ClinicalTrials.gov Protocol Registration and Results System (PRS) Receipt
Release Date: 05/12/2016

ClinicalTrials.gov ID: NCT00444587

Study Identification

Unique Protocol ID:	ML19944
Brief Title:	A Study of Herceptin (Trastuzumab) in Combination With 2nd-Line Chemotherapy in Patients With HER2 Positive Metastatic Breast Cancer.
Official Title:	A Multicenter Phase II Trial of Trastuzumab (Herceptin) Continuation in Combination With 2nd-line Chemotherapies After Progression on a 1st-line Chemotherapy Combined With Trastuzumab in Patients With HER2 Positive Metastatic Breast Cancer (Treatment Beyond Progression, TBP)
Secondary IDs:	

Study Status

Record Verification:	May 2016
Overall Status:	Completed
Study Start:	March 2007
Primary Completion:	August 2011 [Actual]
Study Completion:	August 2011 [Actual]

Sponsor/Collaborators

Sponsor:	Hoffmann-La Roche
Responsible Party:	Sponsor
Collaborators:	

Oversight

FDA Regulated?:	No
IND/IDE Protocol?:	No
Review Board:	Approval Status: Approved Approval Number: 16171-1/2006-1017 EKL Board Name: Ethics Committee for Clinical Pharmacology Board Affiliation: Medical Research Council Phone: +36 1 301-7871 Email: magyari.ilona@eum.hu
Data Monitoring?:	
Plan to Share Data?:	
Oversight Authorities:	Hungary: National Institute of Pharmacology

Study Description

Brief Summary:	This 2 arm study will compare the efficacy and safety of continuation or discontinuation of Herceptin treatment in combination with 2nd line chemotherapy, in patients with HER2 positive metastatic breast cancer whose condition has progressed on 1st line chemotherapy plus Herceptin. Patients will be randomized either to continue or discontinue Herceptin treatment (6mg/kg iv infusion every 3 weeks) while receiving second-line chemotherapy of the investigator's choice. The anticipated time on study treatment is until disease progression, and the target sample size is 100-500 individuals.
Detailed Description:	

Conditions

Conditions:	Breast Cancer
Keywords:	

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 2
Intervention Model:	Parallel Assignment
Number of Arms:	2

Masking:	Open Label
Allocation:	Randomized
Endpoint Classification:	Safety/Efficacy Study
Enrollment:	114 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Trastuzumab + 2nd Line Chemotherapy	Drug: Second line chemotherapy As prescribed Drug: trastuzumab [Herceptin] 6mg/kg iv every 3 weeks
Active Comparator: Only Chemotherapy	Drug: Second line chemotherapy As prescribed

Outcome Measures

[See Results Section.]

Eligibility

Minimum Age:	18 Years
Maximum Age:	
Gender:	Female
Accepts Healthy Volunteers?:	No
Criteria:	Inclusion Criteria:

- female patients, >= 18 years of age;
- metastatic breast cancer;
- HER2 overexpression (IHC 3+ and/or FISH positive);
- disease progression during or after previous 1st line chemotherapy + Herceptin;
- scheduled to receive 2nd line chemotherapy.

Exclusion Criteria:

- concurrent immunotherapy or hormonal therapy;
- anthracyclines as part of previous 1st line chemotherapy or planned 2nd line chemotherapy;
- cardiac toxicity during previous 1st line chemotherapy + Herceptin;
- history of other malignancy within last 5 years.

Contacts/Locations

Study Officials: Clinical Trials
Study Director
Hoffmann-La Roche

Locations: Hungary
Budapest, Hungary, 1145

Budapest, Hungary, 1122

Budapest, Hungary, 1082

Budapest, Hungary, 1135

Budapest, Hungary, 1115

Budapest, Hungary, 1125

Szeged, Hungary, 6725

Debrecen, Hungary, 4032

Nyíregyháza, Hungary, 4400

Gyor, Hungary, 9023

Gyula, Hungary, 5700

Szekesfehervar, Hungary, 8000

Macedonia, The Former Yugoslav Republic of
Skopje, Macedonia, The Former Yugoslav Republic of, 1000

Bulgaria
Sofia, Bulgaria, 1527

Slovakia
Bratislava, Slovakia, 812 50

Kosice, Slovakia, 041 90

Turkey
Ankara, Turkey, 06590

Adana, Turkey, 01330

Estonia
Tallinn, Estonia, 13419

Lithuania
Vilnius, Lithuania, 08660

Kaunas, Lithuania, 50009

Israel
Rehovot, Israel, 76100

Ramat Gan, Israel, 52621

Safed, Israel, 13110

Zerifin, Israel, 70300

Tel Aviv, Israel, 6423906

Haifa, Israel, 31096

Hungary
Szombathely, Hungary, 9700

Israel
Petach Tikva, Israel, 49100

Holon, Israel, 58100

References

Citations:

Links:

Study Data/Documents:

Participant Flow

Recruitment Details	A total of 114 participants were enrolled in this study conducted from March 2007 to August 2011 at 30 centers in 8 countries.
Pre-Assignment Details	Of 114 participants screened, 3 participants were screening failures. The reasons for screening failure were violation of inclusion criteria, refused to take part in the study and bacterial infection. Therefore, 111 participants were randomized to receive study treatment. Two participants were randomized but never started study treatment.

