



Clinical trial results:

An open-label, Phase II, study to evaluate biomarkers associated with response to subsequent therapies in subjects with HER2-positive metastatic breast cancer receiving treatment with trastuzumab in combination with lapatinib or chemotherapy

Summary

EudraCT number	2014-001220-30
Trial protocol	ES IT AT
Global end of trial date	04 June 2020

Results information

Result version number	v1 (current)
This version publication date	20 June 2021
First version publication date	20 June 2021

Trial information

Trial identification

Sponsor protocol code	117165 (CLAP016A2206)
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02213042
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma, AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma, AG, 41 613241111, novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma, AG, 41 613241111, novartis.email@novartis.com

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

Global end of trial reached?	Yes
Global end of trial date	04 June 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate changes in the expression of biomarkers associated with immunomodulation.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 October 2014
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	Argentina: 8
Country: Number of subjects enrolled	Brazil: 9
Country: Number of subjects enrolled	Russian Federation: 13
Country: Number of subjects enrolled	Spain: 9
Country: Number of subjects enrolled	Thailand: 3
Worldwide total number of subjects	42
EEA total number of subjects	9

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)	35
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Overall, 225 subjects were planned and 42 subjects were enrolled in this study

Pre-assignment

Screening details:

The study was designed to address the post-authorization measures as agreed with the Committee for Medicinal Products for Human Use (CHMP). Recruitment of subjs into this study was challenging, and following agreement with the European Medicines Agency (EMA) enrollment into this study was halted after the enrollment of 42 of the 225 planned subjs.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	LAP+TRAS±AI (HER2-Enriched) - Arm A

Arm description:

Lapatinib 1000mg + Trastuzumab in HER2 Enriched In subjects with HER2-overexpressing MBC with a molecular subtype of HER2 Enriched, Lapatinib 1000mg once daily orally along with Trastuzumab (loading dose of 8 milligram/ kilogram (mg/kg) followed by the maintenance dose of 6 mg/kg Intravenous (IV) Every 3 weeks (q3weekly)) or Lapatinib 1000 milligram (mg) once daily orally along with Weekly Trastuzumab (loading dose of 4 mg/kg) followed by maintenance dose of 2 mg/kg IV weekly. For subjects who were hormone receptor positive, an aromatase inhibitor of the investigator's choice was required.

Arm type	Experimental
Investigational medicinal product name	Lapatinib
Investigational medicinal product code	LAP016
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects in Arm A were treated with lapatinib with 1000 mg oral once-daily dose. Lapatinib was provided as 250-mg oval, biconvex, and orange film-coated tablets for oral administration. Each tablet contained 405 mg of lapatinib ditosylate monohydrate, equivalent to 250 mg lapatinib freebase per tablet.

Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Trastuzumab was sourced locally from commercial stock, and was administered by iv infusion on Day 1 (+/-3 day) of the start of lapatinib or in conjunction with the first cycle of chemotherapy, as an 8 mg/kg loading dose. Subsequently, trastuzumab was administered every 3 weeks as a 6 mg/kg maintenance dose.

Arm title	TRAS+CHEM±AI (HER2-Enriched) - Arm B
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Arm description:

Trastuzumab in HER2 Enriched: In subjects with HER2-overexpressing MBC with a molecular subtype of HER2 Enriched, Trastuzumab (loading dose of 8 mg/kg followed by the maintenance dose of 6 mg/kg IV q3weekly) along with chemotherapy of the investigator's choice or Weekly Trastuzumab (loading dose of 4 mg/kg) followed by maintenance dose of 2 mg/kg IV weekly along with chemotherapy of the

investigators choice. Subjects randomized to this arm and hormone receptor positive received an aromatase inhibitor at the discretion of the investigator.

Arm type	Active comparator
Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Trastuzumab was sourced locally from commercial stock, and was administered by iv infusion on Day 1 (+/-3 day) of the start of lapatinib or in conjunction with the first cycle of chemotherapy, as an 8 mg/kg loading dose. Subsequently, trastuzumab was administered every 3 weeks as a 6 mg/kg maintenance dose.

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

Dosage and administration details:

The choice of chemotherapy in Arm B (comparator arm) was at the discretion of the Investigator based on previous treatment and subject status at the time of study entry.

Endocrine therapy with an aromatase inhibitors (AI) was chosen at the discretion of the Investigator.

The AI chosen by the Investigator at randomization was to remain the same throughout the study. The choice for the Investigators to choose from were: choose from were anastrozole (tablet), exemestane (tablet), and letrozole (tablet) and dosing was per product information.

Arm title	Non-HER2- Enriched - Arm C
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Arm description:

Lapatinib 1000mg + Trastuzumab in Non- HER2 Enriched: In subjects with HER2-overexpressing MBC with a molecular subtype of Non- HER2 Enriched (luminal A, luminal B or Basal type), Lapatinib 1000mg once daily orally along with Trastuzumab (loading dose of 8 milligram/ kilogram (mg/kg) followed by the maintenance dose of 6 mg/kg Intravenous (IV) Every 3 weeks (q3weekly)) or Lapatinib 1000 milligram (mg) once daily orally along with Weekly Trastuzumab (loading dose of 4 mg/kg) followed by maintenance dose of 2 mg/kg IV weekly. For subjects who were hormone receptor positive, an aromatase inhibitor of the investigator's choice was required.

