 weeks.	
Investigational medicinal product name	Letrozole or Tamoxifen
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: For HR (+) Letrozole: 2.5 mg; administered daily Tamoxifen: 20 mg; administered daily	
Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

80 mg/m²; administered once weekly

Number of subjects in period 1	Total sample
Started	151
Completed	144
Not completed	7
Physician decision	1
Consent withdrawn by subject	1
Lack of efficacy	5

Period 2

Period 2 title	D-14
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Total sample
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Lapatinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 1000 mg; administered once daily	
Investigational medicinal product name	Transtuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details: Loading dose of 8 mg followed by 6 mg/kg, administered every 3 weeks.	
Investigational medicinal product name	Letrozole or Tamoxifen
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

For HR (+)
Letrozole: 2.5 mg; administered daily
Tamoxifen: 20 mg; administered daily

Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

80 mg/m²; administered once weekly

Number of subjects in period 2	Total sample
Started	144
Completed	144

Baseline characteristics

Reporting groups	
Reporting group title	Treatment period

Reporting group description: -

Reporting group values	Treatment period	Total	
Number of subjects	151	151	
Age categorical Units: Subjects			
Adults >18 years	151	151	
Age continuous Units: years			
geometric mean	55		
full range (min-max)	30 to 86	-	
Gender categorical Units: Subjects			
Female	151	151	

End points

End points reporting groups

Reporting group title	Total sample
Reporting group description: -	
Reporting group title	Total sample
Reporting group description: -	

Primary: Ability of the HER2-E subtype to predict pCR in breast

End point title	Ability of the HER2-E subtype to predict pCR in breast
End point description:	
End point type	Primary
End point timeframe:	
Between October 2013 and December 2015, a total number of 216 patients were screened and signed the informed consent. Of these, 151 patients were Enrolled into the study.	

End point values	Total sample	Total sample		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	44		
Units: Subjects				
HER2-E	41	3		
non HER2-E	5	39		

Statistical analyses

Statistical analysis title	Primary efficacy endpoint
Comparison groups	Total sample v Total sample
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.0004
Method	Chi-squared corrected
Parameter estimate	Odds ratio (OR)
Point estimate	6.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.3
upper limit	16.8

Secondary: Ability of the HER2-E subtype to predict pCR in breast and axila

End point title	Ability of the HER2-E subtype to predict pCR in breast and axila

End point description:

End point type	Secondary

End point timeframe:

Between October 2013 and December 2015, a total number of 216 patients were screened and signed the informed consent. Of these, 151 patients were Enrolled into the study

End point values	Total sample	Total sample		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	151	137		
Units: Subjects				
HER2-E	35	53		
non HER2-E	5	8		

Statistical analyses

No statistical analyses for this end point

Secondary: pCR depending on Gene expression changes

End point title	pCR depending on Gene expression changes

End point description:

End point type	Secondary

End point timeframe:

14 days

End point values	Total sample			
Subject group type	Reporting group			
Number of subjects analysed	144			
Units: percent				
number (confidence interval 95%)				
Total	31 (24 to 39)			
luminal A	8 (3 to 22)			
luminal B	25 (14 to 69)			
HER2-E	14 (12 to 69)			
Basal-Like	38 (14 to 69)			
Normal-Like	49 (37 to 61)			

Statistical analyses

No statistical analyses for this end point

Secondary: Molecular subtype at day 14

End point title	Molecular subtype at day 14

End point description:

End point type	Secondary

End point timeframe:

14 days

End point values	Total sample			
Subject group type	Reporting group			
Number of subjects analysed	144			
Units: Subjects				
Luminal A	36			
Luminal B	4			
Her2-E	26			
Basal-Like	8			
Normal-Like	70			

Statistical analyses

No statistical analyses for this end point

Secondary: pCR rates according to changes in subtype

End point title	pCR rates according to changes in subtype

End point description:

End point type	Secondary

End point timeframe:

15 Days

End point values	Total sample			
Subject group type	Reporting group			
Number of subjects analysed	144			
Units: Subjects				
Normal- Like/ Her2-E	30			
Normal- Like/ non-HER2E	5			
non Normal-Like/HER2-E	10			
non Normal-Like/non-HER2E	0			

Statistical analyses

No statistical analyses for this end point

Secondary: pCR rates within HR-negative disease

End point title	pCR rates within HR-negative disease

End point description:

End point type	Secondary

End point timeframe:

14 Days

End point values	Total sample			
Subject group type	Reporting group			
Number of subjects analysed	74			
Units: Subjects				
Luminal A	0			
Luminal B	0			
HER2E	29			
Basal-like	1			
Normal-like	2			

Statistical analyses

No statistical analyses for this end point

Secondary: pCR rates within HR+ disease

End point title	pCR rates within HR+ disease

End point description:

End point type	Secondary

End point timeframe:

14 days

End point values	Total sample			
Subject group type	Reporting group			
Number of subjects analysed	77			
Units: Subjects				
Luminal A	0			
Luminal B	2			
HER2E	12			
Basal-Like	0			
Normal-Like	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

During treatment

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	Total Sample

Reporting group description: -

Serious adverse events	Total Sample		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 151 (5.30%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 151 (0.66%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Transaminases increased			
subjects affected / exposed	1 / 151 (0.66%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Essential thrombocythaemia			
subjects affected / exposed	1 / 151 (0.66%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 151 (1.99%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		

Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 151 (0.66%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 151 (0.66%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Total Sample		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	150 / 151 (99.34%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	17 / 151 (11.26%)		
occurrences (all)	26		
Nervous system disorders			
Headache			
subjects affected / exposed	18 / 151 (11.92%)		
occurrences (all)	26		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	105 / 151 (69.54%)		
occurrences (all)	241		
Mucositis management			
subjects affected / exposed	43 / 151 (28.48%)		
occurrences (all)	60		
Nausea			
subjects affected / exposed	23 / 151 (15.23%)		
occurrences (all)	29		
Skin and subcutaneous tissue disorders			

Rash subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all) Skin disorder subjects affected / exposed occurrences (all) Dry skin subjects affected / exposed occurrences (all)	77 / 151 (50.99%) 99 19 / 151 (12.58%) 28 23 / 151 (15.23%) 28 23 / 151 (15.23%) 25		
Musculoskeletal and connective tissue disorders Muscle disorder subjects affected / exposed occurrences (all)	43 / 151 (28.48%) 53		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 November 2013	• Expand the centers participating in this study. • Update the ASCO / CAP guidelines for determining HER2, which are used for patient selection. • Add one inclusion criteria for multifocal patients. • Add an inclusion criterion specifying that patients who do not have sufficient sample for the PAM50 analysis (main study objective) and do not want to be re-biopsied will not be enrolled in the study. • Specify the windows allowed for the different test evaluations. • Change the WHO tumor response assessment criteria to RECIST 1.1 because they are the most used by the centers participating in the trial. • Correct the platform to be used for genomic analysis. It is the same gene bank (PAM50) but it is not the version sold under the name ProsignaTM. This is another version that is marketed for use in research only. • Eliminate the independent data monitoring committee (CIMD), since only the Steering Committee of the study will eventually be formed. • Add bibliography relevant to the justification of the study. • Writing and typographical corrections. • Correct the information sheet to the patient according to the changes described above and specify the tests that are performed before the surgery. A new version of informed consent is generated (version 3.0 of November 20, 2013).
17 November 2014	• Protocol version 4.0 dated November 17, 2014 is generated and a new patient information sheet and informed consent for the assignment of surplus samples obtained in the PAMELA study, version 1.0 dated November 17, 2014.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/32938620