Reporting Groups

	Description
Trastuzumab + 2nd Line Chemotherapy	Eligible participants were administered trastuzumab (Herceptin) 6 milligrams per kilograms (mg/kg) of body weight (except in Israel, where the dose was 2 mg/kg body weight), intravenous (IV) infusion every three weeks until disease progression, unacceptable toxicities, or withdrawal from study, in combination with second line chemotherapy.
Only Chemotherapy	Eligible participants were administered second line chemotherapy according to the investigator's decision.

Overall Study

	Trastuzumab + 2nd Line Chemotherapy	Only Chemotherapy
Started	93	16
Completed	10	1
Not Completed	83	15
Death	2	1
Progression of the disease	73	8
Refused treatment/did not cooperate	4	1
Investigator decision	3	0
Protocol Violation	1	0
Missing	0	5

Baseline Characteristics

Analysis Population Description

The Safety Population included all participants who entered the trial and received at least one dose of trial medication.

Reporting Groups

	Description
Trastuzumab + 2nd Line Chemotherapy	Eligible participants were administered trastuzumab 6 mg/kg of body weight (except in Israel, where the dose was 2 mg/kg body weight), IV infusion, every three weeks until disease progression, unacceptable toxicities, or withdrawal from study in combination with second line chemotherapy.
Only Chemotherapy	Eligible participants were administered second line chemotherapy according to the investigator's decision.

Baseline Measures

	Trastuzumab + 2nd Line Chemotherapy	Only Chemotherapy	Total
Number of Participants	93	16	109
Age, Continuous [units: years] Mean (Standard Deviation)	55.4 (12.8)	56.3 (10.2)	55.5 (12.4)
Gender, Male/Female [units: Participants]			
Female	93	16	109
Male	0	0	0

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Median Time to Disease Progression
Measure Description	Time to disease progression (TTP) in days was defined as the time from enrollment to objective disease progression (all categories other than objective disease progression was set to be censored including death before progression). Progression is defined using Response Evaluation Criteria In Solid Tumors Criteria (RECIST v1.0), as a 20% increase in the sum of the longest diameter of target lesions, or a measurable increase in a nontarget lesion, or the appearance of new lesions. Tumor assessments were performed using computer tomography or magnetic resonance imaging. TTP as assessed by investigator, along with a recalculation done by computer algorithm is presented below. Median time was not assessed for 'Only Chemotherapy' group as randomization of participants was not feasible considering Trastuzumab widespread use in routine clinical practice.
Time Frame	Up to 5 years
Safety Issue?	No

Analysis Population Description

The Full-Analysis-Set included all participants who were enrolled and had at least one valid primary efficacy variable on active treatment. n = Numbers of participants included in this analysis.

Reporting Groups

	Description
Trastuzumab + 2nd Line Chemotherapy	Eligible participants were administered trastuzumab 6 mg/kg of body weight (except in Israel, where the dose was 2 mg/kg body weight), IV infusion, every three weeks until disease progression, unacceptable toxicities, or withdrawal from study in combination with second line chemotherapy.

Measured Values

	Trastuzumab + 2nd Line Chemotherapy
Number of Participants Analyzed	73
Median Time to Disease Progression [units: Days] Median (95% Confidence Interval)	
By Computer (n = 65)	171 (136 to 322)
By Investigator (n = 73)	171 (136 to 265)

2. Secondary Outcome Measure:

Measure Title	Objective Response Rate
Measure Description	Objective response rate (ORR) is defined as the percentage of participants with tumor shrinkage of a predefined amount. It is a combination of complete response (CR) and partial response (PR) and was assessed according to the RECIST criteria 1.0. Complete response refers to the disappearance of all target lesions and all non-target non-measurable lesions. Partial Response refers to an at least 30 percent decrease in the sum of longest diameter of target lesions, taking as reference the baseline sum longest diameter. Objective response rate was not assessed for 'Only Chemotherapy' group as randomization of participants was not feasible considering Trastuzumab widespread use in routine clinical practice.
Time Frame	Up to 5 years
Safety Issue?	No

Analysis Population Description

The Full-Analysis-Set participants with measurable disease with CR or PR

Reporting Groups

	Description
Trastuzumab + 2nd Line Chemotherapy	Eligible participants were administered trastuzumab 6 mg/kg of body weight (except in Israel, where the dose was 2 mg/kg body weight), intravenous infusion, every three weeks until progression or withdrawal, in combination with second line chemotherapy.

Measured Values

	Trastuzumab + 2nd Line Chemotherapy
Number of Participants Analyzed	87
Objective Response Rate [units: Percentage of participants] Number (95% Confidence Interval)	
By Investigator (n= 87)	43.7 (33.1 to 54.8)
By computer (n=87)	43.7 (33.1 to 54.8)

3. Secondary Outcome Measure:

Measure Title	Clinical Benefit Rate
Measure Description	Clinical benefit rate (CBR) was defined as the percentage of participants taking a benefit from the treatments. CBR includes 1) Complete response (CR): disappearance of all target lesions and all non-target non-measurable lesions 2) Partial response (PR) : >=30% decrease in the sum of the longest diameter of target lesions and 3) Stable disease (SD): non-PR and non-progressive disease. It was evaluated using Response Evaluation Criteria in Solid Tumors (RECIST 1.0) and assessed by CT or MRI by the investigator. CBR was also assessed by computer. Clinical benefit rate was not assessed for 'Only Chemotherapy' group as randomization of participants was not feasible considering Trastuzumab widespread use in routine clinical practice.
Time Frame	Up to 5 years
Safety Issue?	No

Analysis Population Description

The Full-Analysis-Set participants with measurable disease with CR, PR and SD. Study design was changed to single arm study because herceptin use after progression herceptin-based therapy become widespread.