Arm type	Experimental
Investigational medicinal product name	Lapatinib
Investigational medicinal product code	LAP016
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects in Arm C were treated with lapatinib with 1000 mg oral once-daily dose. Lapatinib was provided as 250-mg oval, biconvex, and orange film-coated tablets for oral administration. Each tablet contained 405 mg of lapatinib ditosylate monohydrate, equivalent to 250 mg lapatinib freebase per tablet.

Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Trastuzumab was sourced locally from commercial stock, and was administered by iv infusion on Day 1 (+/-3 day) of the start of lapatinib or in conjunction with the first cycle of chemotherapy, as an 8 mg/kg loading dose. Subsequently, trastuzumab was administered every 3 weeks as a 6 mg/kg maintenance dose.

Number of subjects in period 1	LAP+TRAS±AI (HER2-Enriched) - Arm A	TRAS+CHEM±AI (HER2-Enriched) - Arm B	Non-HER2- Enriched - Arm C
Started	17	15	10
Total deaths	11	9	6
Completed	0	0	0
Not completed	17	15	10
Consent withdrawn by subject	-	1	1
Adverse event, non-fatal	2	1	-
Disease progression-incl death due to disease prog	14	13	8
Investigator discretion	-	-	1
Protocol deviation	1	-	-

Baseline characteristics

Reporting groups

Reporting group title	LAP+TRAS±AI (HER2-Enriched) - Arm A
Reporting group description:	
Lapatinib 1000mg + Trastuzumab in HER2 Enriched In subjects with HER2-overexpressing MBC with a molecular subtype of HER2 Enriched, Lapatinib 1000mg once daily orally along with Trastuzumab (loading dose of 8 milligram/ kilogram (mg/kg) followed by the maintenance dose of 6 mg/kg Intravenous (IV) Every 3 weeks (q3weekly)) or Lapatinib 1000 milligram (mg) once daily orally along with Weekly Trastuzumab (loading dose of 4 mg/kg) followed by maintenance dose of 2 mg/kg IV weekly. For subjects who were hormone receptor positive, an aromatase inhibitor of the investigator's choice was required.	
Reporting group title	TRAS+CHEM±AI (HER2-Enriched) - Arm B
Reporting group description:	
Trastuzumab in HER2 Enriched: In subjects with HER2-overexpressing MBC with a molecular subtype of HER2 Enriched, Trastuzumab (loading dose of 8 mg/kg followed by the maintenance dose of 6 mg/kg IV q3weekly) along with chemotherapy of the investigator's choice or Weekly Trastuzumab (loading dose of 4 mg/kg) followed by maintenance dose of 2 mg/kg IV weekly along with chemotherapy of the investigators choice. Subjects randomized to this arm and hormone receptor positive received an aromatase inhibitor at the discretion of the investigator.	
Reporting group title	Non-HER2- Enriched - Arm C
Reporting group description:	
Lapatinib 1000mg + Trastuzumab in Non- HER2 Enriched: In subjects with HER2-overexpressing MBC with a molecular subtype of Non- HER2 Enriched (luminal A, luminal B or Basal type), Lapatinib 1000mg once daily orally along with Trastuzumab (loading dose of 8 milligram/ kilogram (mg/kg) followed by the maintenance dose of 6 mg/kg Intravenous (IV) Every 3 weeks (q3weekly)) or Lapatinib 1000 milligram (mg) once daily orally along with Weekly Trastuzumab (loading dose of 4 mg/kg) followed by maintenance dose of 2 mg/kg IV weekly. For subjects who were hormone receptor positive, an aromatase inhibitor of the investigator's choice was required.	

Reporting group values	LAP+TRAS±AI (HER2-Enriched) - Arm A	TRAS+CHEM±AI (HER2-Enriched) - Arm B	Non-HER2- Enriched - Arm C
Number of subjects	17	15	10
Age Categorical			
Units: Participants			
< 65 years	14	15	6
>= 65 years	3	0	4
Sex: Female, Male			
Units: participants			
Female	17	15	10
Male	0	0	0
Race/Ethnicity, Customized			
Units: Subjects			
Caucasian	14	11	10
African American	1	2	0
Asian	1	2	0
Native Hawaiian or Pacific Islander	1	0	0

Reporting group values	Total		
Number of subjects	42		
Age Categorical			
Units: Participants			
< 65 years	35		

>= 65 years	7		
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Sex: Female, Male Units: participants			
Female	42		
Male	0		
Race/Ethnicity, Customized Units: Subjects			
Caucasian	35		
African American	3		
Asian	3		
Native Hawaiian or Pacific Islander	1		