Reporting Groups

	Description
Trastuzumab + 2nd Line Chemotherapy	Eligible participants were administered trastuzumab 6 mg/kg of body weight (except in Israel, where the dose was 2 mg/kg body weight), intravenous infusion, every three weeks until progression or withdrawal, in combination with second line chemotherapy.

Measured Values

	Trastuzumab + 2nd Line Chemotherapy
Number of Participants Analyzed	87
Clinical Benefit Rate [units: Percentage of participants] Number (95% Confidence Interval)	
By Computer (n = 87)	75.9 (65.5 to 84.4)
By Investigator (n = 87)	72.4 (61.8 to 81.5)

4. Secondary Outcome Measure:

Measure Title	Median Time to Treatment Failure
Measure Description	Time to treatment failure is defined as a composite endpoint measuring time (number of days) from enrollment to discontinuation of treatment or change in treatment for any reason, including disease progression, treatment toxicity and death. Median time to treatment failure was not assessed for 'Only Chemotherapy' group as randomization of participants was not feasible considering Trastuzumab widespread use in routine clinical practice.
Time Frame	Up to 5 years
Safety Issue?	No

Analysis Population Description

The Full-Analysis-Set included all participants who were enrolled and had at least one valid primary efficacy variable on active treatment. Only those participants who experienced treatment failure were analyzed.

Reporting Groups

	Description
Trastuzumab + 2nd Line Chemotherapy	Eligible participants were administered trastuzumab 6 mg/kg of body weight (except in Israel, where the dose was 2 mg/kg body weight), intravenous infusion, every three weeks until progression or withdrawal, in combination with second line chemotherapy.

Measured Values

	Trastuzumab + 2nd Line Chemotherapy
Number of Participants Analyzed	80
Median Time to Treatment Failure [units: Days] Median (95% Confidence Interval)	154 (131 to 238)

5. Secondary Outcome Measure:

Measure Title	Overall Survival
Measure Description	Overall Survival is defined as the time (number of days) between enrollment and the date of death due to any cause. Overall survival was not assessed for 'Only Chemotherapy' group as randomization of participants was not feasible considering Trastuzumab widespread use in routine clinical practice.
Time Frame	Up to 5 years
Safety Issue?	No

Analysis Population Description

The Full-Analysis-Set included all participants who were enrolled and had at least one valid primary efficacy variable on active treatment. Only those participants with data available were analyzed.

Reporting Groups

	Description
Trastuzumab + 2nd Line Chemotherapy	Eligible participants were administered trastuzumab 6 mg/kg of body weight (except in Israel, where the dose was 2 mg/kg body weight), intravenous infusion, every three weeks until progression or withdrawal, in combination with second line chemotherapy.

Measured Values

	Trastuzumab + 2nd Line Chemotherapy
Number of Participants Analyzed	41
Overall Survival [units: Days] Median (95% Confidence Interval)	717 (589 to 1057)

6. Secondary Outcome Measure:

Measure Title	Number of Participants With Any Adverse Events and Serious Adverse Events
Measure Description	An adverse event (AE) is any untoward medical occurrence in a participant who is administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. A serious adverse event (SAE) is any untoward medical occurrence that at any dose results in death, are life threatening, requires hospitalization or prolongation of hospitalization or results in disability/incapacity, and congenital anomaly/birth defect.
Time Frame	Up to 5 years
Safety Issue?	No

Analysis Population Description

The Safety Population included all participants who entered the trial and received at least one dose of trial medication.

Reporting Groups

	Description
Trastuzumab + 2nd Line Chemotherapy	Eligible participants were administered trastuzumab 6 mg/kg of body weight (except in Israel, where the dose was 2 mg/kg body weight), intravenous infusion, every three weeks until progression or withdrawal, in combination with second line chemotherapy.
Only Chemotherapy	Eligible participants were administered second line chemotherapy according to the investigator's decision.

Measured Values

	Trastuzumab + 2nd Line Chemotherapy	Only Chemotherapy
Number of Participants Analyzed	93	16
Number of Participants With Any Adverse Events and Serious Adverse Events [units: Number of participants]		
Number of participants with any AE	84	10
Number of participants with any SAE	20	2

7. Secondary Outcome Measure:

Measure Title	Biochemistry Safety Laboratory Parameters: Mean Serum Glutamic Oxaloacetic Transaminase, Serum Glutamic-pyruvic Transaminase and Alkali Phosphatase Levels

Measure Description	Participants in the study were evaluated for the serum glutamic oxaloacetic transaminase (SGOT), serum glutamic-pyruvic transaminase (SGPT) and alkali phosphatase (ALP) at Visit 1 and final study assessments (Up to 5 years). Serum glutamic oxaloacetic transaminase, Serum glutamic-pyruvic transaminase and Alkali Phosphatase levels were not assessed for 'Only Chemotherapy' group as randomization of participants was not feasible considering Trastuzumab widespread use in routine clinical practice.
Time Frame	Visit 1 [Screening Period (6 weeks prior to enrollment)] and Final study Assessments (Up to 5 years)
Safety Issue?	No

Analysis Population Description

The Safety Population included all participants who entered the trial and received at least one dose of trial medication. n = the number of participants analyzed at a given time point.

Reporting Groups

	Description
Trastuzumab + 2nd Line Chemotherapy	Eligible participants were administered trastuzumab 6 mg/kg of body weight (except in Israel, where the dose was 2 mg/kg body weight), intravenous infusion, every three weeks until progression or withdrawal, in combination with second line chemotherapy.

Measured Values

	Trastuzumab + 2nd Line Chemotherapy
Number of Participants Analyzed	93
Biochemistry Safety Laboratory Parameters: Mean Serum Glutamic Oxaloacetic Transaminase, Serum Glutamic-pyruvic Transaminase and Alkali Phosphatase Levels [units: Units per liter] Mean (Standard Deviation)	
SGOT, Visit 1, (n = 93)	31.46 (29.78)
SGOT, Final study assessments, (n = 62)	36.16 (34.91)
SGPT, Visit 1, (n = 93)	25.86 (20.55)
SGPT, Final study assessments, (n = 61)	28.19 (16.92)
ALP, Visit 1, (n = 93)	202.30 (149.98)
ALP, Final study assessments, (n = 62)	193.49 (148.11)

8. Secondary Outcome Measure:

Measure Title	Biochemistry Safety Laboratory Parameters: Mean Total Bilirubin and Serum Creatinine Levels
Measure Description	Participants in the study were evaluated for the total bilirubin and serum creatinine. Total Bilirubin and serum creatinine levels were not assessed for 'Only Chemotherapy' group as randomization of participants was not feasible considering Trastuzumab widespread use in routine clinical practice.
Time Frame	Visit 1 [Screening Period (6 weeks prior to enrollment)] and Final study Assessments (Up to 5 years)
Safety Issue?	No

Analysis Population Description

The Safety Population included all participants who entered the trial and received at least one dose of trial medication. n = the number of participants analyzed at a given time point.

Reporting Groups

	Description
Trastuzumab + 2nd Line Chemotherapy	Eligible participants were administered trastuzumab 6 mg/kg of body weight (except in Israel, where the dose was 2 mg/kg body weight), intravenous infusion, every three weeks until progression or withdrawal, in combination with second line chemotherapy.

Measured Values

	Trastuzumab + 2nd Line Chemotherapy
Number of Participants Analyzed	93
Biochemistry Safety Laboratory Parameters: Mean Total Bilirubin and Serum Creatinine Levels [units: Micromole/liter] Mean (Standard Deviation)	
Total bilirubin, Visit 1, (n = 93)	13.50 (42.74)
Total bilirubin, Final study assessments(n = 60)	19.16 (36.77)
Serum creatinine, Visit 1, (n = 92)	81.18 (61.75)
Serum creatinine,Final study assessment (n = 63)	82.53 (70.86)

9. Secondary Outcome Measure:

Measure Title	Biochemistry Safety Laboratory Parameters: Mean Albumin Levels

Measure Description	Participants in the study were evaluated for the albumin at Visit 1 and Final study assessments. Albumin levels were not assessed for 'Only Chemotherapy' group as randomization of participants was not feasible considering Trastuzumab widespread use in routine clinical practice.
Time Frame	Visit 1 [Screening Period (6 weeks prior to enrollment)] and Final study assessments (Up to 5 years)
Safety Issue?	No

Analysis Population Description

The Safety Population included all participants who entered the trial and received at least one dose of trial medication. n = the number of participants analyzed at a given time point.

Reporting Groups

	Description
Trastuzumab + 2nd Line Chemotherapy	Eligible participants were administered trastuzumab 6 mg/kg of body weight (except in Israel, where the dose was 2 mg/kg body weight), intravenous infusion, every three weeks until progression or withdrawal, in combination with second line chemotherapy.

Measured Values

	Trastuzumab + 2nd Line Chemotherapy
Number of Participants Analyzed	84
Biochemistry Safety Laboratory Parameters: Mean Albumin Levels [units: gram per liter] Mean (Standard Deviation)	
Albumin, Visit 1, (n = 84)	43.99 (3.29)
Albumin, Final study assessments, (n = 54)	41.07 (6.96)

10. Secondary Outcome Measure:

Measure Title	Biochemistry Safety Laboratory Parameters: Mean Urea, Sodium and Potassium Levels
Measure Description	Participants in the study were evaluated for the biochemical safety laboratory parameters urea, sodium and potassium. Urea, sodium and potassium levels were not assessed for 'Only Chemotherapy' group as randomization of participants was not feasible considering Trastuzumab widespread use in routine clinical practice.
Time Frame	Visit 1 [Screening Period (6 weeks prior to enrollment)] and Final study assessments (Up to 5 years)
Safety Issue?	No

Analysis Population Description

The Safety Population included all participants who entered the trial and received at least one dose of trial medication. n = the number of participants analyzed at a given time point.

Reporting Groups

	Description
Trastuzumab + 2nd Line Chemotherapy	Eligible participants were administered trastuzumab 6 mg/kg of body weight (except in Israel, where the dose was 2 mg/kg body weight), intravenous infusion, every three weeks until progression or withdrawal, in combination with second line chemotherapy.

Measured Values

	Trastuzumab + 2nd Line Chemotherapy
Number of Participants Analyzed	92
Biochemistry Safety Laboratory Parameters: Mean Urea, Sodium and Potassium Levels [units: Millimole per liter] Mean (Standard Deviation)	
Urea, Visit 1, (n = 92)	6.33 (3.07)
Urea, Final study assessments, (n = 63)	6.92 (4.93)
Sodium, Visit 1, (n = 92)	140.58 (3.34)
Sodium, Final study assessments, (n = 61)	139.16 (3.71)
Potassium, Visit 1, (n = 91)	4.40 (0.45)
Potassium, Final study assessments, (n = 61)	4.22 (0.40)

11. Secondary Outcome Measure:

Measure Title	Hematology Safety Laboratory Parameters: Mean Hemoglobin Levels
Measure Description	Participants in the study were evaluated for the Hemoglobin up to 5 years. Hemoglobin levels were not assessed for 'Only Chemotherapy' group as randomization of participants was not feasible considering Trastuzumab widespread use in routine clinical practice.
Time Frame	Visit 1 [Screening Period (6 weeks prior to enrollment)] and final study assessments (Up to 5 years)
Safety Issue?	No

Analysis Population Description

The Safety Population included all participants who entered the trial and received at least one dose of trial medication. n = the number of participants analyzed at a given time point.