End points

End points reporting groups

Reporting group title	LAP+TRAS±AI (HER2-Enriched) - Arm A
Reporting group description: Lapatinib 1000mg + Trastuzumab in HER2 Enriched In subjects with HER2-overexpressing MBC with a molecular subtype of HER2 Enriched, Lapatinib 1000mg once daily orally along with Trastuzumab (loading dose of 8 milligram/ kilogram (mg/kg) followed by the maintenance dose of 6 mg/kg Intravenous (IV) Every 3 weeks (q3weekly)) or Lapatinib 1000 milligram (mg) once daily orally along with Weekly Trastuzumab (loading dose of 4 mg/kg) followed by maintenance dose of 2 mg/kg IV weekly. For subjects who were hormone receptor positive, an aromatase inhibitor of the investigator's choice was required.	
Reporting group title	TRAS+CHEM±AI (HER2-Enriched) - Arm B
Reporting group description: Trastuzumab in HER2 Enriched: In subjects with HER2-overexpressing MBC with a molecular subtype of HER2 Enriched, Trastuzumab (loading dose of 8 mg/kg followed by the maintenance dose of 6 mg/kg IV q3weekly) along with chemotherapy of the investigator's choice or Weekly Trastuzumab (loading dose of 4 mg/kg) followed by maintenance dose of 2 mg/kg IV weekly along with chemotherapy of the investigators choice. Subjects randomized to this arm and hormone receptor positive received an aromatase inhibitor at the discretion of the investigator.	
Reporting group title	Non-HER2- Enriched - Arm C
Reporting group description: Lapatinib 1000mg + Trastuzumab in Non- HER2 Enriched: In subjects with HER2-overexpressing MBC with a molecular subtype of Non- HER2 Enriched (luminal A, luminal B or Basal type), Lapatinib 1000mg once daily orally along with Trastuzumab (loading dose of 8 milligram/ kilogram (mg/kg) followed by the maintenance dose of 6 mg/kg Intravenous (IV) Every 3 weeks (q3weekly)) or Lapatinib 1000 milligram (mg) once daily orally along with Weekly Trastuzumab (loading dose of 4 mg/kg) followed by maintenance dose of 2 mg/kg IV weekly. For subjects who were hormone receptor positive, an aromatase inhibitor of the investigator's choice was required.	

Primary: Fold change in expression profile of genes and/or proteins for Arm A (LAP+TRAS±AI (HER2-Enriched)) from screening to approx. 3.5 years

End point title	Fold change in expression profile of genes and/or proteins for Arm A (LAP+TRAS±AI (HER2-Enriched)) from screening to approx. 3.5 years ^{[1][2]}
End point description: Evaluate changes in biomarkers associated with immunomodulation between pre-treatment biopsy and disease progression biopsy within each arm. Biomarker analysis was performed using an mRNA gene expression panel derived from Nanostring platform in a total of 20 subjects who received the study treatment as per the study design and with baseline tumor biopsies available. For the selected biomarkers associated with immunomodulation, the median fold changes of gene expression level and 95% confidence interval are presented. The fold change was calculated as the ratio of the expression level of a biomarker at disease progression over the baseline.	
End point type	Primary
End point timeframe: At screening and at disease progression, assessed up to approx. 3.5 years	

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: Statistical analysis was not planned for this endpoint

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Statistical analysis was not planned for this endpoint

End point values	LAP+TRAS±AI (HER2- Enriched) - Arm A			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: Ratio of gene expression level				
median (confidence interval 95%)				
Membrane spanning 4-domains A1; n = 5	0.25 (0.078 to 0.589)			
POU class 2 associating factor 1; n = 5	0.32 (0.183 to 0.543)			
CD19+; n = 5	0.35 (0.106 to 0.904)			
Interleukin 6; n = 5	0.36 (0.033 to 0.832)			
G antigen 1; n = 5	0.43 (0.030 to 0.901)			
ubiquitin specific peptidase 9, Y-linked; n = 5	0.50 (0.321 to 0.770)			
Thy-1 cell surface antigen; n = 5	0.50 (0.113 to 0.902)			
Chemerin chemokine-like receptor 1; n = 5	0.51 (0.345 to 0.862)			
Maj histocompatibility complx,cls II, DR beta4;n=5	0.51 (0.320 to 0.984)			
Collectin subfamily member 12; n = 5	0.51 (0.151 to 0.794)			
Complement C3b/C4b receptor 1 (Knops bld grp); n=5	0.51 (0.227 to 0.901)			
CD33 molecule; n = 5	0.56 (0.458 to 0.826)			
B-cell linker; n = 5	0.56 (0.326 to 0.874)			
Interleukin 12A; n = 5	0.57 (0.228 to 0.892)			
CD163+; n = 5	0.57 (0.417 to 0.911)			
C-C motif chemokine ligand 8; n = 5	0.58 (0.138 to 0.954)			
Chemokine (C-C motif) receptor 1; n = 5	0.59 (0.501 to 0.792)			
POU class 2 homeobox 2; n = 5	0.60 (0.440 to 0.944)			
Cyclin dependent kinase inhibitor 1A; n = 5	0.62 (0.453 to 0.873)			
CD27 molecule; n = 5	0.62 (0.357 to 0.886)			
Lymphocyte antigen 86; n = 5	0.63 (0.383 to 0.906)			
TNF superfamily member 8; n = 5	0.64 (0.476 to 0.879)			
CD34+; n = 5	0.67 (0.558 to 0.863)			
Integrin subunit alpha 6; n = 5	0.68 (0.470 to 0.827)			
C-type lectin domain containing 7A; n = 5	0.69 (0.326 to 0.944)			
CD180 molecule; n = 5	0.70 (0.347 to 0.869)			