Reporting Groups

	Description
Trastuzumab + 2nd Line Chemotherapy	Eligible participants were administered trastuzumab 6 mg/kg of body weight (except in Israel, where the dose was 2 mg/kg body weight), intravenous infusion, every three weeks until progression or withdrawal, in combination with second line chemotherapy.

Measured Values

	Trastuzumab + 2nd Line Chemotherapy
Number of Participants Analyzed	93
Hematology Safety Laboratory Parameters: Mean Hemoglobin Levels [units: grams per deciliter] Mean (Standard Deviation)	
Hemoglobin, Visit 1, (n = 93)	12.67 (2.03)
Hemoglobin, Final study assessments, (n = 67)	11.00 (3.57)

12. Secondary Outcome Measure:

Measure Title	Hematology Safety Laboratory Parameters: Mean Total Leukocytes Counts
Measure Description	Participants in the study were evaluated for the total leukocytes up to 5 years. Total leukocytes counts were not assessed for 'Only Chemotherapy' group as randomization of participants was not feasible considering Trastuzumab widespread use in routine clinical practice.
Time Frame	Visit 1 [Screening Period (6 weeks prior to enrollment)] and final study assessments (Up to 5 years)
Safety Issue?	No

Analysis Population Description

The Safety Population included all participants who entered the trial and received at least one dose of trial medication. n = the number of participants analyzed at a given time point.

Reporting Groups

	Description
Trastuzumab + 2nd Line Chemotherapy	Eligible participants were administered trastuzumab 6 mg/kg of body weight (except in Israel, where the dose was 2 mg/kg body weight), intravenous infusion, every three weeks until progression or withdrawal, in combination with second line chemotherapy.

Measured Values

	Trastuzumab + 2nd Line Chemotherapy
Number of Participants Analyzed	92
Hematology Safety Laboratory Parameters: Mean Total Leukocytes Counts [units: 10^9 leukocytes/L] Mean (Standard Deviation)	
Total Leukocytes, Visit 1, (n = 92)	8.00 (8.60)
Total Leukocytes, Final study assessment (n =67)	7.53 (6.88)

13. Secondary Outcome Measure:

Measure Title	Hematology Safety Laboratory Parameters: Percent of Differential for Neutrophils, Basophils, Eosinophils, Lymphocytes and Monocytes Counts
Measure Description	Participants in the study were evaluated for the Neutrophils, Basophils, Eosinophils, Lymphocytes and Monocytes at Visit 1 and final study assessments. Neutrophils, Basophils, Eosinophils, Lymphocytes and Monocytes counts were not assessed for 'Only Chemotherapy' group as randomization of participants was not feasible considering Trastuzumab widespread use in routine clinical practice.
Time Frame	Visit 1 [Screening Period (6 weeks prior to enrollment)] and final study assessments (Up to 5 years)
Safety Issue?	No

Analysis Population Description

The Safety Population included all participants who entered the trial and received at least one dose of trial medication. n = the number of participants analyzed at a given time point.

Reporting Groups

	Description
Trastuzumab + 2nd Line Chemotherapy	Eligible participants were administered trastuzumab 6 mg/kg of body weight (except in Israel, where the dose was 2 mg/kg body weight), intravenous infusion, every three weeks until progression or withdrawal, in combination with second line chemotherapy.

Measured Values

	Trastuzumab + 2nd Line Chemotherapy
Number of Participants Analyzed	93
Hematology Safety Laboratory Parameters: Percent of Differential for Neutrophils, Basophils, Eosinophils, Lymphocytes and Monocytes Counts [units: percent of differential] Mean (Standard Deviation)	
Neutrophils, Visit 1, (n = 93)	64.89 (10.66)
Neutrophils, Final study assessments, (n = 64)	62.22 (14.80)
Basophils, Visit 1, (n = 86)	0.38 (0.33)
Basophils, Final study assessments, (n = 59)	1.28 (6.34)
Eosinophils, Visit 1, (n = 88)	2.36 (2.15)
Eosinophils, Final study assessments, (n = 61)	2.50 (3.56)
Lymphocytes, Visit 1, (n = 93)	26.34 (9.37)
Lymphocytes, Final study assessments, (n = 64)	26.48 (12.85)
Monocytes, Visit 1, (n = 89)	5.92 (2.22)
Monocytes, Final study assessments, (n = 59)	7.25 (3.56)

14. Secondary Outcome Measure:

Measure Title	Hematology Safety Laboratory Parameter: Mean Platelets Counts
Measure Description	Participants in the study were evaluated for the platelets at Visit 1 and final study assessments. Platelet counts were not assessed for 'Only Chemotherapy' group as randomization of participants was not feasible considering Trastuzumab widespread use in routine clinical practice.
Time Frame	Visit 1 [Screening Period (6 weeks prior to enrollment)] and final study assessments (Up to 5 years)
Safety Issue?	No

Analysis Population Description

The Safety Population included all participants who entered the trial and received at least one dose of trial medication. n = the number of participants analyzed at a given time point.

Reporting Groups

	Description
Trastuzumab + 2nd Line Chemotherapy	Eligible participants were administered trastuzumab 6 mg/kg of body weight (except in Israel, where the dose was 2 mg/kg body weight), intravenous infusion, every three weeks until progression or withdrawal, in combination with second line chemotherapy.

Measured Values

	Trastuzumab + 2nd Line Chemotherapy
Number of Participants Analyzed	93
Hematology Safety Laboratory Parameter: Mean Platelets Counts [units: Number of cells x 10^9/L] Mean (Standard Deviation)	
Platelets, Visit 1, (n = 93)	263.14 (63.91)
Platelets, Final study assessments, (n = 67)	256.64 (78.64)

15. Secondary Outcome Measure:

Measure Title	Mean Left Ventricular Ejection Fraction
Measure Description	Left ventricular ejection fraction (LVEF) is a measure of the percent of blood ejected from the ventricle in one heartbeat. It is a measure of cardiac function and was assessed by echocardiogram or multigated angiogram at Visit 0 [Screening period (6 weeks prior to enrollment)] and final study assessments (Up to 5 years).
Time Frame	Visit 0 [Screening period (6 weeks prior to enrollment)] and final study assessments (Up to 5 years).
Safety Issue?	No

Analysis Population Description

The Safety Population included all participants who entered the trial and received at least one dose of trial medication. n = the number of participants analyzed at a given time point.

Reporting Groups

	Description
Trastuzumab + 2nd Line Chemotherapy	Eligible participants were administered trastuzumab 6 mg/kg of body weight (except in Israel, where the dose was 2 mg/kg body weight), intravenous infusion, every three weeks until progression or withdrawal, in combination with second line chemotherapy.
Only Chemotherapy	Eligible participants received second line chemotherapy according to the investigator's decision.

Measured Values

	Trastuzumab + 2nd Line Chemotherapy	Only Chemotherapy
Number of Participants Analyzed	92	16
Mean Left Ventricular Ejection Fraction [units: percent of blood pumped from LV chamber]] Mean (Standard Deviation)		
Visit 0 (n = 92, 16)	63.3 (6.8)	62.6 (6.9)
Final study assessment (n= 53, 5)	61.2 (7.4)	68.6 (5.9)

Reported Adverse Events

Time Frame	Up to 5 years
Additional Description	The Safety Population included all participants who entered the trial and received at least one dose of trial medication.

Reporting Groups

	Description
Trastuzumab + 2nd Line Chemotherapy	Eligible participants were administered trastuzumab 6 mg/kg of body weight (except in Israel, where the dose was 2 mg/kg body weight), IV infusion, every three weeks until disease progression, unacceptable toxicities, or withdrawal from study in combination with second line chemotherapy.
Only Chemotherapy	Eligible participants were administered second line chemotherapy according to the investigator’s decision.

Serious Adverse Events

	Trastuzumab + 2nd Line Chemotherapy	Only Chemotherapy
	Affected/At Risk (%)	Affected/At Risk (%)
Total	20/93 (21.51%)	2/16 (12.5%)
Blood and lymphatic system disorders		
Granulocytosis [A] †	1/93 (1.08%)	0/16 (0%)
Leukopenia [A] †	2/93 (2.15%)	0/16 (0%)
Cardiac disorders		
Angina pectoris [A] †	0/93 (0%)	1/16 (6.25%)
Atrial fibrillation [A] †	1/93 (1.08%)	0/16 (0%)
Cardiopulmonary failure [A] †	2/93 (2.15%)	0/16 (0%)
Eye disorders		
Retinal detachment [A] †	1/93 (1.08%)	0/16 (0%)
Gastrointestinal disorders		
Diarrhoea [A] †	3/93 (3.23%)	0/16 (0%)
Nausea [A] †	1/93 (1.08%)	0/16 (0%)
Vomiting [A] †	1/93 (1.08%)	0/16 (0%)
General disorders		
Chest pain [A] †	1/93 (1.08%)	0/16 (0%)
Death [A] †	0/93 (0%)	1/16 (6.25%)
Pyrexia [A] †	1/93 (1.08%)	0/16 (0%)
Infections and infestations		
Gastroenteritis [A] †	1/93 (1.08%)	0/16 (0%)
Pneumonia [A] †	5/93 (5.38%)	0/16 (0%)
Sepsis [A] †	1/93 (1.08%)	0/16 (0%)

	Trastuzumab + 2nd Line Chemotherapy	Only Chemotherapy
	Affected/At Risk (%)	Affected/At Risk (%)
Urinary tract infection [A] †	1/93 (1.08%)	0/16 (0%)
Injury, poisoning and procedural complications		
Femoral neck fracture [A] †	1/93 (1.08%)	0/16 (0%)
Humerus fracture [A] †	1/93 (1.08%)	0/16 (0%)
Musculoskeletal and connective tissue disorders		
Pain in extremity [A] †	1/93 (1.08%)	0/16 (0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Tumour pain [A] †	1/93 (1.08%)	0/16 (0%)
Nervous system disorders		
Brain oedema [A] †	1/93 (1.08%)	0/16 (0%)
Respiratory, thoracic and mediastinal disorders		
Asthma [A] †	1/93 (1.08%)	0/16 (0%)
Chronic obstructive pulmonary disease [A] †	1/93 (1.08%)	0/16 (0%)
Pulmonary embolism [A] †	1/93 (1.08%)	0/16 (0%)
Vascular disorders		
Superior vena cava syndrome [A] †	1/93 (1.08%)	0/16 (0%)

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA (18.1)