Integrin subunit alpha M; n = 5	0.72 (0.411 to 0.957)			
Toll like receptor 6; n = 5	0.72 (0.511 to 0.836)			
Autophagy related 10; n = 5	0.73 (0.662 to 0.864)			
C-C motif chemokine ligand 3 like 1; n = 5	0.74 (0.499 to 0.996)			
Bone marrow stromal cell antigen 1; n = 5	0.75 (0.345 to 0.922)			
CD22+; n = 5	0.76 (0.629 to 0.936)			
CD37 molecule; n = 5	0.76 (0.553 to 0.884)			
NEG_A; n = 5	0.77 (0.674 to 0.949)			
Sperm auto antigenic protein 17; n = 5	0.79 (0.697 to 0.968)			
CD200 molecule; n = 5	0.79 (0.598 to 0.945)			
TNF receptor associated factor 3; n = 5	0.82 (0.718 to 0.962)			
Interferon alpha and beta receptor subunit 1;n=5	1.10 (1.036 to 1.124)			
TNF receptor associated factor 6; n = 5	1.21 (1.016 to 1.332)			

Statistical analyses

No statistical analyses for this end point

Primary: Fold change in expression profile of genes and /or proteins for Arm B (TRAS+CHEM±AI (HER2-Enriched)) from screening to approx. 3.5 years

End point title	Fold change in expression profile of genes and /or proteins for Arm B (TRAS+CHEM±AI (HER2-Enriched)) from screening to approx. 3.5 years ^{[3][4]}
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End point description:

Evaluate changes in biomarkers associated with immunomodulation between pre-treatment biopsy and disease progression biopsy within each arm. Biomarker analysis was performed using an mRNA gene expression panel derived from Nanostring platform in a total of 20 subjects who received the study treatment as per the study design and with baseline tumor biopsies available.

For the selected biomarkers associated with immunomodulation, the median fold changes of gene expression level and 95% confidence interval are presented. The fold change was calculated as the ratio of the expression level of a biomarker at disease progression over the baseline.

End point type	Primary
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End point timeframe:

At screening and at disease progression, assessed up to approx. 3.5 years

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: Statistical analysis was not planned for this endpoint

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Statistical analysis was not planned for this endpoint

End point values	TRAS+CHEM± AI (HER2- Enriched) - Arm B			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: Ratio of gene expression level				
median (confidence interval 95%)				
C-type lectin domain containing 5A; n = 5	0.16 (0.020 to 0.440)			
Interferon induced transmembrane protein 1; n = 5	0.25 (0.183 to 0.421)			
Fibronectin 1; n = 5	0.27 (0.077 to 0.393)			
C-C motif chemokine ligand 7; n = 5	0.27 (-0.064 to 0.888)			
Triggering receptr express on myeloid cells 1;n=5	0.27 (-0.018 to 0.959)			
Plasminogen activator, urokinase; n = 5	0.27 (0.112 to 0.545)			
Interleukin 22 receptor subunit alpha 2; n = 5	0.28 (0.192 to 0.425)			
C-C motif chemokine ligand 8; n = 5	0.28 (0.044 to 0.699)			
Tmr necrosis factor(ligand)superfam memb4 gene;n=5	0.31 (0.147 to 0.651)			
Maj histocompatibility complx, Cls I-related; n=5	0.32 (0.139 to 0.832)			
Cathepsin L; n = 5	0.32 (0.066 to 0.820)			
SPP-1 (Osteopontin); n = 5	0.33 (0.076 to 0.501)			
Thy-1 cell surface antigen; n = 5	0.34 (0.157 to 0.648)			
Transforming growth factor beta 2; n = 5	0.35 (0.120 to 0.504)			
Hepatitis A virus cellular receptor 2; n = 5	0.36 (0.138 to 0.614)			
Bone marrow stromal cell antigen 1; n = 5	0.37 (0.133 to 0.864)			
C-type lectin domain containing 7A; n = 5	0.37 (0.166 to 0.570)			
C-X-C motif chemokine ligand 5; n = 5	0.38 (0.040 to 0.943)			
Collagen type III alpha 1 chain; n = 5	0.40 (0.130 to 0.685)			
Complement C1s; n = 5	0.41 (0.088 to 0.717)			
IFIT1 gene; n = 5	0.41 (0.148 to 0.921)			
Maj histocompatibility complex, cls I, G; n=5	0.41 (0.147 to 0.698)			
Tumour necrosis factor gene; n = 5	0.42 (0.108 to 0.945)			
Integrin subunit beta 1; n = 5	0.43 (0.231 to 0.864)			
Pro-melanin concentrating hormone; n = 5	0.43 (0.081 to 0.972)			
CD86+; n = 5	0.44 (0.102 to 0.700)			

FCGR3A SNP rs396991; n = 5	0.44 (0.107 to 0.696)			
TNF receptor superfamily member 10c; n = 5	0.44 (0.165 to 0.925)			
Integrin subunit alpha M; n = 5	0.45 (0.166 to 0.797)			
TNF receptor superfamily member 11b; n = 5	0.45 (0.114 to 0.923)			
Platelet derived growth factor C; n = 5	0.45 (0.231 to 0.797)			
Mannan binding lectin serine peptidase 1; n = 5	0.46 (0.304 to 0.896)			
Recombination activating 1; n = 5	0.46 (0.394 to 0.597)			
Interleukin 22; n = 5	0.47 (0.229 to 0.609)			
Tmr necros fact.(ligand)superfam memb 13b gene;n=5	0.47 (0.179 to 0.697)			
BMI1 proto-oncogene, polycomb ring finger; n = 5	0.47 (0.322 to 0.735)			
CXCL10 gene; n = 5	0.48 (0.074 to 0.986)			
Leukocyte immunoglobulin like receptor B1; n = 5	0.48 (0.142 to 0.747)			
MX1 gene; n = 5	0.48 (0.155 to 0.781)			
Tmr necros fact.(ligand)superfam. memb 11 gene;n=5	0.48 (0.227 to 0.798)			
Cathepsin S; n = 5	0.49 (0.138 to 0.807)			
Interferon induced transmembrane protein 2; n = 5	0.49 (0.245 to 0.887)			
LYN proto-oncogene, Src family tyrosine kinase;n=5	0.50 (0.360 to 0.685)			
Platelet deriv. growth factor receptor beta; n=5	0.50 (0.160 to 0.801)			
OAS3 gene; n = 5	0.50 (0.284 to 0.899)			
CD58 molecule; n = 5	0.50 (0.398 to 0.619)			
complement C3a receptor 1; n = 5	0.51 (0.147 to 0.949)			
Chemokine (C-C motif) receptor 1; n = 5	0.52 (0.159 to 0.815)			
Interleukin 24 gene; n = 5	0.52 (0.161 to 0.706)			
Chemokine (C-X-C motif) receptor 2; n = 5	0.53 (0.295 to 0.629)			
Strawberry notch homolog 2; n = 5	1.13 (1.045 to 1.300)			
Zinc finger protein 205; n = 5	1.42 (1.144 to 1.815)			
Fas associated via death domain; n = 5	1.58 (1.107 to 2.043)			
CD3e molecule associated protein; n = 5	1.67 (1.244 to 2.075)			
Baculoviral IAP repeat containing 5; n = 5	1.73 (1.003 to 2.635)			
Interleukin 17 receptor B; n = 5	2.01 (1.151 to 2.975)			

Statistical analyses

No statistical analyses for this end point

Primary: Fold change in expression profile of genes and /or proteins for Arm C (Non-HER2- Enriched) from screening to approx. 3.5 years

End point title	Fold change in expression profile of genes and /or proteins for Arm C (Non-HER2- Enriched) from screening to approx. 3.5 years ^[5] ^[6]
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End point description:

Evaluate changes in biomarkers associated with immunomodulation between pre-treatment biopsy and disease progression biopsy within each arm. Biomarker analysis was performed using an mRNA gene expression panel derived from Nanostring platform in a total of 20 subjects who received the study treatment as per the study design and with baseline tumor biopsies available.

For the selected biomarkers associated with immunomodulation, the median fold changes of gene expression level and 95% confidence interval are presented. The fold change was calculated as the ratio of the expression level of a biomarker at disease progression over the baseline.

End point type	Primary
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End point timeframe:

At screening and at disease progression, assessed up to approx. 3.5 years

Notes:

[5] - 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: Statistical analysis was not planned for this endpoint

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Statistical analysis was not planned for this endpoint

End point values	Non-HER2-Enriched - Arm C			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: Ratio of gene expression level				
median (confidence interval 95%)				
Triggering recept. express on myeloid cells 1;n=5	0.50 (0.294 to 0.995)			
Interleukin 1 receptor, type 1 gene; n = 5	1.58 (1.235 to 2.328)			
Complement component 2; n = 5	2.13 (1.011 to 3.567)			
Coagulation factor XII; n = 5	2.69 (1.062 to 4.229)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival (PFS)

End point title	Progression-free survival (PFS)
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End point description:

PFS was defined as the time from the date of randomization (for Arm A and B) / treatment start date (for Arm C) to the date of the first documented disease progression or death due to any cause, whichever was earlier. If a subject had not progressed or died at the analysis cutoff date, PFS was censored at the time of the last adequate tumor assessment. PFS was summarized using Kaplan-Meier estimates.