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 2%

	Trastuzumab + 2nd Line Chemotherapy	Only Chemotherapy
	Affected/At Risk (%)	Affected/At Risk (%)
Total	81/93 (87.1%)	9/16 (56.25%)
Blood and lymphatic system disorders		

	Trastuzumab + 2nd Line Chemotherapy	Only Chemotherapy
	Affected/At Risk (%)	Affected/At Risk (%)
Agranulocytosis [A] †	5/93 (5.38%)	0/16 (0%)
Anemia [A] †	25/93 (26.88%)	5/16 (31.25%)
Febrile neutropenia [A] †	2/93 (2.15%)	0/16 (0%)
Granulocytopenia [A] †	0/93 (0%)	1/16 (6.25%)
Leukocytosis [A] †	1/93 (1.08%)	2/16 (12.5%)
Leukopenia [A] †	76/93 (81.72%)	3/16 (18.75%)
Neutropenia [A] †	80/93 (86.02%)	1/16 (6.25%)
Thrombocytopenia [A] †	3/93 (3.23%)	0/16 (0%)
Thrombocytosis [A] †	4/93 (4.3%)	0/16 (0%)
Cardiac disorders		
Cardiac failure [A] †	6/93 (6.45%)	0/16 (0%)
Cardiomyopathy [A] †	2/93 (2.15%)	0/16 (0%)
Palpitations [A] †	4/93 (4.3%)	1/16 (6.25%)
Tachycardia [A] †	2/93 (2.15%)	0/16 (0%)
Eye disorders		
Cataract [A] †	2/93 (2.15%)	0/16 (0%)
Keratitis [A] †	2/93 (2.15%)	0/16 (0%)
Lacrimation increased [A] †	4/93 (4.3%)	0/16 (0%)
Gastrointestinal disorders		
Abdominal discomfort [A] †	0/93 (0%)	1/16 (6.25%)
Abdominal pain [A] †	12/93 (12.9%)	1/16 (6.25%)
Abdominal pain upper [A] †	2/93 (2.15%)	1/16 (6.25%)

	Trastuzumab + 2nd Line Chemotherapy	Only Chemotherapy
	Affected/At Risk (%)	Affected/At Risk (%)
Constipation [A] †	4/93 (4.3%)	0/16 (0%)
Diarrhoea [A] †	52/93 (55.91%)	1/16 (6.25%)
Dyspepsia [A] †	3/93 (3.23%)	0/16 (0%)
Flatulence [A] †	3/93 (3.23%)	0/16 (0%)
Gastrooesophageal reflux disease [A] †	2/93 (2.15%)	1/16 (6.25%)
Nausea [A] †	53/93 (56.99%)	0/16 (0%)
Stomatitis [A] †	3/93 (3.23%)	0/16 (0%)
Toothache [A] †	1/93 (1.08%)	1/16 (6.25%)
Vomiting [A] †	21/93 (22.58%)	1/16 (6.25%)
General disorders		
Asthenia [A] †	15/93 (16.13%)	0/16 (0%)
Chest pain [A] †	3/93 (3.23%)	0/16 (0%)
Chills [A] †	2/93 (2.15%)	0/16 (0%)
Face oedema [A] †	0/93 (0%)	1/16 (6.25%)
Fatigue [A] †	30/93 (32.26%)	7/16 (43.75%)
Gait disturbance [A] †	4/93 (4.3%)	0/16 (0%)
Infusion site inflammation [A] †	2/93 (2.15%)	0/16 (0%)
Infusion site pain [A] †	7/93 (7.53%)	0/16 (0%)
Local swelling [A] †	0/93 (0%)	1/16 (6.25%)
Oedema peripheral [A] †	8/93 (8.6%)	4/16 (25%)
Pain [A] †	2/93 (2.15%)	0/16 (0%)
Peripheral swelling [A] †	2/93 (2.15%)	1/16 (6.25%)

	Trastuzumab + 2nd Line Chemotherapy	Only Chemotherapy
	Affected/At Risk (%)	Affected/At Risk (%)
Pyrexia [A] †	11/93 (11.83%)	0/16 (0%)
Immune system disorders		
Hypersensitivity [A] †	4/93 (4.3%)	0/16 (0%)
Infections and infestations		
Bronchitis [A] †	3/93 (3.23%)	0/16 (0%)
Cellulitis [A] †	2/93 (2.15%)	0/16 (0%)
Conjunctivitis [A] †	2/93 (2.15%)	0/16 (0%)
Cystitis [A] †	2/93 (2.15%)	0/16 (0%)
Erysipelas [A] †	2/93 (2.15%)	0/16 (0%)
Eye infection [A] †	2/93 (2.15%)	0/16 (0%)
Herpes zoster [A] †	2/93 (2.15%)	0/16 (0%)
Infection [A] †	2/93 (2.15%)	0/16 (0%)
Pharyngitis [A] †	3/93 (3.23%)	1/16 (6.25%)
Pneumonia [A] †	4/93 (4.3%)	0/16 (0%)
Upper respiratory tract infection [A] †	6/93 (6.45%)	0/16 (0%)
Urinary tract infection [A] †	3/93 (3.23%)	0/16 (0%)
Viral infection [A] †	3/93 (3.23%)	0/16 (0%)
Investigations		
Blood bilirubin increased [A] †	2/93 (2.15%)	0/16 (0%)
Blood glucose increased [A] †	2/93 (2.15%)	0/16 (0%)
Ejection fraction decreased [A] †	2/93 (2.15%)	0/16 (0%)
Hepatic enzyme increased [A] †	2/93 (2.15%)	0/16 (0%)