End point type	Secondary
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End point timeframe:

From randomization to disease progression or death, up to approx. 5.6 years

End point values	LAP+TRAS±AI (HER2- Enriched) - Arm A	TRAS+CHEM± AI (HER2- Enriched) - Arm B	Non-HER2- Enriched - Arm C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	17	15	10	
Units: Months				
median (confidence interval 95%)	6.0 (2.10 to 10.60)	7.2 (2.10 to 14.80)	6.0 (1.60 to 8.30)	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall response rate (ORR)

End point title	Overall response rate (ORR)
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End point description:

Overall response rate was defined as the percentage of subjects achieving either a confirmed complete response (CR) or partial response (PR) and was calculated from the Investigator's assessment of response per RECIST 1.1 criteria. . The confirmed CR or PR was derived using the following rules: confirmed CR - at least two determinations of CR at least 4 weeks apart before disease progression; confirmed PR - at least two determinations of PR or better at least 4 weeks apart before progression.

End point type	Secondary
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End point timeframe:

From enrollment/randomization to the end of study, approximately 5.6 years

End point values	LAP+TRAS±AI (HER2- Enriched) - Arm A	TRAS+CHEM± AI (HER2- Enriched) - Arm B	Non-HER2- Enriched - Arm C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	17	15	10	
Units: Percentage of participants				
number (confidence interval 95%)	35.3 (14.2 to 61.7)	33.3 (11.8 to 61.6)	30.0 (6.7 to 65.3)	

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical benefit rate (CBR)

End point title	Clinical benefit rate (CBR)
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End point description:

CBR is defined as percentage of subjects with a complete response (CR), partial response (PR), or maintaining stable disease (SD) for at least 24 weeks while on study according to the investigator assessment of response per RECIST 1.1 criteria. CR and PR are confirmed responses derived using the following rules: Confirmed CR - at least 2 determinations of CR at least 4 weeks apart before disease progression. Confirmed PR - at least 2 determinations of PR or better at least 4 weeks apart before progression.

End point type	Secondary
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End point timeframe:

From enrollment/randomization the end of study, approximately 5.6 years

End point values	LAP+TRAS±AI (HER2- Enriched) - Arm A	TRAS+CHEM± AI (HER2- Enriched) - Arm B	Non-HER2- Enriched - Arm C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	17	15	10	
Units: Percentage of participants				
number (confidence interval 95%)	35.3 (14.2 to 61.7)	46.7 (21.3 to 73.4)	30.0 (6.7 to 65.3)	

Statistical analyses

No statistical analyses for this end point

Secondary: Association between biomarkers and PFS

End point title	Association between biomarkers and PFS
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End point description:

Describe if a change at disease progression in biomarker correlates with PFS

End point type	Secondary
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End point timeframe:

From randomization to disease progression or death, up to approx. 5.6 years

End point values	LAP+TRAS±AI (HER2- Enriched) - Arm A	TRAS+CHEM± AI (HER2- Enriched) - Arm B	Non-HER2- Enriched - Arm C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0 ^[7]	0 ^[8]	0 ^[9]	
Units: unitless				
number (not applicable)				

Notes:

[7] - Analysis was not performed due to insufficient sample size and early stop of recruitment.

[8] - Analysis was not performed due to insufficient sample size and early stop of recruitment.

[9] - Analysis was not performed due to insufficient sample size and early stop of recruitment.

Statistical analyses

No statistical analyses for this end point

Secondary: All-Collected Deaths

End point title	All-Collected Deaths
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End point description:

On treatment deaths were collected from FPFT up to 30 days after study drug discontinuation, for a maximum duration of 168 weeks for Lapatinib, (treatment duration ranged from 151 to 164 weeks), 164 weeks for Trastuzumab (treatment duration ranged from 0 to 160 weeks), 168 weeks for Aromatase Inhibitors (treatment duration ranged from 9 to 164 weeks).

Deaths post treatment survival follow up were collected after the on- treatment period, up to approx. 5.6 years.

End point type	Secondary
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End point timeframe:

On-treatment deaths: up to approx. 168 weeks, Total deaths: up to approx. 5.6 years

End point values	LAP+TRAS±AI (HER2- Enriched) - Arm A	TRAS+CHEM± AI (HER2- Enriched) - Arm B	Non-HER2- Enriched - Arm C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	17	15	10	
Units: Participants				
Total Deaths	11	9	6	
On-treatment deaths	3	1	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse events are reported in this record from First Patient First Treatment until Last Patient Last Visit up to approx. 5.6 years.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	HER2-Enriched-Lapatinib(1000mg)+Trastuzumab(6mg per kg)+AI
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Reporting group description:

HER2-Enriched-Lapatinib(1000mg)+Trastuzumab(6mg per kg)+AI

Reporting group title	Non-HER2-Enriched-Lapatinib(1000mg)+Trastuzumab(6mg per kg)+AI
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Reporting group description:

Non-HER2-Enriched-Lapatinib(1000mg)+Trastuzumab(6mg per kg)+AI

Reporting group title	HER2-Enriched-Trastuzumab(6mg per kg)+Chemo+AI
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Reporting group description:

HER2-Enriched-Trastuzumab(6mg per kg)+Chemo+AI

Serious adverse events	HER2-Enriched-Lapatinib(1000mg)+Trastuzumab(6mg per kg)+AI	Non-HER2-Enriched-Lapatinib(1000mg)+Trastuzumab(6mg per kg)+AI	HER2-Enriched-Trastuzumab(6mg per kg)+Chemo+AI
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 17 (5.88%)	2 / 10 (20.00%)	1 / 15 (6.67%)
number of deaths (all causes)	3	0	1
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast neoplasm			
subjects affected / exposed	0 / 17 (0.00%)	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac arrest			

subjects affected / exposed	1 / 17 (5.88%)	0 / 10 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Nervous system disorders			
Seizure			
subjects affected / exposed	0 / 17 (0.00%)	1 / 10 (10.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 17 (0.00%)	1 / 10 (10.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 10 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Infections and infestations			
Escherichia sepsis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 10 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 10 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 17 (5.88%)	0 / 10 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypoalbuminaemia			

subjects affected / exposed	1 / 17 (5.88%)	0 / 10 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 10 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 10 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypomagnesaemia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 10 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 10 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic disorder			
subjects affected / exposed	1 / 17 (5.88%)	0 / 10 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	HER2-Enriched-Lapatinib(1000mg)+Trastuzumab(6mg per kg)+AI	Non-HER2-Enriched-Lapatinib(1000mg)+Trastuzumab(6mg per kg)+AI	HER2-Enriched-Trastuzumab(6mg per kg)+Chemo+AI
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 17 (88.24%)	10 / 10 (100.00%)	14 / 15 (93.33%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			

subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1
Tumour pain subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 10 (0.00%) 0	0 / 15 (0.00%) 0
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1
Lymphoedema subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 10 (0.00%) 0	2 / 15 (13.33%) 2
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all)	3 / 17 (17.65%) 3	2 / 10 (20.00%) 2	4 / 15 (26.67%) 4
Face oedema subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1
Fatigue subjects affected / exposed occurrences (all)	2 / 17 (11.76%) 2	0 / 10 (0.00%) 0	2 / 15 (13.33%) 2
Influenza like illness subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1
Mucosal inflammation subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	1 / 10 (10.00%) 1	2 / 15 (13.33%) 2
Pain subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1
Respiratory, thoracic and mediastinal disorders Catarrh subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	1 / 10 (10.00%) 1	0 / 15 (0.00%) 0
Cough			

subjects affected / exposed occurrences (all)	2 / 17 (11.76%) 2	0 / 10 (0.00%) 0	0 / 15 (0.00%) 0
Dyspnoea subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	1 / 10 (10.00%) 1	0 / 15 (0.00%) 0
Pleurisy subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 10 (0.00%) 0	1 / 15 (6.67%) 2
Psychiatric disorders Depression subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 10 (0.00%) 0	0 / 15 (0.00%) 0
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 10 (0.00%) 0	5 / 15 (33.33%) 7
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	2 / 17 (11.76%) 2	0 / 10 (0.00%) 0	2 / 15 (13.33%) 5
Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 3	2 / 10 (20.00%) 2	2 / 15 (13.33%) 5
Blood sodium decreased subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 10 (0.00%) 0	0 / 15 (0.00%) 0
Ejection fraction decreased subjects affected / exposed occurrences (all)	2 / 17 (11.76%) 3	0 / 10 (0.00%) 0	0 / 15 (0.00%) 0
Neutrophil count decreased subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 10 (0.00%) 0	1 / 15 (6.67%) 2
Weight decreased subjects affected / exposed occurrences (all)	2 / 17 (11.76%) 3	2 / 10 (20.00%) 2	0 / 15 (0.00%) 0
Weight increased			

subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1
Injury, poisoning and procedural complications			
Incision site pain			
subjects affected / exposed	0 / 17 (0.00%)	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Rib fracture			
subjects affected / exposed	1 / 17 (5.88%)	0 / 10 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Left ventricular dysfunction			
subjects affected / exposed	1 / 17 (5.88%)	0 / 10 (0.00%)	0 / 15 (0.00%)
occurrences (all)	2	0	0
Sinus tachycardia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Ventricular extrasystoles			
subjects affected / exposed	0 / 17 (0.00%)	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	2
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 17 (0.00%)	0 / 10 (0.00%)	3 / 15 (20.00%)
occurrences (all)	0	0	3
Headache			
subjects affected / exposed	1 / 17 (5.88%)	0 / 10 (0.00%)	2 / 15 (13.33%)
occurrences (all)	1	0	2
Neuropathy peripheral			
subjects affected / exposed	0 / 17 (0.00%)	0 / 10 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	0	2
Neurotoxicity			
subjects affected / exposed	0 / 17 (0.00%)	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Paraesthesia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Somnolence			

subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 17 (11.76%)	2 / 10 (20.00%)	3 / 15 (20.00%)
occurrences (all)	2	2	5
Leukopenia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	3
Lymphopenia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	2
Neutropenia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 10 (0.00%)	4 / 15 (26.67%)
occurrences (all)	1	0	8
Eye disorders			
Eyelid oedema			
subjects affected / exposed	0 / 17 (0.00%)	1 / 10 (10.00%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Visual impairment			
subjects affected / exposed	1 / 17 (5.88%)	0 / 10 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 17 (0.00%)	1 / 10 (10.00%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Abdominal pain upper			
subjects affected / exposed	3 / 17 (17.65%)	0 / 10 (0.00%)	2 / 15 (13.33%)
occurrences (all)	3	0	2
Constipation			
subjects affected / exposed	0 / 17 (0.00%)	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Diarrhoea			
subjects affected / exposed	9 / 17 (52.94%)	6 / 10 (60.00%)	1 / 15 (6.67%)
occurrences (all)	22	8	1
Nausea			