	Trastuzumab + 2nd Line Chemotherapy	Only Chemotherapy
	Affected/At Risk (%)	Affected/At Risk (%)
Weight decreased [A] †	5/93 (5.38%)	0/16 (0%)
Metabolism and nutrition disorders		
Decreased appetite [A] †	15/93 (16.13%)	0/16 (0%)
Dehydration [A] †	2/93 (2.15%)	1/16 (6.25%)
Diabetes mellitus [A] †	2/93 (2.15%)	0/16 (0%)
Hypercholesterolaemia [A] †	3/93 (3.23%)	0/16 (0%)
Hyperlipidaemia [A] †	3/93 (3.23%)	0/16 (0%)
Hypertriglyceridaemia [A] †	3/93 (3.23%)	0/16 (0%)
Hyperuricaemia [A] †	2/93 (2.15%)	0/16 (0%)
Musculoskeletal and connective tissue disorders		
Arthralgia [A] †	6/93 (6.45%)	0/16 (0%)
Back pain [A] †	7/93 (7.53%)	0/16 (0%)
Bone pain [A] †	13/93 (13.98%)	1/16 (6.25%)
Muscular weakness [A] †	3/93 (3.23%)	0/16 (0%)
Musculoskeletal chest pain [A] †	3/93 (3.23%)	0/16 (0%)
Musculoskeletal pain [A] †	2/93 (2.15%)	1/16 (6.25%)
Myalgia [A] †	2/93 (2.15%)	0/16 (0%)
Neck pain [A] †	3/93 (3.23%)	0/16 (0%)
Pain in extremity [A] †	6/93 (6.45%)	2/16 (12.5%)
Nervous system disorders		
Dizziness [A] †	13/93 (13.98%)	1/16 (6.25%)
Dysgeusia [A] †	2/93 (2.15%)	0/16 (0%)

	Trastuzumab + 2nd Line Chemotherapy	Only Chemotherapy
	Affected/At Risk (%)	Affected/At Risk (%)
Headache [A] †	8/93 (8.6%)	0/16 (0%)
Hypoaesthesia [A] †	10/93 (10.75%)	0/16 (0%)
Neuropathy peripheral [A] †	5/93 (5.38%)	3/16 (18.75%)
Paraesthesia [A] †	4/93 (4.3%)	0/16 (0%)
Peripheral sensory neuropathy [A] †	3/93 (3.23%)	0/16 (0%)
Polyneuropathy [A] †	3/93 (3.23%)	0/16 (0%)
Psychiatric disorders		
Confusional state [A] †	2/93 (2.15%)	0/16 (0%)
Depression [A] †	0/93 (0%)	1/16 (6.25%)
Insomnia [A] †	3/93 (3.23%)	0/16 (0%)
Renal and urinary disorders		
Dysuria [A] †	2/93 (2.15%)	0/16 (0%)
Reproductive system and breast disorders		
Breast pain [A] †	2/93 (2.15%)	0/16 (0%)
Respiratory, thoracic and mediastinal disorders		
Asthma [A] †	2/93 (2.15%)	0/16 (0%)
Cough [A] †	16/93 (17.2%)	0/16 (0%)
Dyspnoea [A] †	11/93 (11.83%)	1/16 (6.25%)
Epistaxis [A] †	6/93 (6.45%)	0/16 (0%)
Hydrothorax [A] †	3/93 (3.23%)	0/16 (0%)
Oropharyngeal pain [A] †	10/93 (10.75%)	0/16 (0%)
Rhinorrhoea [A] †	2/93 (2.15%)	1/16 (6.25%)
Skin and subcutaneous tissue disorders		

	Trastuzumab + 2nd Line Chemotherapy	Only Chemotherapy
	Affected/At Risk (%)	Affected/At Risk (%)
Alopecia [A] †	12/93 (12.9%)	2/16 (12.5%)
Dermatitis [A] †	4/93 (4.3%)	0/16 (0%)
Nail disorder [A] †	2/93 (2.15%)	0/16 (0%)
Palmar-plantar erythrodysaesthesia syndrome [A] †	37/93 (39.78%)	4/16 (25%)
Pruritus [A] †	2/93 (2.15%)	0/16 (0%)
Rash [A] †	11/93 (11.83%)	0/16 (0%)
Scar pain [A] †	2/93 (2.15%)	0/16 (0%)
Skin exfoliation [A] †	2/93 (2.15%)	0/16 (0%)
Skin hyperpigmentation [A] †	1/93 (1.08%)	1/16 (6.25%)
Vascular disorders		
Deep vein thrombosis [A] †	4/93 (4.3%)	0/16 (0%)
Hypertension [A] †	19/93 (20.43%)	1/16 (6.25%)
Phlebitis [A] †	3/93 (3.23%)	0/16 (0%)

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA (18.1)

Limitations and Caveats

[Not specified]

More Information

Certain Agreements:

Principal Investigators are NOT employed by the organization sponsoring the study.

There IS an agreement between the Principal Investigator and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

The Study being conducted under this Agreement is part of the Overall Study. Investigator is free to publish in reputable journals or to present at professional conferences the results of the Study, but only after the first publication or presentation that involves the Overall Study. The Sponsor may request that Confidential Information be deleted and/or the publication be postponed in order to protect the Sponsor's intellectual property rights.

Results Point of Contact:

Name/Official Title: Roche Trial Information Hotline
Organization: F. Hoffmann-La Roche AG
Phone: +41 616878333
Email: global.trial_information@roche.com