subjects affected / exposed	1 / 17 (5.88%)	3 / 10 (30.00%)	5 / 15 (33.33%)
occurrences (all)	1	4	5
Stomatitis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 10 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	0	3
Vomiting			
subjects affected / exposed	1 / 17 (5.88%)	4 / 10 (40.00%)	1 / 15 (6.67%)
occurrences (all)	2	5	1
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 10 (0.00%)	5 / 15 (33.33%)
occurrences (all)	0	0	5
Dermatitis acneiform			
subjects affected / exposed	1 / 17 (5.88%)	0 / 10 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Dry skin			
subjects affected / exposed	2 / 17 (11.76%)	0 / 10 (0.00%)	0 / 15 (0.00%)
occurrences (all)	2	0	0
Nail discolouration			
subjects affected / exposed	0 / 17 (0.00%)	1 / 10 (10.00%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Nail disorder			
subjects affected / exposed	2 / 17 (11.76%)	1 / 10 (10.00%)	1 / 15 (6.67%)
occurrences (all)	2	1	1
Nail dystrophy			
subjects affected / exposed	0 / 17 (0.00%)	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Palmar-plantar erythrodysesthesia syndrome			
subjects affected / exposed	3 / 17 (17.65%)	1 / 10 (10.00%)	1 / 15 (6.67%)
occurrences (all)	3	1	1
Pruritus			
subjects affected / exposed	2 / 17 (11.76%)	0 / 10 (0.00%)	0 / 15 (0.00%)
occurrences (all)	2	0	0
Rash			

subjects affected / exposed occurrences (all)	3 / 17 (17.65%) 6	0 / 10 (0.00%) 0	2 / 15 (13.33%) 3
Rash maculo-papular subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	1 / 10 (10.00%) 1	0 / 15 (0.00%) 0
Skin toxicity subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 2	0 / 10 (0.00%) 0	0 / 15 (0.00%) 0
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1
Back pain subjects affected / exposed occurrences (all)	2 / 17 (11.76%) 2	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1
Muscle spasms subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1
Musculoskeletal chest pain subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 10 (0.00%) 0	0 / 15 (0.00%) 0
Myalgia subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 10 (0.00%) 0	3 / 15 (20.00%) 19
Pain in extremity subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	1 / 10 (10.00%) 1	1 / 15 (6.67%) 1
Infections and infestations			
Bronchitis subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 10 (0.00%) 0	0 / 15 (0.00%) 0
Cellulitis subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1
Nasopharyngitis			

subjects affected / exposed	1 / 17 (5.88%)	0 / 10 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Paronychia			
subjects affected / exposed	4 / 17 (23.53%)	0 / 10 (0.00%)	0 / 15 (0.00%)
occurrences (all)	5	0	0
Pharyngitis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 10 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Respiratory tract infection			
subjects affected / exposed	1 / 17 (5.88%)	0 / 10 (0.00%)	0 / 15 (0.00%)
occurrences (all)	2	0	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 17 (5.88%)	0 / 10 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Urinary tract infection			
subjects affected / exposed	1 / 17 (5.88%)	0 / 10 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 17 (11.76%)	3 / 10 (30.00%)	0 / 15 (0.00%)
occurrences (all)	2	3	0
Hyperglycaemia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	3
Hyperkalaemia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 10 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	0	2
Hypermagnesaemia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 10 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Hypoalbuminaemia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Hypocalcaemia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1

Hypokalaemia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 10 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 March 2014	Amendment 1 was issued following feedback from various countries to not include a third biopsy. At the time of this amendment, no subjects were enrolled.
23 March 2017	Amendment 2 was issued when 42 subjects were enrolled and study recruitment was halted, the key changes included changes to the primary and secondary objectives as described below. The primary objective of the study was updated to remove the evaluation of changes in the expression of biomarkers associated with HER family, apoptosis, and ABC transporters. The amended primary objective evaluated the changes in the expression of biomarkers associated with immunomodulation. The secondary objectives were updated to remove OS and PFS on first next line and subsequent lines of anticancer therapies. Patient-reported outcomes (PRO) and health-related quality of life (HRQOL) objectives were also removed. An exploratory objective was included to explore the changes in molecular subtype determined by PAM50 assay and selected biomarkers.
15 May 2017	Amendment 3 was issued subsequent to the acquisition of GlaxoSmithKline (GSK) compound GW572016 by Novartis, when 42 subjects had received treatment (with 34 having completed or discontinued study treatment). The protocol was amended to remove references to GlaxoSmithKline and its staff and these were either deleted or replaced with that of Novartis and its authorized agents to align with the change of sponsorship. Administrative changes were made to align with Novartis processes and procedures.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported