TITLE PAGE

CLINICAL STUDY REPORT NO: 1097136

STUDY INFORMATION

TITLE:	**NON-INTERVENTIONAL, POST-MARKETING SURVEILLANCE STUDY (NIS) OF HERCEPTIN® IN PATIENTS WHO RELAPSED AFTER ANTI-HER2-THERAPY FOR EARLY BREAST CANCER**
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1. SYNOPSIS/ABSTRACT

Title

NON-INTERVENTIONAL, POST-MARKETING SURVEILLANCE STUDY (NIS) OF HERCEPTIN® IN PATIENTS WHO RELAPSED AFTER ANTI-HER2-THERAPY FOR EARLY BREAST CANCER

NIS Data Science Responsible:

Roche Pharma AG

Grenzach-Wyhlen, Germany

Date of the abstract: 16 October 2019

Keywords

Recurrent/metastatic breast cancer ▪ HER2 ▪ Herceptin® re-therapy ▪ Germany ▪ non-interventional post-marketing surveillance study

Research Question and Objectives

This NIS was designed to evaluate the effectiveness and safety of reapplication (hereinafter referred to as “re-therapy”) of Herceptin® (trastuzumab) in routine clinical practice in patients with human epidermal growth factor receptor 2 (HER2)-positive breast cancer (BC) having relapsed following completed (neo-) adjuvant anti-HER2-therapy with Herceptin for HER2-positive early breast cancer (EBC).

Study objectives

The questions of key importance included:

- How long is the median time span between the adjuvant anti-HER2 treatment and the onset of Herceptin re-therapy for first-line treatment of recurrent BC/metastatic breast cancer (MBC)?
- How long is the average duration of Herceptin re-therapy?
- Which criteria influence the choice of Herceptin re-therapy?
- Which criteria determine the choice of chemotherapy regimens in combination with Herceptin re-therapy in routine clinical practice?
- Which kind of therapy regimens are chosen in second- and further-line settings following completed Herceptin re-therapy?

- Is there a difference in outcome depending on selected adjuvant anti-HER2-therapy?
- Are the positive effects in terms of disease-free survival (DFS) intervals shown in registration studies reproducible in this NIS?
- Are there any new side effects?
- What are the experiences with cardiac events in terms of frequency, management and outcome?

Study design

This study was a multicenter, non-interventional post-marketing surveillance study conducted in Germany in accordance with §67 section 6 of the German Drug Act (AMG), which involved primary data collection.

Target Population

Patients were recruited from 23 October 2008 (first-patient-in) through 9 January 2013 (last-patient-in) in 122 study sites across Germany including oncologists and gynecologists in hospitals and outpatient clinics, and independent oncology practices (220 sites participated, of these, 98 were non-recruiting). Eligible patients were aged ≥18 years, diagnosed with HER2-positive, locally recurrent BC or MBC having relapsed following completed (neo-) adjuvant anti-HER2-therapy with Herceptin for HER2-positive EBC and with decision for first-line Herceptin re-therapy in routine clinical practice. The maximum duration of documentation period per patient was 60 months (5 years) after enrollment, comprising a basic observational period of Herceptin re-therapy for a maximum of 12 months or until premature discontinuation of Herceptin re-therapy due to any reason, and a follow-up period until date of death or for a maximum of 4 years. The individual follow-up period was independent of whether Herceptin re-therapy was discontinued during or continued beyond the 12-month basic observational period, or whether other further-line antineoplastic treatments were given following end of Herceptin re-therapy. Database lock was performed on 24 October 2018.

Study size

In this study, 239 patients were enrolled in 122 sites, of these, 23 patients were excluded from final data analysis as they did not meet the inclusion criteria.

Studied medicinal product

Herceptin® (trastuzumab)

Variables

The following variables were captured from medical records as per documentation procedure in routine clinical practice:

- Demographic characteristics and medical history
- HER2 diagnosis
- Comorbidities
- Tumor anamnesis
- Prognostic factors (including number of lymph nodes with cancer, tumor stage, hormone receptor status, and HER2 status)
- (Neo-) adjuvant anti-HER2 therapy and outcome
- Herceptin re-therapy and outcome (monotherapy and combination therapy)
- Manifestation of new metastases in organ systems not affected at enrollment (course of neoplastic disease)
- Further-line treatments following discontinuation of Herceptin re-therapy
- Cardiac monitoring
- Adverse events (AEs) including AEs requiring expedited reporting and AEs of special interest (AESI), serious AEs (SAEs), adverse drug reactions (ADRs), serious ADRs (SADRs) and pregnancies including management and outcome
- Concomitant medication for management of (S)AEs and (S)ADRs
- Disease and survival status

Data Sources

The electronic data capture system was provided by iOMEDICO AG, i.e. the CRO which supported the study as full-service provider. Data were derived from electronic Case Report Form (eCRF)-entries made by the sites as part of routine clinical practice. Data were transferred from source documents (i.e., patient's medical records) to the eCRF. All steps of quality checks were performed and recorded according to iOMEDICO- and Roche-specific SOPs.

Statistical and Epidemiological Methods

Time-to-event endpoints including progression-free survival (PFS) and overall survival (OS) were estimated by using the Kaplan-Meier method to present time-to-event data together with number of censored cases as well as quartiles, rates, and corresponding 95% confidence interval (CI).

PFS was defined as the time from diagnosis of local recurrent tumor / distant metastasis, which led to the initiation of anti-HER2 re-therapy with Herceptin to progression or death due to any cause.

The OS was defined as the time from initial tumor resection to death due to any cause. As a further Kaplan-Meier analysis, the “OS-2” was estimated, defined as the time from diagnosis of local recurrent tumor / distant metastasis, which led to the initiation of anti-HER2 re-therapy with Herceptin to death due to any cause.

Duration of the observational period was estimated by using the reverse Kaplan-Meier method and is presented using median together with corresponding 95% CI.

A multivariable logistic regression analysis and a multivariable Cox regression analysis (Efron method used to control for ties) were performed to identify potential independent factors (baseline demographics and clinical characteristics), which might have an impact on the clinical response rate or PFS, respectively. No variable selection process was conducted.

Analysis Populations

- Study population (Analysis population, AP): The AP comprised all patients considered eligible according to the Data Review Meeting. Patients without (neo-) adjuvant treatment, with HER2-negative tumor, without Herceptin treatment, with tumor recurrence during adjuvant treatment, with antineoplastic therapy for metastatic or locally advanced disease prior to Herceptin re-therapy or with retrospective documentation >1 year were excluded from analysis.

- Summary of Product Characteristics (SmPC)-population: The SmPC-population comprised patients with a strict “in-label” combination treatment during Herceptin re-therapy, i.e. patients treated with Herceptin and taxanes +/- endocrine treatment.

This population was defined *post-hoc* to gain a further insight into effectiveness and tumor and disease characteristics in the subset of patients with treatment combinations according to SmPC of Herceptin.

Results

The report includes data from 216 patients (AP), and 49 patients (SmPC-population).

Herceptin Re-Therapy

	AP (N=216)
Deciding factors for choice of Herceptin re-therapy[1] (>30% of patients), n (%)	
HER2-status	202 (93.5)
Efficacy of (neo-) adjuvant anti-HER2 therapy	102 (47.2)
Tolerability of (neo-) adjuvant anti-HER2 therapy	100 (46.3)
Study results/publications	94 (43.5)
Patient's performance status	73 (33.8)
Median time span between end of adjuvant anti-HER2 treatment and onset of Herceptin re-therapy (months) [min – max]	21.1 months [0.6 – 98.3]
Initial dose of Herceptin re-therapy n (%)	
8 mg/kg	111 (51.4)
4 mg/kg	76 (35.2)
Other dose	29 (13.4)
Median duration of Herceptin re-therapy (months) [min – max]	9.0 months [0.0- 74.7]
Modification of Herceptin re-therapy, n (%)	
Patients with ≥1 therapy modification	82 (38.0)
Type of modification of Herceptin re-therapy[1], n (%)	
≥1 dose modification	57 (26.4)
≥1 therapy delay	25 (11.6)
≥1 therapy interruption	23 (10.6)
Reason for discontinuation of Herceptin re-therapy (>5% of patients), n (%)	
Disease progression (recurrence/metastasis)	111 (51.4)
Patient death	22 (10.2)
Treating physician's decision	21 (9.7)
Patient's request	13 (6.0)

AP = Analysis population; HER2 = Human epidermal growth factor receptor 2; Min = Minimum; Max = Maximum; N/n = Number
[1]Multiple entries per patient possible.

Concomitant Treatments With Herceptin Re-Therapy

	AP (N=216)
Concomitant chemotherapy (N=145)	
Deciding factors for choice of concomitant chemotherapy[1] (>30% of patients), n (%)	
Guidelines	105 (48.6)
Patient's performance status	84 (38.9)
Study results/Publications	78 (36.1)
Patient age	71 (32.9)
Drugs used in the first line of concomitant chemotherapy with Herceptin re-therapy[1] (>10% of patients), n (%)	
Paclitaxel	53 (24.5)
Vinorelbine	40 (18.5)
Capecitabine	31 (14.4)
Docetaxel	23 (10.6)
Concomitant endocrine therapy (N=69)	
Drugs used in concomitant endocrine therapy with Herceptin re-therapy[1] (>5% of patients), n (%)	
Exemestane	19 (8.8)
Fulvestrant	18 (8.3)
Tamoxifen	18 (8.3)
Anastrozole	16 (7.4)
Letrozole	16 (7.4)

AP = Analysis population; N/n = Number
[1]Multiple entries per patient possible.

LVEF <50% During Study

	AP (N=216)
Number of patients with ≥1 documented post-baseline LVEF measurement, N (%)	129 (100)[1]
Lowest post-baseline LVEF <50%[2], n (%)	14 (10.9)
Lowest post-baseline LVEF ≥50%, n (%)	115 (89.1)

AP = Analysis population; LVEF = Left ventricular ejection fraction; N/n = Number
[1]This corresponds to 60% of the patients in the total AP, who were reported with post-baseline LVEF measurement following start of re-therapy with Herceptin.
[2]To be reported as an AE if the LVEF was <45% or in cases where the LVEF had dropped by >10% compared to baseline measurement. However, in cases where LVEF <45% or LVEF drop >10%, a corresponding AE had not been reported in all affected patients.

LVEF Decrease >10% Compared to Baseline

	AP (N=216)
Number of patients with a documented baseline LVEF measurement and ≥1 post-baseline LVEF measurement, N (%)	84 (100)[1]
LVEF nadir at least 10% lower than the baseline value, n (%)	30 (35.7)
Difference in LVEF nadir of less than 10% versus baseline (or nadir greater than baseline value), n (%)	54 (64.3)

AP = Analysis population; LVEF = Left ventricular ejection fraction; N/n = Number
[1]The analysis included data from patients with a documented baseline LVEF (4 weeks before or after initiation of re-therapy with Herceptin) and at least one post-baseline LVEF measurement over the course of the study.
The nadir was defined as the lowest post-baseline LVEF documented over the course of the study (including follow-up documentation and the period after discontinuation of Herceptin re-therapy). However, in cases where LVEF <45% or LVEF drop >10%, a corresponding AE had not been reported in all affected patients.

EFFECTIVENESS

Progression-Free Survival

	Total population (AP)	SmPC-population[1]
Total number of patients	*216*	*49*
Events, n (%)	166 (76.9)	45 (91.8)
Median PFS (months) [95% CI]	12.7 (10.5 - 14.8)	9.8 (7.9 - 12.7)
PFS rates (%) [95% CI]		
6-month	82.0% (76.1% - 86.5%)	77.6% (63.1% - 86.9%)
12-month	52.8% (45.7% - 59.4%)	38.3% (24.8% - 51.7%)

AP = Analysis population; CI = Confidence interval; n = Number; PFS = Progression-free survival; SmPC = Summary of Product Characteristics
[1]The SmPC-population was defined *post-hoc*.

Progression-Free Survival – Subgroup[1] "Metastases / Local Recurrence Only"

	No metastases (local recurrence only)	Non-visceral	Visceral
Analysis population (AP): Total N=216			
Total number of patients (subgroups)[2], N	*43*	*61*	*110*
Events, n (%)	24 (55.8)	44 (72.1)	97 (88.2)
Median PFS (months) [95% CI]	26.1 (12.7 - NA)	16.3 (9.6 - 21.5)	10.2 (8.0 - 11.4)
SmPC-population[3]: Total N=49			
Total number of patients (subgroups), N	*6*	*8*	*35*
Events, n (%)	4 (66.7)	6 (75.0)	35 (100)
Median PFS (months) [95% CI]	36.9 (10.2 - NA)	17.5 (3.3 - 18.6)	7.9 (6.6 - 9.8)

AP = Analysis population; CI = Confidence interval; N/n = Number; NA = Not reached; PFS = Progression-free survival; SmPC = Summary of Product Characteristics
[1]Subgroups of patients with no metastases (local recurrence only), patients with non-visceral metastases (± local recurrence, no visceral metastases) and patients with visceral metastases (± non-visceral metastases ± local recurrence).
[2]The metastatic status of 2 patients could not be classified as only the free-text entries "secondary contralateral carcinoma" and "increased tumor marker" were recorded in the eCRF, respectively.
[3]The SmPC-population was defined *post-hoc*.

Progression-Free Survival – Subgroup[1] "Combination Therapy"

	Herceptin mono re-therapy	Taxanes	Endocrine therapy	Other CTx	CTx and endocrine therapy
Analysis population (AP): Total N=216 Total number of patients (subgroups)	*36*	*51*	*35*	*74*	*20*
Events, n (%)	22 (61.1)	49 (96.1)	26 (74.3)	56 (75.7)	13 (65.0)
Median PFS (months) [95% CI]	18.2 (10.4 - 35.0)	8.9 (7.2 - 10.3)	12.2 (8.3 - 27.3)	13.4 (10.2 - 16.6)	19.9 (12.7 - 54.6)

AP = Analysis population; CI = Confidence interval; CTx = Chemotherapy; N/n = Number; NA = Not reached; PFS = Progression-free survival;
[1]Subgroups of patients having received combination therapy with Herceptin re-therapy.

Progression-Free Survival – Subgroup[1] "Chemotherapy"

	Taxane	Vinorelbine	Capecitabine
Analysis population (AP): Total N=216 Total number of patients (subgroups), N	*51*	*27*	*23*
Events, n (%)	49 (96.1)	18 (66.7)	16 (69.6)
Median PFS (months) [95% CI]	8.9 (7.2 - 10.3)	12.1 (9.3 - 31.3)	12.5 (6.4 - 17.1)

AP = Analysis population; CI = Confidence interval; N/n = Number; PFS = Progression-free survival
[1]Subgroups of patients having received mono-chemotherapy (no endocrine therapy) in combination with Herceptin re-therapy.

Overall Survival (OS)

	Total population (AP)	SmPC-population[1]
Total number of patients, N	*216*	*49*
Events, n (%)	134 (62.0)	37 (75.5)
Median OS (months) [95% CI]	77.3 (66.2 - 88.8)	76.4 (57.6 - 88.8)
OS rates (%) [95% CI]		
12-month	100.0% (100.0% - 100.0%)	100.0% (100.0% - 100.0%)
24-month	99.5% (96.7% - 99.9%)	100.0% (100.0% - 100.0%)
36-month	92.9% (88.5% - 95.7%)	91.7% (79.3% - 96.8%)
48-month	80.3% (74.3% - 85.1%)	81.2% (67.1% - 89.8%)

AP = Analysis population; CI = Confidence interval; N/n = Number; OS = Overall survival; SmPC = Summary of Product Characteristics
[1]The SmPC-population was defined *post-hoc*.

Overall Survival (OS-2)

	Total population (AP)	SmPC-population[1]
Total number of patients, N	*216*	*49*
Events, n (%)	134 (62.0)	37 (75.5)

	Total population (AP)	SmPC-population[1]
Median OS-2 (months) [95% CI]	31.6 (28.8 - 38.4)	21.8 (15.0 - 36.1)
OS-2 rates (%) [95% CI]		
12-month	82.9% (77.1% - 87.4%)	73.4% (58.6% - 83.6%)
24-month	62.9% (55.9% - 69.2%)	48.9% (34.0% - 62.3%)
36-month	45.3% (38.2% - 52.0%)	37.8% (24.0% - 51.5%)
48-month	37.1% (30.4% - 43.9%)	26.7% (14.9% - 39.9%)

AP = Analysis population; CI = Confidence interval; N/n = Number; OS = Overall survival; SmPC = Summary of Product Characteristics
[1]The SmPC-population was defined *post-hoc*.

Overall Survival (OS-2) – Subgroup[1] "Metastases / Local Recurrence Only"

	No metastases (local recurrence only)	Non-visceral	Visceral
Analysis population (AP): Total N=216 *Total number of patients (subgroups)[2], N*	*43*	*61*	*110*
Events, n (%)	18 (41.9)	32 (52.5)	84 (76.4)
Median OS-2 (months) [95% CI]	NA	49.2 (33.1 - NA)	20.8 (17.3 - 28.8)
SmPC-population[3]: Total N=49 *Total number of patients (subgroups), N*	*6*	*8*	*35*
Events, n (%)	3 (50.0)	5 (62.5)	29 (82.9)
Median OS-2 (months) [95% CI]	NA	67.4 (15.6 - 98.6)	16.3 (9.0 - 27.6)

AP = Analysis population; CI = Confidence interval; N/n = Number; NA = Not reached; OS = Overall survival; SmPC = Summary of Product Characteristics
[1]Subgroups of patients with no metastases (local recurrence only), patients with non-visceral metastases (± local recurrence, no visceral metastases) and patients with visceral metastases (± non-visceral metastases ± local recurrence).
[2]The metastatic status of 2 patients could not be classified as only the free-text entries "secondary contralateral carcinoma" and "increased tumor marker" were recorded in the eCRF, respectively.
[3]The SmPC-population was defined *post-hoc*.

Overall Survival (OS-2) – Subgroup[1] "Combination Therapy"

	Herceptin mono re-therapy	Taxanes	Endocrine therapy	Other CTx	CTx and endocrine therapy
Analysis population (AP): Total N=216 *Total number of patients (subgroups)*	*36*	*51*	*35*	*74*	*20*
Events, n (%)	16 (44.4)	43 (84.3)	20 (57.1)	44 (59.5)	11 (55.0)
Median OS-2 (months) [95% CI]	58.7 (33.1 - NA)	18.5 (15.0 - 27.6)	36.1 (27.0 - NA)	29.6 (25.4 - 47.1)	57.6 (21.6 - NA)

AP = Analysis population; CI = Confidence interval; CTx = Chemotherapy; N/n = Number; NA = Not reached; OS = Overall survival;
[1]Subgroups of patients having received combination therapy with Herceptin re-therapy.
"

Overall Survival (OS-2) – Subgroup[1] "Chemotherapy"

	Taxane	Vinorelbine	Capecitabine
Analysis population (AP): Total N=216			
Total number of patients (subgroups), N	*51*	*27*	*23*
Events, n (%)	43 (84.3)	18 (66.7)	12 (52.2)
Median OS-2 (months) [95% CI]	18.5 (15.0 - 27.6)	29.6 (17.3 - 49.2)	25.4 (11.1 - NA)

AP = Analysis population; CI = Confidence interval; N/n = Number; NA = Not reached; OS = Overall survival
[1]Subgroups of patients having received mono-chemotherapy (no endocrine therapy) in combination with Herceptin re-therapy.

Overall Response (ORR)

	Total population (AP)	SmPC-population[1]
Total number of patients, N	*216*	*49*
Best tumor response[2] (ORR), n (%)		
CR	20 (9.3)	6 (12.2)
PR	56 (25.9)	18 (36.7)
ORR	76 (35.2)	24 (49.0)

AP = Analysis population; CR = Complete remission; N/n = Number; ORR = Overall response rate; PR = Partial remission; SmPC = Summary of Product Characteristics
[1]The SmPC-population was defined *post-hoc*.
[2]As assessed by the respective treating physician. There were 41 (19.0%) patients with unknown tumor response (AP).

SAFETY

For safety analysis, AEs including situations requiring expedited reporting and AESIs, SAEs, ADRs, SADRs and fatal events (regardless of causality) have been collected. Fatal events can be either fatal SADR (assessed as related to Herceptin treatment) or fatal SAE (assessed as not related to Herceptin). The collection of AEs, SAEs, ADRs and SADRs reflects the real-world situation in which the treating physicians with best knowledge of their patients assessed whether an observed event could be related to Herceptin.

Prior to the amendment to the study protocol (Amendment 3), study sites were requested to only document Herceptin-related events (ADRs), whereas following Amendment 3 study sites were required to document all AEs including all ADRs. This change was implemented in the eCRF on 10 April 2014 and was also applied retroactively until July 2012; hence, also applicable to AEs that had already occurred before Amendment 3 came into effect, with a possibility of incomplete data and/or underreporting of AEs. Therefore, the AEs assessed as not related to Herceptin treatment are not displayed for the overall AP, but separately as indicated below:

- AEs onset before 10 April 2014

- AEs onset on or after 10 April 2014

The NCI's standardized definitions for CTCAE v4.03 were used for severity grading of all AEs and MedDRA v20.0 for classification of reported terms within respective SOC and PT.

Number of Patients With (S)AEs

	Patients N (%)	Cases N
Total number of patients (AP), N	*216 (100)*	
Onset of the (S)AE before 10 April 2014 (not related to Herceptin treatment) n (%), n (cases)		
Patients reported with AEs of any CTCAE grade	48 (22.2%)	125
Patients reported with an SAE	22 (10.2%)	37
Patients reported with AEs of CTCAE grade 3/4	19 (8.8%)	38
Onset of the (S)AE on or after 10 April 2014 (not related to Herceptin treatment) n (%), n (cases)		
Patients reported with an AE (all AEs of CTCAE grade 2)	3 (1.4%)	5
Patients with a SAE	0	0

AE = Adverse event; AP = Analysis population; CTCAE = Common Terminology Criteria for Adverse Events; N/n = Number; SAE = Serious adverse event

Most Frequent (S)AEs

- Onset of the (S)AEs before 10 April 2014 (not related to Herceptin; retrospective documentation)
    - Most frequently reported AEs (>2% of patients): nausea (n=7; 3.2%), leukopenia (n=6; 2.8%), dyspnea (n=5; 2.3%), general physical health deterioration (n=5; 2.3%), and polyneuropathy (n=5; 2.3%).
    - Most commonly reported AEs of CTCAE grade 3/4 (≥2 patients): leukopenia (n=4; 1.9%), nausea (n=3; 1.4%), dyspnea (n=2; 0.9%), gastrointestinal pain (n=2; 0.9%), urinary tract infection (n=2; 0.9%) and vomiting (n=2; 0.9%).
    - Most frequently reported SAEs (≥2 patients): general physical health deterioration (n=5; 2.3%), dyspnea (n=4; 1.9%), malignant neoplasm progression (n=3; 1.4%), nausea (n=3; 1.4%), death (n=2; 0.9%) and vomiting (n=2; 0.9%).
- Onset of AEs on or after 10 April 2014 (not related to Herceptin)

- The documented AEs were arthralgia, blood creatinine increased, bone pain, osteonecrosis and syncope (all CTCAE grade 2, n=1; 0.5%).

Number of Patients With (S)ADRs

	Patients N (%)	Cases N
Total number of patients (AP), N	*216 (100)*	
Patients reported with a (S)ADR, n (%), n (cases)		
Patients reported with an ADR	52 (24.1)	186
Patients reported with an SADR	17 (7.9)	27
Patients with ADRs of CTCAE grade 3	18 (8.3)	24
Patients with ADRs of CTCAE grade 4	0	0

ADR = Adverse drug reaction; AP = Analysis population; CTCAE = Common Terminology Criteria for Adverse Events; N/n = Number; SADR = Serious adverse drug reaction

Most Frequent (S)ADRs (continuously monitored)

- Most frequently reported ADRs (>2% of patients): headache (n=8; 3.7%), chills (n=7; 3.2%), diarrhea (n=7; 3.2%), nausea (n=7; 3.2%), bone pain (n=6; 2.8%), dyspnea (n=6; 2.8%), peripheral neuropathy (n=6; 2.8%), decreased ejection fraction (n=5; 2.3%) and dizziness (n=5; 2.3%).

- Most frequently reported ADRs of CTCAE grade 3 (≥2 patients): chills (n=3; 1.4%), headache (n=2; 0.9%) and left ventricular dysfunction (n=2; 0.9%).

- Most frequent SADRs (>1 patient): decreased ejection fraction (n=4; 1.9%) and dyspnea (n=3; 1.4%).

Pregnancy Cases

- In total, 2 patients were documented with a pregnancy during the entire study period
  - 1 of these patients was reported with oligohydramnios assessed as related to Herceptin treatment (ADR)

Death Cases and Fatal Serious Adverse Events

- 135 (62.5%) patients died in total during the whole study period

- 9 (4.2%) patients were reported with fatal SAEs and/or fatal SADRs (one patient was documented with both non-related and related fatal events)

- 8 (3.7%) patients with fatal SAEs not related to Herceptin (8 cases): general physical health deterioration (n=3), death (n=2), dyspnea (n=1), malignant neoplasm progression (n=1), and toxic epidermal necrolysis (n=1).

- 2 (0.9%) patients with fatal SADRs (4 cases): general physical health deterioration, pleural effusion, pneumonia (all reported for the same patient) and multiple organ dysfunction syndrome.

SECOND-LINE THERAPY

- In total, 98 (45.4%) patients were documented with second-line therapy following end of Herceptin re-therapy (AP).

- In second-line therapy, combination therapy with capecitabine and lapatinib (n=21; 9.7%) or monotherapy with trastuzumab (n=14; 6.5%) were the most common treatments reported.

Conclusions

The data obtained in this study provide a valuable and important estimate of how clinical efficacy documented in controlled, randomized clinical studies translates into effectiveness in routine clinical practice in Germany.

Herceptin re-therapy is effective in routine clinical practice, while a direct comparison with the results obtained in the pivotal study is subject to limitations due to differences in patient characteristics and study settings including clear cut inclusion and exclusion criteria, assessment schemes and assessment specifications..

The safety information reported in this study is consistent with the known safety profile of Herceptin.

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
AGO	Gynecological Oncology Working Group (Arbeitsgemeinschaft Gynäkologische Onkologie)
AMG	German Drug Act (deutsches Arzneimittelgesetz)
AML	Acute myeloid leukemia
AP	Analysis population
BC	Breast cancer
BMI	Body mass index
CA15-3	Cancer antigen 15-3 (tumor marker)
CDB	Clinical Database CRO
CHF	Congestive heart failure
CI	Confidence interval
CISH	Chromogenic in situ hybridization
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CR	Complete remission
CRO	Contract research organization
CT	Computer tomography
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CTx	Chemotherapy
DBL	Database lock
DCIS	Ductal carcinoma in situ
DFS	Disease-free survival
DHC	Ductus hepatocholedochus (common bile duct)
DMP	Data management plan
DRM	Data review meeting
EBC	Early breast cancer
eCRF	Electronic case report form
EDC	Electronic data capture
ET	Endocrine therapy
FISH	Fluorescence in situ hybridization
FPI	First-patient-in
HER2	Human epidermal growth factor receptor 2
HR	Hazard ratio / Hormone receptor
ICF	Informed consent form
IHC	Immunohistochemistry
LCIS	Lobular carcinoma in situ
LN	Lymph node
LOE	Lack of efficacy
LPI	Last-patient-in

Abbreviation	Definition
LPLV	Last-patient-last-visit
LVEF	Left ventricular ejection fraction
MAH	Marketing authorization holder
Max	Maximum
MBC	Metastatic breast cancer
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
MPA	Medroxyprogesterone acetate
MUGA	Multiple-gated acquisition scan
N/n	Number of patients / Number of observations
NA	Not applicable / Not reached
NC	No change / Not calculated
NCI	National Cancer Institute
NE	Non-evaluable
NIO	Niedergelassener internistischer Onkologe
NIS	Non-interventional study
OR	Odds ratio
ORR	Overall response rate
OS	Overall survival (from time of initial tumor resection)
OS-2	Overall survival (from time of diagnosis of local relapse / metastases)
pCR	Pathologic complete remission
PD	Progressive disease
PFS	Progression-free survival
PP	Per-protocol population
PR	Partial remission
PT	Preferred term
RECIST	Response Evaluation Criteria In Solid Tumors
SADR	Serious adverse drug reaction
SAE	Serious adverse event
SAPV	Spezialisierte ambulante palliativmedizinische Versorgung (specialized outpatient palliative care team)
SD	Stable disease
SDB	Safety Database Roche
SmPC	Summary of Product Characteristics
STIAMP	Suspected transmission of infectious agent by medicinal product
SOC	System organ class
SOP	Standard operating procedure
STD	Standard deviation
TCH	Docetaxel, carboplatin and Herceptin
T-DM1	Trastuzumab-Emtansine (Kadcyla®)
TEN	Toxic epidermal necrolysis
TFLs	Tables, figures, listings
TMF	Trial master file
WHO	World Health Organization

3. MILESTONES

Table 3-1 Study milestones

Milestone	Actual Date	Comments, if any
Start of data collection	23 October 2008	FPI
End of data collection	12 January 2018	LPLV
Study status report 1	5 November 2008	No regular study status reports were provided to the sponsor (Roche Pharma AG) as they were directly viewable on the iOMEDICO AG (CRO) study portal.
Study status report 2	19 February 2009	
Study status report 3	6 May 2009	
Study status report 4	6 July 2009	
Study status report 5	21 August 2009	
Study status report 6	19 November 2009	
Study status report 7	1 February 2010	
Study status report 8	24 May 2010	
Study status report 9	24 August 2010	
Study status report 10	24 November 2010	
Study status report 11	25 February 2011	
Study status report 12	30 May 2011	
Study status report 13	13 February 2012	
Interim report 1	19 September 2010	The date of respective interim report reflects the time point for database cut.
Interim report 2	18 March 2012	
Interim report 3	30 November 2012	
Interim report 4	31 January 2014	
Interim report 5	27 September 2015	
Final report of study results	16 October 2019	DBL: 24 October 2018

CRO = Contract research organization; DBL = Database lock; FPI = First-patient-in; LPLV = Last-patient-last-visit

4. RATIONALE AND BACKGROUND

Overexpression or gene amplification of the human epidermal growth factor receptor 2 (HER2) occurs in 15% to 30% of breast cancer (BC) patients (1–4). HER2 overexpression is associated with high recurrence rates and poor clinical outcome (5). In the “pre-trastuzumab” era, affected patients had a worse prognosis presenting with a more aggressive disease and reduced overall survival (OS) (1,6). Today, in breast cancer, HER2 is a well-established predictive biomarker of benefit from HER2-directed therapies, the most widely used being trastuzumab (a recombinant humanized anti-HER2 monoclonal antibody). Since the introduction of Herceptin® (trastuzumab) in the (neo-) adjuvant setting in treatment of HER2-positive BC, there has been a reduction in the mortality by approximately one-third and disease recurrences by 50% in this subtype of BC patients (7).

In pre-clinical studies, the murine monoclonal antibody 4D5, directed against the extracellular domain of HER2, has been shown to exhibit a potent inhibitory activity against HER2-overexpressing tumors *in vivo* (7). The possibility of its use in clinical investigations opened up in 1992 as it became possible to humanize antibodies to such an extent that even after one year of administration to humans no antibodies to mouse immunoglobulins were detected (8,9).

The results of the multinational pivotal study of Herceptin monotherapy showed that a significant proportion of patients with HER2-overexpressing metastatic breast cancer (MBC) and with extensive prior therapy still could benefit from Herceptin monotherapy with an objective response rate (ORR) of 15% (5). In the pivotal studies evaluating the addition of Herceptin to chemotherapy with either paclitaxel (Taxol®) or docetaxel (Taxotere®) as first-line therapy for HER2-overexpressing MBC, the median survival for Herceptin in combination with paclitaxel (22.1 months) or docetaxel (31.2 months) was superior to chemotherapy alone with paclitaxel (18.4 months) or docetaxel (22.7 months) (10,11).

Based on the favorable clinical outcomes in the metastatic setting, four major trials were launched worldwide investigating Herceptin adjuvant therapy including the pivotal HERA trial (12–16). In the HERA trial, an international, multicenter, open-label, phase III randomized trial of patients with HER2-positive early breast cancer (EBC), the efficacy of 1-year treatment with Herceptin was tested in a 3-weekly dosing schedule following completed surgery, chemotherapy and (if indicated) radiation therapy (13). The US studies NSABP B31 and NCCTG N9831 evaluated the efficacy after four cycles of therapy with doxorubicin and cyclophosphamide followed by paclitaxel in combination (in one arm also in sequence) with Herceptin over one year (17,18). In the BCIRG006 trial, four cycles of therapy with doxorubicin and cyclophosphamide followed by docetaxel every 3 weeks for four doses and Herceptin for 1 year were compared with an anthracycline-free regimen of six cycles of TCH (docetaxel, carboplatin and Herceptin) followed by Herceptin for an additional 34 weeks (19). At time of the interim analysis of respective study, all four studies consistently showed that the addition of 1 year of adjuvant Herceptin therapy resulted in a 50% reduction in the risk of recurrence as well as an improved OS and a beneficial tolerability profile (16).

Since 2005, the standard of care has been to give Herceptin for 1 year after surgery and chemotherapy to reduce the risk of recurrence of HER2-positive EBC. The risk of recurrence after 1 year of Herceptin treatment has been reported to be 15% to 20% (20).

The RHEA study, a non-randomized, international, open-label, phase II trial of 43 patients with HER2-positive MBC, assessed the efficacy and safety of Herceptin retreatment in combination with taxane as first-line treatment for MBC after relapse on adjuvant Herceptin for HER2-positive EBC (21). In this trial, the overall response rate (ORR) was 61% (25 of 41 patients) including 1 (2.4%) patient with a complete remission (CR) and 24 (58.5%) patients with a partial remission (PR), whereas stable disease (SD) was reported in 17.1% of patients. Median progression-free survival (PFS) was 8.0 months and the median OS was 25.0 months. Hence, Herceptin, in combination with a taxane, was reported to be an effective and well-tolerated first-line treatment for MBC in patients who relapse after Herceptin-based adjuvant therapy (21).

Herceptin is listed as *Essential Medicine* by the WHO (22). Herceptin has market approval for the following therapeutic indications in EBC and MBC as per current Summary of Product Characteristics (SmPC) of Herceptin (23):

Metastatic breast cancer

Herceptin is indicated for the treatment of adult patients with HER2-positive MBC:

- as monotherapy for the treatment of those patients who have received at least two chemotherapy regimens for their metastatic disease. Prior chemotherapy must have included at least an anthracycline and a taxane unless patients are unsuitable for these treatments. Hormone receptor (HR)-positive patients must also have failed hormonal therapy, unless patients are unsuitable for these treatments.

- in combination with paclitaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease and for whom an anthracycline is not suitable.

- in combination with docetaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease.

- in combination with an aromatase inhibitor for the treatment of postmenopausal patients with HR-positive MBC, not previously treated with Herceptin.

Early breast cancer

Herceptin is indicated for the treatment of adult patients with HER2-positive EBC:

- following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable).

- following adjuvant chemotherapy with doxorubicin and cyclophosphamide, in combination with paclitaxel or docetaxel.

- in combination with adjuvant chemotherapy consisting of docetaxel and carboplatin.

- in combination with neoadjuvant chemotherapy followed by adjuvant Herceptin therapy, for locally advanced (including inflammatory) disease or tumors >2 cm in diameter.

The present non-interventional study (NIS) was initiated in 2008 designed to evaluate the effectiveness and safety of reapplication (hereinafter referred to as “re-therapy”) of Herceptin in routine clinical practice in patients with HER2-positive BC having relapsed following completed (neo-) adjuvant anti-HER2-therapy with Herceptin for HER2-positive EBC.

5. RESEARCH QUESTIONS AND OBJECTIVES

This NIS was designed to evaluate the effectiveness and safety of re-therapy with Herceptin in routine clinical practice in patients with HER2-positive BC having relapsed following completed (neo-) adjuvant anti-HER2-therapy with Herceptin for HER2-positive EBC. Eligible patients were those with decision for first-line Herceptin re-therapy in routine clinical practice, in accordance with current SmPC of Herceptin (23) (please refer to section 7.3 for detailed inclusion / exclusion criteria). Every medical decision and course of treatment of each patient reflects exclusively the decision of the treating physician in routine clinical practice. At any time, the current version of SmPC of Herceptin was to be used as reference for treatment (23). The concept of this NIS and its documentation procedure did not affect routine clinical practice in any aspect.

The questions of key importance included:

- How long is the median time span between the adjuvant anti-HER2-treatment and the onset of Herceptin re-therapy for first-line treatment of recurrent BC/MBC?

- How long is the average duration of Herceptin re-therapy?

- Which criteria influence the choice of Herceptin re-therapy?
- Which criteria determine the choice of chemotherapy regimens in combination with Herceptin re-therapy in routine clinical practice?
- Which kind of therapy regimens are chosen in second- and further-line settings following completed Herceptin re-therapy?
- Is there a difference in outcome depending on selected adjuvant anti-HER2-therapy?
- Are the positive effects in terms of disease-free survival (DFS) intervals shown in registration studies reproducible in this NIS?
- Are there any new side effects?
- What are the experiences with cardiac events in terms of frequency, management and outcome?

6. AMENDMENTS AND UPDATES TO PROTOCOL

Table 6-1 Amendments to the study protocol[1]

Number	Date	Section of Study Protocol	Amendment or Update	Reason
1	*Not implemented*	*Synopsis* *Section 3.2* *Section 3.3* *Section 4.2* *Section 5.1* *Section 5.2* *Section 6.1* *Section 6.2* *Section 7.1* *Section 7.3*	*Amendment 1* *Study protocol v2.0*	*Reduction of number of patients (from 1500 to 250) and study sites (from 300 to 250). Retrospective documentation (9 weeks after start of Herceptin re-therapy). Definition of patient population, duration of study, study objectives / variables, and rationale for choice of method.*
2	07 July 2011	Synopsis Section 5.2	Amendment 2 Study protocol v3.1	Reduction of number of patients (from 1500 to 250) and study sites (from 300 to 250). Retrospective documentation (9 weeks after start of Herceptin re-therapy).
3	23 December 2013	Section 6.4 Section 6.5	Amendment 3 Study protocol v4.0	Safety directive: Documentation of all (serious) adverse events and adverse events of special interest in addition to all (serious) adverse drug reactions.

NA = Not applicable

[1]Original version and amended versions of the study protocol are listed as stand-alone documents in Table1 in Annex 1. List of stand-alone documents.

7. RESEARCH METHODS

7.1 STUDY DESIGN

The present NIS was conducted according to §67 section 6 of the German Drug Act (AMG; Arzneimittelgesetz), which involved primary data collection. This study was designed to document effectiveness and safety data from routine clinical practice in Germany regarding Herceptin re-therapy in patients with locally recurrent or metastatic HER2-positive BC for up to 5 years per patient. In total, 239 patients were included into the study. Eligibility criteria for inclusion were defined according the SmPC of Herceptin (23).

Patients were assigned to a therapeutic strategy within routine clinical practice, not according to a trial protocol. Consequently, the diagnostic and monitoring procedures were only those applied in routine clinical practice. Prescription of study medication was independent of the decision to include the patient into the study. Patient treatment, including diagnosis and follow-up, was solely accountable to the treating physician. Patient follow-up visits were carried out as per routine clinical practice.
The choice of this methodical approach reflects the character of a NIS. There were no specified dose regimens or medical procedures defined within the NIS protocol. Every medical decision and course of Herceptin re-therapy and further-line therapy reflect exclusively the decision of the treating physician in routine clinical practice. The concept of this NIS and its documentation procedure did not affect routine clinical practice in any aspect.

The sponsor of the study was Roche Pharma AG (Grenzach-Wyhlen, Germany). iOMEDICO AG (CRO, Freiburg, Germany) supported the study as full-service provider. The responsible parties and study administrative structure of the study are presented in Table 1 in Annex 3. Additional Information.

7.2 SETTING

Patients were recruited from 23 October 2008 (first-patient-in; FPI) through 9 January 2013 (last-patient-in; LPI) in 122 study sites across Germany including oncologists and gynecologists in hospitals and outpatient clinics, and independent oncology practices (220 sites participated, of these, 98 were non-recruiting; Table 1; Annex 1. List of stand-alone documents). The study sites were selected by the gynecologic sales force at Roche Pharma AG. The maximum duration of documentation period per patient was 60 months

(5 years) after enrollment, comprising a basic observational period of Herceptin re-therapy for a maximum of 12 months or until premature discontinuation of Herceptin re-therapy due to any reason, and a follow-up period until date of death or for a maximum of 4 years. The individual follow-up period was independent of whether Herceptin re-therapy was discontinued during or continued beyond the 12-month basic observational period, or whether other further-line antineoplastic treatments were given following end of Herceptin re-therapy. Hence, irrespective of the therapeutic decision made following discontinuation of Herceptin re-therapy, each patient status was to be assessed and documented during the (maximum) 4-year-follow-up period. During the follow-up period, patients were followed up every 6 months to collect data on current treatment and disease/survival status. Database lock was performed on 24 October 2018, which was carried out more than 5 years after LPI due to further remote/on-site monitoring and reconciliation of safety data. Last-patient-last-visit took place on 12 January 2018.

7.3 PATIENTS

Eligible patients were those diagnosed with HER2-positive, locally recurrent BC or MBC having relapsed following completed (neo-) adjuvant anti-HER2-therapy with Herceptin for HER2-positive EBC and with decision for first-line Herceptin re-therapy in routine clinical practice. The treating physician at respective study site was responsible for obtaining written informed consent from each patient participating in this study after adequate explanations of the aims, methods, and objectives of the study prior to study participation. The signed informed consent form (ICF) was retained by the study site as part of the study records and the date of consent was documented in the electronic Case Report Form (eCRF). A representative ICF and example CRF screen shots are provided as stand-alone documents in Table 1 in Annex 1. List of stand-alone documents. The treating physician assured the anonymity of the patients (pseudonymized data) and confidentiality of data being strictly maintained and protected from unauthorized parties. Only a unique identifier and a unique study identification code were recorded on any study-related document or used for eCRF entries. Signed ICFs and patient identification lists were kept strictly confidential at the study site. Of note, patient enrollment was permitted up to 9 weeks after initiation of Herceptin re-therapy. Prior to enrollment of a patient, the participating physician verified that the patient fulfilled the inclusion / exclusion criteria (please refer to sections 7.3.1 and 7.3.2).

7.3.1 Inclusion Criteria

Patients were eligible for inclusion into the study if they met *all* the following inclusion criteria:

- aged ≥18 years
- written and signed informed consent obtained prior to onset of documentation
- pre- and postmenopausal female patients with histologically and/or cytologically confirmed locally recurrent or metastatic HER2-positive BC
- HER2-positive tumor (IHC 3+ and/or FISH/CISH-positive)
- patients must have received anti-HER2-therapy as systemic treatment for EBC in the (neo-) adjuvant or adjuvant setting
- patients relapsing after completed (neo-) adjuvant anti-HER2-therapy
- no chemotherapy and/or immunotherapy for locally recurrent BC or MBC before start of Herceptin re-therapy

7.3.2 Exclusion Criteria

Patients were ineligible for the study if they met *any* of the following exclusion criteria:

- pregnancy or lactation
- patients having relapsed during the (neo-) adjuvant anti-HER2 therapy
- Left ventricular ejection fraction (LVEF) ≤50% at baseline (start Herceptin re-therapy), measured by echocardiography or MUGA
- severe dyspnea at rest
- requirement of supplementary oxygen therapy
- patients with symptomatic heart failure or documented coronary artery disease

- hypersensitivity to Chinese hamster ovary cell products, other recombinant human or humanized antibodies, trastuzumab or any of the excipients

7.4 VARIABLES

All types of treatment medications administered including (neo-) adjuvant anti-HER2 therapy and all subsequent treatment lines were to be documented to provide detailed information on the choice of chemotherapy as well as the timing of different chemotherapy regimens and anti-HER2 therapies during the disease.

The anti-HER2 therapies applied were to be documented over the entire observational period for a maximum of 5 years and included:

- (neo-) adjuvant anti-HER2 therapy (prior therapy; retrospective baseline documentation)

- first-line re-therapy with Herceptin after relapse following completed (neo-) adjuvant anti-HER2-therapy (12-month basic observational period; 9 weeks of retrospective documentation was permitted)

- subsequent therapy lines after completion of Herceptin re-therapy (follow-up phase, prospective documentation for a maximum of 4 years)

The study schedule in Table 7-1 delineates the schedule for all study activities, assessments and data capture as per final study protocol v4.0, dated 23 December 2013 (Table 1; Annex 1. List of stand-alone documents). Scheduled time points for these are marked with an “x”.

Table 7-1 Variables[1] – study schedule of activities and assessments

	Baseline documentation	12-month basic observational period[2]	Follow-up period[3]
Registration	x		
Patient informed consent	x		
Demographic data	x		
Comorbidities	x		
Tumor anamnesis	x		
Prognostic factors	x		
Prior treatments, systemic therapy[4]	x		
Prior treatments, additional information	x		
Cardiac diagnostics	x		
Concomitant medication		x	x
Chemotherapy and immunotherapy[5]		x	x
Endocrine therapy		x	x
Herceptin re-therapy		x	x
Tumor assessment		x	x
Cardiac monitoring		x	x
(Serious) AEs and (serious) ADRs[6]		x	x
Situations requiring expedited reporting[7]		x	x
AEs of special interest (AESI)[6]		x	x
Pregnancy[6]		x	x
End of therapy		x	
End of documentation[8]			x
Signature	x	x	x

ADR = Adverse drug reaction; AE = Adverse event; AESI = Adverse event of special interest
[1]All variables were to be captured from medical records as per documentation procedure in routine clinical practice by using an electronic data capture system. [2]For a maximum of 12 months or until premature end of Herceptin re-therapy. [3]Every 6 months until death or for a maximum of 4 years per patient. [4]Information on radiotherapy, endocrine therapy, (neo-) adjuvant chemo- / immunotherapy, and (neo-) adjuvant anti-HER2 therapy. [5]Including documentation of second-line and further-line therapy during the follow-up period. [6]Adverse events and pregnancy were to be documented from date of patient inclusion until 90 days after completion of the treatment phase (end of Herceptin re-therapy). [7]Including quality deficiencies, counterfeits (or suspicion), and occupational exposure. These were to be reported even in the absence of an AE. [8]Including documentation of patient status.

7.4.1 Primary Effectiveness Variable

The primary effectiveness parameter in this study was selected out of several primary questions for the calculation of sample size and was therefore from a statistical perspective established as a primary effectiveness variable. The primary effectiveness variable in this study was as follows:

- PFS defined as the time from diagnosis of local recurrent tumor / distant metastasis, which led to the initiation of anti-HER2 re-therapy with Herceptin to progression or death due to any cause.

7.4.2 Secondary Effectiveness Variable

The secondary effectiveness variables in this study were as follows:

- OS defined as the time from initial tumor resection to death due to any cause.
- OS-2 defined as the time from diagnosis of local recurrent tumor / distant metastasis, which led to the initiation of anti-HER2 re-therapy with Herceptin to death due to any cause.
- Best response and ORR during the 12-month basic observational period.
- DFS defined as the time from initial tumor resection to documentation of the first local recurrent tumor / distant metastases, which led to the initiation of anti-HER2 re-therapy with Herceptin.

7.4.3 Safety Variables

For safety analysis, all adverse events (AEs) including AEs of special interest (AESIs: cardiac events, infusion-related reaction and / or pulmonary events) and situations requiring expedited reporting, serious AEs (SAEs), adverse drug reactions (ADRs) and serious ADRs (SADRs) were to be documented in the eCRF from date of patient inclusion until 90 days after completion of the treatment phase (end of Herceptin re-therapy).

An AE was defined as any untoward medical occurrence in a patient administered a drug, and which not necessarily had a causal relationship with that treatment. This included the following untoward events:

- Abnormal laboratory values if:
    - associated with clinical symptoms
    - resulting in a change in therapy (e.g., dose adjustment, treatment interruption, discontinuation of treatment)
    - requiring medical intervention
    - considered as clinically relevant by the treating physician

  - evidence of cardiac toxicity, infusion-related reaction and / or pulmonary event (AESIs)

- Special situations, i.e. overdose, abuse, misuse including medication error or near-misses
- Lack of efficacy (LOE)
- Suspected transmission of infectious agent by medicinal product (STIAMP)
- Drug interaction with other products
- AEs related to product quality and / or technical complaints
- AEs related to suspect counterfeit or counterfeit drugs / falsified medicinal products

Disease progression (PD) was to be recorded in the eCRF, but not to be documented as an AE.

For documentation of AEs that were not to be reported according to the accelerated procedure, a documentation in the eCRF within 30 days of awareness was to be observed. All SAEs, AESIs, situations regarding quality deficiencies / complaints, suspect counterfeits or counterfeit drugs and pregnancies were to be reported to the sponsor (Roche Pharma AG) within 24 hours of awareness (for further details, please refer to final study protocol v4.0, dated 23 December 2013; Table 1; Annex 1. List of stand-alone documents).

Documentation of an AE was to include at least the following details:

- Description of the event (diagnosis)
- Start and end date of event
- Term and system organ class (SOC) according to Common Terminology Criteria for Adverse Events (CTCAE) v4.03
- Severity grading of the event according to CTCAE v4.03

- Seriousness of event
- Causal relationship with the treatment
- Management and outcome of event

The incidence of pregnancies (pregnancy / lactation, father's exposure) was to be recorded in the eCRF from date of patient inclusion until 90 days after completion of the treatment phase (end of Herceptin re-therapy). In addition, any pregnancy had to be reported to Roche by the treating physician within 24 hours of awareness by using a designated pregnancy reporting form. Pregnancies were to be documented and reported separately from potential, simultaneous AEs / ADRs. The treating physician was to advise the patient on the risks of continuing the pregnancy including possible effects on the fetus. Pregnancies were to be followed up accordingly (for further details, please refer to final study protocol v4.0, dated 23 December 2013; Table 1; Annex 1. List of stand-alone documents).

For documentation of pregnancies, the following information was to be included by using a designated, expedited pregnancy reporting form:

- Course of pregnancy
- Pregnancy outcome (fetus)
- Seriousness (fetus)
- Causal relationship with the treatment
- Data on the infant

7.4.4 Other Variables of Interest

Other variables of interest included:

- Decision criteria for Herceptin re-therapy
- Decision criteria for choice of chemotherapy in combination with Herceptin re-therapy
- Drugs used in second-line and further-line palliative therapy (following end of Herceptin re-therapy)

7.5 DATA SOURCE(S) AND MEASUREMENT

The electronic data capture (EDC) system (*iostudy office edc*) used in this study was provided to the study sites by iOMEDICO AG. The data were derived from electronic Case Report Form (eCRF)-entries made by the study sites as part of routine clinical practice. Data were transferred from source documents (i.e., patient's medical records) to the eCRF. Data were fully pseudonymized and all information collected in this study was treated strictly confidentially.

The database quality was reviewed and validated by remote and on-site monitoring of data entered in the eCRF (source data verification). Completed eCRF data entries were checked for compliance with study protocol and for completeness, consistency, and accuracy. The data analysis only began once an accurate, validated dataset had been assured. All steps of quality checks were performed and recorded according to iOMEDICO- and Roche-specific SOPs.

For data analysis, a statistical analysis plan (SAP) was developed and approved both by iOMEDICO AG (CRO) and the sponsor of the study (Roche Pharma AG). Final data analysis was based on the final SAP v2.2, dated 22 August 2018, and a Note-to-File pertinent to the SAP specifying the *post-hoc* analyses performed (Table 1; Annex 1. List of stand-alone documents). The SAP described the variables to be used for data analysis in detail according to the defined endpoints. The NCI's standardized definitions for CTCAE v4.03 were used for severity grading of all AEs and Medical Dictionary for Regulatory Activities (MedDRA) v20.0 for classification of reported terms within respective SOC and preferred term (PT).

7.6 BIAS

Patients were included according to the respective treating physician's discretion including retrospective inclusion of patients (up to 9 weeks following start of Herceptin re-therapy). The medical decision and course of treatment with Herceptin re-therapy and further-lines reflect exclusively the decision of respective treating physician in routine clinical practice. Therefore, during data collection, much attention and efforts were made to ensure inclusion criteria and exclusion criteria were met and data quality was high. Regular data checks by remote monitoring were performed.

In this study, tumor assessment was not standardized according to Response Evaluation Criteria In Solid Tumors (RECIST), which is a potential bias for PFS and ORR, but this however reflects routine clinical practice.

This report includes missing data records, reflecting the character of a NIS. For partially unknown dates, the most conservative imputation method was used. For further details, please refer to final SAP v2.2, dated 22 August 2018 (Table 1; Annex 1. List of stand-alone documents).

The NIS setting of this study *per se* may have led to underreporting of AEs. Furthermore, prior to the amendment to the study protocol (Amendment 3), study sites were requested to only document Herceptin-related events (ADRs), whereas following Amendment 3 study sites were required to document all AEs (in addition to all ADRs). This change was implemented in the eCRF on 10 April 2014 and was also applied retroactively until July 2012; hence, also applicable to AEs that had already occurred before Amendment 3 came into effect with a possibility of incomplete data and/or underreporting of AEs. Due to this retrospective documentation, an underestimation of AEs with no causal relationship to Herceptin in the period before Amendment 3 became effective is to be expected.

7.7 DATA TRANSFORMATION

Data were collected via eCRFs containing data as available from routine clinical practice, which were transmitted to a database. The eCRF contained a data dictionary providing a detailed description of each variable used in this NIS.

7.7.1 Duration of Therapy

Duration of (neo-) adjuvant anti-HER2 therapy, Herceptin re-therapy, chemo- / immunotherapy (concomitant therapy), endocrine therapy (concomitant therapy), prior chemo- / immunotherapy, prior endocrine therapy, and further-line therapy (following end of Herceptin re-therapy) were calculated by using the formulas detailed in Table 7-2.

Table 7-2 Summary of formulas used for calculation of duration of therapy

Variable	Formula
Duration of Herceptin re-therapy, chemo- and/or immunotherapy and endocrine therapy[1]	Duration [months] = (end of therapy – start of therapy + 1) / 30.4
Duration of (neo-) adjuvant anti-HER2 therapy	Duration [months] = (end of therapy – start of therapy + 1) / 30.4
Duration of prior chemo- and immunotherapy[2]	Duration [months] = (end of therapy – start of therapy + 1) / 30.4
Duration of prior (neo-) adjuvant endocrine therapy	Duration [years] = (end of therapy – start of therapy + 1) / 365.25
Duration of second-line and further-line therapies[3]	Duration [months] = (end of therapy – start of therapy + 1) / 30.4

HER2 = Human epidermal growth factor receptor 2
[1]Combination therapy with Herceptin re-therapy. [2]Assessed for each type of therapy and line. [3]Palliative therapy following end of Herceptin re-therapy.

Number of patients with respective therapy (yes / no) is represented by absolute and relative frequencies.

7.7.2 Safety Analyses

The NCI's standardized definitions for CTCAE v4.03 were used for severity grading of all AEs and MedDRA v20.0 for classification of reported terms within respective SOC and PT. The incidence rate of AEs, SAEs, ADRs and SADRs including severity grade as well as AEs and ADRs leading discontinuation of Herceptin re-therapy are summarized in table format according to SOC and within each SOC by PT.

Prior to the amendment to the study protocol (Amendment 3), study sites were requested to only document Herceptin-related events (ADRs), whereas following Amendment 3 study sites were required to document all AEs (in addition to all ADRs). This change was implemented in the eCRF on 10 April 2014 and was also applied retroactively until July

2012; hence, also applicable to AEs that had already occurred before Amendment 3 came into effect with a possibility of incomplete data and/or underreporting of AEs. Due to this retrospective documentation, an underestimation of AEs with no causal relationship to Herceptin in the period before Amendment 3 became effective is to be expected. Therefore, the summary tables of AEs assessed as not related to Herceptin treatment are not displayed for the overall AP, but separately as indicated below:

- AEs with onset before 10 April 2014
- AEs with onset on or after 10 April 2014

7.7.2.1 Cardiac Monitoring

Duration of LVEF assessment period, time span to LVEF nadir or first LVEF <50% during Herceptin re-therapy were calculated by using respective formula displayed in Table 7-3.

Table 7-3 Formulas used in the analysis of cardiac monitoring

Variable	Formula
Duration of LVEF assessment period	Duration [months] = (last LVEF measurement – start of Herceptin re-therapy + 1) / 30.4
Time span to LVEF nadir	Time span to LVEF nadir [months] = (date of LVEF nadir - start of Herceptin re-therapy) / 30.4
Time span to first LVEF <50%	Time span to first LVEF <50% [months] = (date of first LVEF <50% - start of Herceptin re-therapy) / 30.4

LVEF = Left ventricular ejection fraction

In addition, the number of patients with a LVEF nadir >10% lower compared to baseline measurement was determined including data from patients with a documented baseline LVEF (4 weeks before or after initiation Herceptin re-therapy) and at least one post-baseline LVEF measurement over the course of the study. The nadir was defined as the lowest post-baseline LVEF documented over the course of the study (including follow-up documentation and the period after discontinuation of Herceptin re-therapy).

7.7.2.2 Secondary Carcinoma

The incidence, specification (free-text entry) and metastasis of secondary carcinoma during the study are listed for all patients included in the study (by-patient-listing).

7.7.2.3 Concomitant Medication

The concomitant medication is listed per patient with all associated parameters (by-patient-listing).

7.7.2.4 Pregnancies

All pregnancies and according information (basic documentation / follow-up documentation) are listed for each patient reported with a pregnancy during the study (by-patient-listing).

7.7.3 Effectiveness Analyses

7.7.3.1 Course of Disease

Time span between initial diagnosis and first local recurrence / distant metastases or time span between diagnosis of local recurrence / distant metastases and first manifestation of metastases in new organ systems not affected at enrollment were calculated by using respective formula shown in Table 7-4.

Table 7-4 Formulas used in analysis of course of disease

Variable	Formula
Time span between initial diagnosis and first local recurrence / distant metastasis	Duration [months] = (date of first local recurrence / distant metastasis – date of initial diagnosis) / 30.4
Time span between diagnosis of local recurrence / distant metastases and first manifestation of metastases in new organ systems[1]	Duration [months] = (date of first emergence of metastases in organ systems not affected at enrollment – date of diagnosis of local recurrence / distant metastases after completed adjuvant anti-HER2 therapy) / 30.4

HER2 = Human epidermal growth factor receptor 2

[1]Included in the analysis were metastases emerging for the first time in organ systems not affected at enrollment (course of neoplastic disease during or after discontinuation of Herceptin re-therapy). Data entries in “prognostic factors” in eCRF served as a reference.

Time span until first occurrence of metastases in a new organ system was analyzed by organ system by descriptive statistics. New organ systems affected by metastases are presented with absolute and relative frequencies, considering the first occurrence only.

7.7.3.2 Overall Response Rate

The best tumor response (as assessed by the respective treating physician) was evaluated and is displayed in the categories CR, PR, SD, PD and non-evaluable (NE) with

absolute and relative frequencies for the study population (analysis population, AP), per-protocol population (PP) and SmPC-population.

7.7.3.3 Progression-Free Survival

PFS was defined as the time from diagnosis of local recurrent tumor / distant metastasis, which led to the initiation of anti-HER2 re-therapy with Herceptin to progression or death due to any cause.

PFS was estimated in the AP, PP, SmPC-population and predefined subgroups (refer to section 7.7.4.7) by using the Kaplan-Meier method (24). Patients without an event (PD or death) before change of therapy or at end of study participation were censored using the earliest date of one of the following:

- Date of change of therapy (start of second-line therapy)
- Date of last patient contact

If none of the above dates was available, the date of last documented dose of Herceptin was used for the censored case.

For PFS, the median and quartiles as well as the 6- and 12-month rates together with corresponding 95% confidence interval (CI) are displayed. Furthermore, number of censored cases are given. Kaplan-Meier estimates are displayed in table format and graphically in Kaplan-Meier plots.

7.7.3.4 Overall Survival

The OS was defined as the time from initial tumor resection to death due to any cause. As a further analysis, the “OS-2” was estimated, defined as the time from diagnosis of local recurrent tumor / distant metastasis, which led to the initiation of anti-HER2 re-therapy with Herceptin to death due to any cause.

OS and OS-2 were estimated in the AP, PP, SmPC-population and predefined subgroups (refer to section 7.7.4.7) by using the Kaplan-Meier method (24). Patients without documented date of death at the end of study were censored at the last date known to be alive. If this date was not available, the date of the last documented dose of Herceptin was used for the censored case.

For OS and OS-2, the median and quartiles as well as the 12-, 24-, 36-, and 48-month rates are displayed together with corresponding 95% CI. Furthermore, number of censored cases are given. Kaplan-Meier estimates are displayed in table format and graphically in Kaplan-Meier plots.

7.7.4 Other Analyses

Baseline demographics and clinical characteristics were additionally analyzed in predefined subgroups (refer to section 7.7.4.7).

7.7.4.1 Comorbidities

Documented comorbidities were, if possible, assigned to predefined categories (for instance, COPD was recoded as chronic lung disease and removed from the list of “other comorbidities”). For each patient, the Charlson score was calculated on the basis of Charlson score-relevant comorbidities (25). Number of patients with at least one comorbidity and the Charlson score are presented with absolute and relative frequencies.

7.7.4.2 Tumor History

To determine the earliest surgery that the patients had been subjected to, the dates within the categories breast conserving surgery, mastectomy, ablatio mammae, and “other surgeries” were used. Initial tumor resection was determined by medical experts of the CRO (iOMEDICO) using type and date of surgery. Determination of initial tumor resection was necessary for DFS and OS calculation, but not for analyses concerning tumor anamnesis. The location of the tumor, surgery, “other surgeries”, histology, “other histology” as well as accompanying DCIS and LCIS for invasive tumors are presented with relative and absolute frequencies.

7.7.4.3 Prognostic Factors

The tumor stage (Stage 0-IV) was determined according to the American Joint Committee on Cancer (AJCC) staging system for breast cancer, which in part utilizes TNM scoring system.

The HER2 status was considered positive if the IHC test came out as +++ positive or if the FISH or CISH test was positive. An IHC with ++ positive without a positive FISH or CISH test was considered unknown.

Tumor stage, grade, resection outcome, ER status, PR status, HR status and HER2 status at initial diagnosis are presented in absolute and relative frequencies.

7.7.4.4 Effectiveness of (Neo-) Adjuvant Anti-HER2 Therapy

Tumor response in the neoadjuvant anti-HER2 therapy setting is presented with absolute and relative frequencies together with corresponding 95% CI.

Time span between end of adjuvant anti-HER2 therapy and start of Herceptin re-therapy was calculated by using the following formula:

- Duration [months] = (start of Herceptin re-therapy – end of adjuvant anti-HER2 therapy) / 30.4

DFS, defined as the time from initial tumor resection to documentation of the first local recurrent tumor / distant metastases, which led to the initiation of anti-HER2 therapy with Herceptin, was evaluated both for the AP and PP.

7.7.4.5 Decision Criteria for Choice of Herceptin Re-Therapy

Decision criteria for choice of Herceptin re-therapy and concurrent chemotherapy (overall and by type of chemotherapy [anthracycline-containing / taxane-containing / anthracycline- and taxane-containing, other]) are presented with absolute and relative frequencies.

7.7.4.6 Observational Period

Duration of the observational period was estimated by using the reverse Kaplan-Meier method (24). In the analysis, the time span between the beginning of the Herceptin re-therapy and the last documented patient contact was used. For patients having died during the study, the date of death was used instead of the last patient contact (censored observation). The median observational period is presented together with corresponding 95% CI.

7.7.4.7 Subgroup Analyses

Baseline demographics and clinical characteristics (age, BMI, comorbidities, tumor anamnesis, prognostic factors) were additionally evaluated in the subgroup “Combination therapy”, DFS in the subgroup “Anthracycline / Taxane”, and PFS and OS-2 in the subgroups “Metastases”, “Combination therapy” and “Chemotherapy” as detailed in Table 7-5.

Table 7-5 Summary of subgroups used in the statistical analysis

Categories	Subgroups
Metastases / local recurrence only (no metastases)	No metastases: Patients without metastases at start of Herceptin re-therapy (local recurrence only) Non-visceral: Patients with non-visceral metastases only, i.e. bone, skin, lymph node and soft tissue metastases (± local recurrence, no visceral metastases) Visceral: Patients with visceral metastases, i.e. lung, liver, CNS, pleural effusion, ascites, and other metastases (free-text entries) coded as visceral by medical experts (± non-visceral metastases ± local recurrence). This group comprises all patients with visceral metastases including those having additional non-visceral metastases.
Prior adjuvant Anthracycline / Taxane[1]	Anthracycline: Patients receiving an anthracycline-based regimen in combination with adjuvant Herceptin therapy (but no taxanes) Taxane: Patients receiving a taxane-based regimen in combination with adjuvant Herceptin therapy (but no anthracyclines) Anthracycline + Taxane: Patients receiving anthracycline and taxane-based regimen in combination with adjuvant Herceptin therapy Other: patients receiving a regimen not containing an anthracycline or taxane in combination with adjuvant Herceptin therapy
Combination partner for Herceptin re-therapy	Herceptin mono re-therapy: Patients who did not receive any combination therapy (neither chemo-/immunotherapy nor endocrine therapy) with their Herceptin re-therapy Taxanes: Patients receiving a taxane in combination with their Herceptin re-therapy (but no endocrine therapy) Endocrine therapy: Patients receiving endocrine therapy in combination with their Herceptin re-therapy (but no chemo-/immunotherapy)

Categories	Subgroups
Mono-chemotherapy[3]	Other CTx: Patients receiving chemo-/immunotherapy other than taxanes in combination with their Herceptin re-therapy (but no endocrine therapy) CTx and endocrine therapy: Patients receiving any chemo-/immunotherapy (taxanes or other CTx) and endocrine therapy in combination with their Herceptin re-therapy. This group is referred to as "Taxanes and endocrine therapy" for the PP and SmPC-population[2] as chemotherapy comprised taxanes only in these populations. Taxane: Patients receiving a taxane in combination with their Herceptin re-therapy (no other chemotherapy and no endocrine therapy) Vinorelbine: Patients receiving vinorelbine in combination with their Herceptin re-therapy (no other chemotherapy and no endocrine therapy) Capecitabine: Patients receiving capecitabine in combination with their Herceptin re-therapy (no other chemotherapy and no endocrine therapy)

ADR = Adverse drug reaction; AP = Analysis population; CNS = Central nervous system; CTx = Chemotherapy; eCRF = Electronic case report form; ET = Endocrine therapy; PP = Per-protocol population
[1]Type of chemotherapeutic regimen in combination with adjuvant Herceptin therapy. [2]The SmPC-population was defined *post-hoc*. [3]Patients with mono-chemotherapy in combination with Herceptin re-therapy (no endocrine therapy).

7.7.5 Interim and Final Analysis and Timing of Analyses

In total, 5 interim analysis (interim reports) have been performed:

- Interim analysis 1 with database cut on 19 September 2010
- Interim analysis 2 with database cut on 18 March 2012
- Interim analysis 3 with database cut on 30 November 2012
- Interim analysis 4 with database cut on 31 January 2014
- Interim analysis 5 with database cut on 27 September 2015

The contents of all interim analyses are detailed in the "Statistical Analysis Plan for Interim Analyses" v1.0, dated 29 January 2014 (Table 1; Annex 1. List of stand-alone documents). All 5 interim reports are to be found in the Roche Trial Master File (TMF; Table 1; Annex

1. List of stand-alone documents). The interim data have been presented previously at international conferences (26–30).

As per final study protocol v4.0, dated 23 December 2013 (Table 1; Annex 1. List of stand-alone documents), the final report of this study (final analysis) was planned for 6 months after termination of study.

7.8 STATISTICAL METHODS

All statistical analyses performed to address the objectives (endpoints) in this NIS as well as the nature and extent of data presentation are detailed in the final SAP v2.2, dated 22 August 2018 (Table 1; Annex 1. List of stand-alone documents). The first version of the SAP was developed and finalized prior to the fourth interim analysis. For interim analyses, a separate SAP was prepared (v1.0, dated 29 January 2014; Table 1; Annex 1. List of stand-alone documents).

All variables were analyzed in a descriptive manner:

- Categorical variables: absolute and relative frequencies within the single categories including “missings”
- Continuous variables: Number of valid observations and missing values, mean, standard deviation, minimum, median, maximum
- Corresponding 95% CI where applicable

Time-to-event endpoints including PFS, OS, and OS-2 were estimated by using the Kaplan-Meier method to present time-to-event data together with number of censored cases as well as quartiles, rates, and corresponding 95% CI (24). The Kaplan-Meier estimates are displayed in table format and graphically in Kaplan-Meier plots.

Duration of the observational period was estimated by using the reverse Kaplan-Meier method and is presented using median together with corresponding 95% CI (24).

A multivariable logistic regression analysis and a multivariable Cox regression analysis (Efron method used to control for ties) were performed for the AP to identify potential factors (baseline demographics and clinical characteristics), which might have an impact

on the clinical response rate (CR/PR versus no response (SD, PD, NE) or missing data) or PFS, respectively. No variable selection process was conducted. The following parameters were included in the models as independent variables:

- age at inclusion
- BMI at inclusion
- DFS since the adjuvant Herceptin therapy
- tumor stage at time of initial diagnosis
- HR status (estrogen receptor/progesterone receptor)
- visceral versus non-visceral metastases at inclusion

7.8.1 Amendments to the Statistical Analysis Plan

The original SAP version 1.0, dated 1 February 2013, was amended prior to final analysis to meet all pertinent Roche-specific SOPs and is reflected in final SAP version 2.2, dated 22 August 2018 (Table 1; Annex 1. List of stand-alone documents). The amendments made are detailed in Table 7-6. The *post-hoc* analyses performed including analysis of the SmPC-population were defined and described in a Note-to-File pertinent to the SAP (Table 1; Annex 1. List of stand-alone documents), therefore, the per-protocol population (PP) is no longer relevant for the main part of the CSR. The definition and the data of the PP are to be found in the Appendices.

Table 7-6 Amendments to the statistical analysis plan

	SAP version 1.0, dated 01 February 2013	SAP version 2.2, dated 22 August 2018
Analysis Populations	For analysis, all patients having received at least one dose of trastuzumab (Herceptin) will be considered (Full Analysis Set, “as treated”).	All analyses will be conducted for the Analysis Population (AP). This population comprises all patients assessed as eligible according to Data Review Meeting (DRM). Especially patients without (neo-) adjuvant treatment, with HER2-negative tumor, without Herceptin administration, with disease progression while on adjuvant treatment and who were enrolled >1

	SAP version 1.0, dated 01 February 2013	SAP version 2.2, dated 22 August 2018
		year retrospectively are excluded. The SmPC-population comprised patients with a strict “in-label” combination treatment during Herceptin re-therapy, i.e. patients treated with Herceptin and taxanes +/- endocrine treatment. This population was defined *post-hoc* to gain a further insight into effectiveness and tumor and disease characteristics in the subset of patients with treatment combinations according to SmPC of Herceptin. The exact assignment to analysis populations is described in the DRM. For patients excluded from the AP, all documented AEs will be listed.
Overall Survival		For further OS analysis, “OS-2” will be calculated defined as time interval between diagnosis of recurrence / (distant) metastasis, which led to initiation of anti-HER2 re-therapy with Herceptin and death due to any cause.
Specification of independent parameters for model building		The following parameters will be entered in the model as independent variables: • age at inclusion into the study (continuous) • BMI at inclusion into the study • DFS since adjuvant Herceptin therapy (continuous) • stage at primary diagnosis • HR status • metastases at inclusion into the study [visceral / non-visceral only].
Adverse events	A summary table will display the number of AEs, ADRs, SAEs, and serious ADRs (SADRs) by CTC-toxicity with absolute and relative frequencies. A further summary table displays number patients in total, proportion of patients with AEs, proportion with ADRs, proportion with ADRs of grade 3/4, proportion with SAEs, proportion with SADRs and proportion of patients deceased during the treatment period or within	A summary table of AEs comprising the following parameters will be generated. This table contains respective absolute count of AEs as well as number of patients with respective AE for the following categories: • AEs without relation to Herceptin treatment and onset before 10 April 2014 • AEs without relation to Herceptin treatment and onset on or after 10 April 2014 • ADRs

	SAP version 1.0, dated 01 February 2013	SAP version 2.2, dated 22 August 2018
	30 days after end of treatment with absolute and relative frequencies. AEs, ADRs, SAEs, and SADRs will be displayed with absolute and relative frequencies.	• SAEs without relation to Herceptin treatment and onset before 10 April 2014 • SAEs without relation to Herceptin treatment and onset on or after 10 April 2014 • SADRs • ADRs with o CTCAE grade 1 o CTCAE grade 2 o CTCAE grade 3 o CTCAE grade 4 o CTCAE grade 5 o CTCAE grade 3 or 4 • ADRs leading to discontinuation of Herceptin re-therapy • AEs without relation to Herceptin treatment and onset before 10 April 2014 with o CTCAE grade 1 o CTCAE grade 2 o CTCAE grade 3 o CTCAE grade 4 o CTCAE grade 5 o CTCAE grade 3 or 4 • AEs without relation to Herceptin treatment and onset before 10 April 2014 leading to discontinuation of the Herceptin re-therapy • AEs without relation to Herceptin treatment and onset on or after 10 April 2014 o CTCAE grade 1 o CTCAE grade 2 o CTCAE grade 3 o CTCAE grade 4 o CTCAE grade 5 o CTCAE grade 3 or 4 • AEs without relation to Herceptin treatment and onset on or after 10 April 2014 leading to discontinuation of Herceptin re-therapy. For the categories mentioned above, frequency tables of MedDRA preferred terms sorted by system organ class will be generated in addition.
Subgroup analyses		Demographics and baseline characteristics (age, BMI, concomitant diseases, tumor

	SAP version 1.0, dated 01 February 2013	SAP version 2.2, dated 22 August 2018
		anamnesis, prognostic factors) will additionally be analyzed in the following subgroups: • Combination treatment with Herceptin o none (Herceptin mono) o exclusively taxane-containing chemotherapy o exclusively endocrine therapy o other chemotherapy (taxane-free chemotherapy) For DFS, a subgroup analysis by type of the chemotherapy regime, which was applied concomitant to adjuvant Herceptin therapy, will be conducted in addition to the total analysis. Data of patients, who received such an adjuvant chemotherapy, will be analyzed separately in the following groups: anthracycline / taxane / anthracycline+taxane / other. For analysis of OS-2 and PFS, the following stratification in addition to the total analysis is provided: • separated by type of metastatic disease at start of Herceptin re-therapy [visceral / non-visceral only / no metastases] • separated by combination therapy with the Herceptin re-therapy [none (Herceptin monotherapy) / taxane-containing chemotherapy / endocrine therapy / taxane-containing chemotherapy and endocrine therapy] • for the subgroup of patients with concomitant mono-chemotherapy: separated by type of chemotherapy [taxane / vinorelbine / capecitabine / carboplatin / other chemotherapy partner]

	SAP version 1.0, dated 01 February 2013	SAP version 2.2, dated 22 August 2018
		Since the collection of AEs has changed during course of study (for further details, refer to SAP section 6.3.2), AEs will be displayed separately for the following subgroups: • End of Herceptin re-therapy before July 2012 • Start of Herceptin re-therapy after July 2012 • Continuation of Herceptin re-therapy beyond April 2014
Sample size	With the planned total number of 250 patients to be included (with an expected analyzability of treatment data of about 80%), a sufficiently precise estimate of population parameters concerning effectiveness and safety is given.	A significance test (two-sided, α = 0.05), using confidence interval, statistically proving that median PFS for Herceptin treatment is greater than 4.6 months (lower limit of confidence interval >4.6), would have a power of >90%.
Missings	Partially unknown dates will be set to the 15th of respective month in case only day is missing. If day and month are unknown, the date will be set to 1st of July in case longer time periods shall be analyzed or set to "Missing" in case of shorter time periods. If calculation of time periods (e.g. treatment duration) results in negative durations, the respective durations will be set to "Missing".	For partially unknown dates, the most conservative imputation method is to be used. For further details, refer to SAP sections 6.2 – 6.4 and table 4.

AE = Adverse event; ADR = Adverse drug reaction; AP = Analysis population; CTC = Common Toxicity Criteria; CTCAE = Common Terminology Criteria for Adverse Events; DFS = Disease-free survival; DRM = Data review meeting; HER2 = Human epidermal growth factor receptor 2; HR = Hormone receptor; OS = Overall survival; PFS = Progression-free survival; PP = Per-protocol population; SADR = Serious adverse drug reaction; SAE = Serious adverse event; SAP = Statistical analysis plan; SmPC = Summary of Product Characteristics

7.8.2 Statistical Considerations and Planned Sample Size

The primary effectiveness parameter in this study (PFS) was selected based on the sample size calculation. As per final study protocol v4.0, dated 23 December 2013 (Table 1; Annex 1. List of stand-alone documents), this NIS was planned to enroll 250 patients in about 250 study sites (study protocol Amendment 2). With the LPI taking place on 09 January 2013, 239 patients had been recruited in 122 study sites across Germany (220

sites participated, of these, 98 were non-recruiting); of these, 23 patients were excluded from final data analysis as they did not meet the inclusion criteria. The following analysis populations were used in the statistical analysis:

- Study population (Analysis population, AP): The AP comprised all patients considered eligible according to DRM protocol. Patients without (neo-) adjuvant treatment, with HER2-negative tumor, without Herceptin treatment, with tumor recurrence during adjuvant treatment, with antineoplastic therapy for metastatic or locally advanced disease prior to Herceptin re-therapy or with retrospective documentation >1 year were excluded from analysis.

- SmPC-population: The SmPC-population comprised patients with a strict “in-label” combination treatment during Herceptin re-therapy, i.e. patients treated with Herceptin and taxanes +/- endocrine treatment. This population was defined *post-hoc* to gain a further insight into effectiveness and tumor and disease characteristics in the subset of patients with treatment combinations according to SmPC of Herceptin. The *post-hoc* analyses performed on the SmPC-population were defined and described in a Note-to-File pertinent to the SAP (Table 1; Annex 1. List of stand-alone documents).

All analyses were performed using the AP. For certain effectiveness analyses, the SmPC-population were used as well. For further details on analysis populations, please refer to the DRM protocol.

The subgroups used in the statistical analysis (AP and SmPC-population) are summarized in Table 7-5.

Free-text entries were evaluated as documented. No statistical methods were used to replace missing values. Essential missing values (i.e., informed consent, relevant inclusion and exclusion criteria, no administration of study drug) led to the exclusion of the patient from the analytical data set (i.e., patient not evaluable). The amount of missing values will be presented as percentage of the overall sample or according subgroup. For partially unknown dates, the most conservative imputation method was used.

7.8.3 Sample Size Justification

The primary effectiveness parameter in this study (PFS) was selected based on the calculation of sample size and was therefore from a statistical perspective established as a primary effectiveness variable. The sample size justification according to final SAP v2.2, dated 22 August 2018 (Table 1; Annex 1. List of stand-alone documents), was as follows:

"The primary aim of this NIS is to estimate the median PFS with adequate accuracy in patients who have relapsed after adjuvant anti-HER2 therapy and are being treated with Herceptin. The accuracy of the estimate of the median PFS should be reflected in an CI of about ⩽2 months (point estimator approx. ± 1 month). The calculation of the number of patients needed is based on the assumption of exponentially distributed PFS data (constant PFS rate). The basis for this is a uniform recruitment rate and no losses due to lost to follow-up (Lawless 1982).

There are no published data from studies or observational studies on the efficacy of Herceptin treatment for relapse after adjuvant anti-HER2 / neu therapy. It is assumed that chemotherapy with Herceptin-re-therapy is superior to chemotherapy without Herceptin in this therapeutic setting. In the study by Slamon et al. in 2001, a PFS of 4.6 months (equivalent to a 6-month PFS rate of approximately 40%) for various chemotherapy regimens (anthracyclines or taxanes) without Herceptin and a PFS of 7.4 months with Herceptin was published. In a cautiously estimated median PFS of 6 months (6-month PFS rate = 50%) under Herceptin therapy and with a recruitment period of 50 months and a follow-up of 60 months based on a 95% CI, 200 evaluable patients are required to achieve a median PFS estimation accuracy of ± 0.9 months. The calculated number of patients is based on a parametric model, whereas data analysis (estimation) will be performed by using the Kaplan-Meier method. With this non-parametric approach, the accuracy will be slightly lower, but within the range of about 6 ± 1 month. With an expected loss to follow-up of 20%, 250 patients will be required. A significance test (two-tailed, α = 0.05), statistically proving that the median PFS during Herceptin therapy is over 4.6 months (lower limit of CI > 4.6), would have a power of >90%."

Based on this initially planned sample size, the median for the primary endpoint PFS is reported together with corresponding 95% CI.

7.9 QUALITY CONTROL

For data capturing and data management, Java-based validated software (i.e., *iostudy office edc*) was deployed. The eCRFs for data capturing included online validation of eCRFs during data capturing, e.g. check on range, plausibility, typing errors. In addition to the system-based plausibility checks, computerized and manual consistency checks were undertaken, i.e. logical checks on data entries to check for inconsistencies. A formal query process was implemented to solve inconsistencies in documented data. A data management plan (DMP) defined how to deal with missing data and invalid entries, how data should be cleaned, and to which level of error would be acceptable. The DMP described how data were to be tracked and coded, how query reports should be generated and resolved, and how data should be stored and secured. Finally, the DMP described a quality assurance system for data entry. All steps of quality checks were performed and recorded according to iOMEDICO- and Roche-specific SOPs.

8. RESULTS

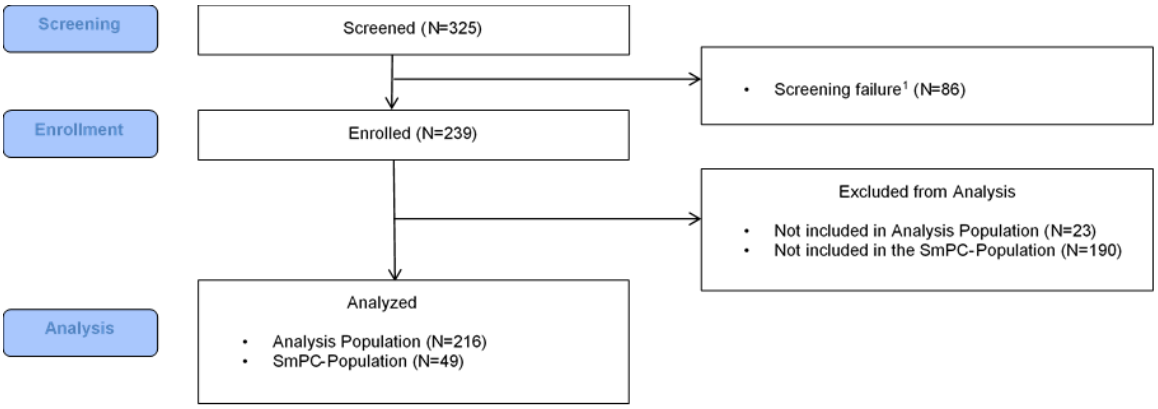
The data presented are based on the final Tables, Figures, and Listings (TFLs) v1.2, dated 25 April 2019 (Table 1; Annex 1. List of stand-alone documents). Source table(s) and figure(s) are indicated below each depicted table and figure in the report, respectively. In the same way; source Listings are being referred to (below the table or in the text body) in certain cases where further information to the data presented are provided.

8.1 PATIENT POPULATION

8.1.1 Patient Disposition Overall and in Subgroups

Patients were recruited from 23 October 2008 (FPI) through 9 January 2013 (LPI) in 122 study sites across Germany. In total, 239 patients were registered in the EDC with signed ICF and included into the study (CONSORT flow diagram; Figure 8-1), of these, 23 patients were excluded from the AP (N=216; Table 8-2). A further population, the SmPC-population, which was defined *post-hoc* for analysis of effectiveness and tumor and disease characteristics in the subset of patients with treatment combinations according to the SmPC of Herceptin, comprised 49 patients in total (excluded from analysis: N=190). The number of patients in the various subgroups in the AP and SmPC-population used in the analysis of different objectives are detailed in Table 8-1.

Figure 8-1 CONSORT flow diagram (total population)



[Source: Herceptin_Abschlussanalyse_Tables; Table 1.2, Table 1.3-a, Table 1.3-b; protocol of Data Review Meeting taking place on 7 June 2018].
N = Number; SmPC = Summary of Product Characteristics
[1]Regarding patients not eligible for study inclusion, the procedure was changed during study conduct:
- Initially, patients were deleted from the EDC system (n=20)
- Then only deactivated in the EDC (n=66)
- From 2015 onwards, no action was taken

Hence, there are at least 86 "Screening Failures" defined as violation of inclusion / exclusion criteria and deleted / deactivated in the EDC.

Table 8-1 Patient disposition – subgroups[1] (AP/SmPC-population)

	AP	SmPC-population[2]
Total number of patients, N	*216*	*49*
Number of patients in respective subgroup, N		
Metastases[3]		
No metastases (local recurrence only)	43	6
Non-visceral	61	8
Visceral	110	35
Anthracycline / Taxane [(neo-) adjuvant CTx][4]		
Anthracycline	46	NC[8]
Taxane	13	NC[8]
Anthracycline + Taxane	146	NC[8]
Other	2	NC[8]
No (neo)adjuvant CTx	9	NC[8]
Combination therapy[5]		
Herceptin Monotherapy	36	0
Taxanes	51	40
Endocrine therapy	35	0
Other CTx	74	0
CTx[6] and endocrine therapy	20	9
Mono-chemotherapy[7]		
Taxane	51	40

	AP	SmPC-population[2]
Vinorelbine	27	0
Capecitabine	23	0

[Source: Herceptin_Abschlussanalyse_Tables; Table 9.4-a, Table 21.1-b, Table 21.1-c, Table 21.1-d, Table 21.1-g, Table 23.1.b].
AP = Analysis population; CTx = Chemotherapy; N = Number; NC = Not calculated; SmPC = Summary of Product Characteristics
[1]Definition of the subgroups is provided in Table 7-5 (section 7.7.4.7 Subgroup Analyses). [2]The SmPC-population was defined *post-hoc* and only further evaluated in the subgroup "metastases". [3]The metastatic status of 2 patients (AP) at start of Herceptin re-therapy could not be classified as only the free-text entries "secondary contralateral carcinoma" and "increased tumor marker" were recorded in the eCRF, respectively. [4]Type of chemotherapeutic regimen in combination with adjuvant Herceptin therapy. [5]Comination therapy with Herceptin re-therapy. [6]This is only taxanes for the /SmPC-population. [7]Patients with mono-chemotherapy in combination with Herceptin re-therapy (no endocrine therapy). [8]Determination of the number of patients in the subgroup "Anthracycline / Taxane" was not included in the final analysis for the SmPC.

8.1.2 Reasons for Exclusion from the Analysis Population

The most common reason for exclusion of patients (n=23; 9.6%) from the AP (N=216) was patients having received chemotherapy or immunotherapy for recurrent/metastatic disease before initiation of Herceptin re-therapy (n=11; 4.6%; Table 8-2).

Table 8-2 Reasons for exclusion from the analysis population (total population)

	N	%
Total number of patients enrolled, N	*239*	*100*
Excluded from the study population (AP), n, %	23	9.6
Reasons, n, %		
Chemotherapy or immunotherapy for recurrent/metastatic disease before initiation of Herceptin re-therapy	11	4.6
Adjuvant Herceptin therapy <1 year	1	0.4
No Herceptin given in the context of the study	1	0.4
No systemic adjuvant, or neoadjuvant and adjuvant anti-HER2 therapy for early breast cancer	1	0.4
No systemic adjuvant, or neoadjuvant and adjuvant anti-HER2 therapy for early breast cancer; no Herceptin given in the context of the study	1	0.4
Adjuvant treatment with lapatinib instead of Herceptin	1	0.4
M1 at primary diagnosis	1	0.4
No recurrence/no (distant) metastasis after completion of adjuvant anti-HER2 therapy. No further documentation. No Herceptin given in the context of the study	1	0.4
Retrospective inclusion >1 year	1	0.4
Recurrence/(distant) metastases during (neo)adjuvant anti-HER2 therapy	1	0.4
Recurrence/(distant) metastases during (neo)adjuvant anti-HER2 therapy; adjuvant treatment with lapatinib instead of Herceptin	1	0.4

	N	%
Study medication presumably used as adjuvant therapy for contralateral breast cancer (secondary cancer)	1	0.4
Study medication presumably administered as (second-line) adjuvant therapy	1	0.4

[Source: Herceptin_Abschlussanalyse_Tables; Table 1.3-a].
AP = Analysis population; HER2 = Human epidermal growth factor receptor 2; N/n = Number

8.1.3 Violation of Inclusion and Exclusion Criteria

At least one inclusion or exclusion criterion was violated in 22 patients (9.2%) of the patients enrolled (N=239). The most frequently violated criterion documented was the inclusion criterion "I7: No chemo- and/or immunotherapy for recurrent/metastatic disease before initiation of Herceptin re-therapy", which was reported in 11 patients (4.6%; Table 8-3).

Table 8-3 Violation of inclusion and exclusion criteria (total population)

	N	%
Total number of patients enrolled, N	*239*	*100*
At least one inclusion or exclusion criterion violated, n, %	22	9.2
Violated criteria, n, %		
I7: No chemo- and/or immunotherapy for recurrent/metastatic disease before initiation of Herceptin re-therapy	11	4.6
I5: The patient must have received systemic adjuvant, or neoadjuvant and adjuvant anti-HER2 therapy for her early breast cancer	3	1.3
E2: The patient experienced disease progression [recurrence/(distant) metastases] during anti-HER2 neoadjuvant and/or adjuvant therapy	2	0.8
E3: LVEF ≤50% at baseline (=start of Herceptin re-therapy) Measuring method: echocardiography or MUGA scan	2	0.8
I3: Pre- and postmenopausal patients with histologically or cytologically proven locally recurrent or first-line metastatic (distant metastases) HER2-positive breast cancer	2	0.8
E6: Patient with symptomatic heart failure or coronary heart disease	1	0.4
I6: No recurrence/(distant) metastasis after completion of adjuvant anti-HER2 therapy	1	0.4

[Source: Herceptin_Abschlussanalyse_Tables; Table 1.4].
HER2 = Human epidermal growth factor receptor 2; LVEF = Left ventricular ejection fraction; MUGA = Multiple-gated acquisition scan; N/n = Number
The table shows the number of patients who were in violation of a particular inclusion criterion (I1-I7) or met a particular exclusion criterion (E1-E7).

8.1.4 Duration of the Observational Period

The estimated median duration (95% CI) of the observational period was 59.3 months (57.3 – 59.9 months; Table 8-4).

Table 8-4 Observational period (AP)

	Kaplan-Meier estimator
Total number of patients, N	*216*
Events, n (%)	82 (38.0)
Quartile (months)	
25% quantile [95% CI]	48.5 (42.8 - 55.0)
50% quantile [95% CI] (median)	59.3 (57.3 - 59.9)
75% quantile [95% CI]	60.4 (60.1 - 60.9)

[Source: Herceptin_Abschlussanalyse_Tables; Table 20.1].
AP = Analysis population; CI = Confidence interval; N/n = Number
The observational period (starting at beginning of Herceptin re-therapy) was determined by using the reverse Kaplan-Meier method. For patients alive at end of study, the last available date of patient contact was considered as "event date". Deaths were included in the analysis as censored observations. The date of death was unknown for one patient; for this patient, the date of last contact was used as event date.

8.1.5 Completion of the 12-Month Basic Documentation Period

In total, 80 (37.0%) patients completed the 12-month basic documentation period (Table 8-5). The main reason for premature end of basic documentation period was premature discontinuation of Herceptin re-therapy (n=82; 38.0%). For 24 (11.1%) patients, the basic documentation period was not completed due to patient's death.

Table 8-5 Reasons for premature end of basic documentation period (AP)

	N	%
Total number of patients, N	*216*	*100*
Patients with 12 months of basic documentation, n, %	80	37.0
Reasons for premature end of basic documentation period, n, %		
Premature discontinuation of Herceptin re-therapy	82	38.0
Patient death	24	11.1
Other	17	7.9
Patient's request	8	3.7
Investigator's decision	5	2.3

[Source: Herceptin_Abschlussanalyse_Tables; Table 17.1].
AP = Analysis population; N/n = Number

8.1.5.1 Cause of Death

Twenty-four patients (11.1%) were reported having died during the 12-month basic documentation period (Table 8-5); most patients died from neoplastic disease (n=21; 87.5%; Table 8-6).

Table 8-6 Number of deaths during the 12-month basic documentation period and cause of death (AP)

	N	%
Total number of patients, N	*216*	
Total number of deaths during the 12-month basic documentation period, N	24	100
Cause of death, n, %		
Neoplastic disease	21	87.5
Unknown[1]	3	12.5

[Source: Herceptin_Abschlussanalyse_Tables; Table 17.3, Table 17.4, Table 17.5].
AP = Analysis population; N/n = Number
This table only considers deaths that occurred during the one-year basic documentation period. Deaths that occurred after the end of the one-year basic documentation period are not included in this table
[1]The cause of death was not specified in the eCRF. Follow-up queries were generated for these 3 patients:

- Pat ID 407001: Response: The cause of death is unknown; event-term verbatim: death, unknown cause
- Pat ID 859001: Response: The cause of death is unknown; event-term verbatim: death
- Pat ID 859002: Response: The patient was transferred on 8 October 2010 in a reduced general condition to a palliative care unit of another hospital. The cause of death is unknown. No SAE documented

8.1.6 End of Documentation

Completion of the 5 years' documentation was reported for 49 (22.7%) patients (Table 8-7). The main reason for premature end of documentation was death (n=135; 62.5%) including documented cases of death occurring during the 12-month basic documentation period and during the 4-year follow-up period.

Table 8-7 Reasons for end of documentation (AP)

	N	%
Total number of patients, N	*216*	*100*
Reasons for end of documentation, n, %		
Patient death[1]	135	62.5
Regular completion after 5 years	49	22.7
Lost to follow-up	22	10.2
Other	8	3.7
Missing	2	0.9
Specification of "other" reasons, n, %		
Progression	2	0.9
Physician's decision	1	0.5
No evidence of recurrence	1	0.5
Patient non-compliance	1	0.5
Patient's request	1	0.5
Patient no longer wants to participate in the study.	1	0.5
Progression 3 September 2015	1	0.5

[Source: Herceptin_Abschlussanalyse_Tables; Table 19.1, Table 19.2].

AP = Analysis population; N/n = Number
[1]All cases of death that occurred during the study (including follow-up) were considered.

8.1.6.1 Cause of Death

In total, 135 (62.5%) patients were reported having died during the entire study (Table 8-7); the main cause of death was neoplastic disease (n=119; 88.1%; Table 8-8). One patient (0.7%) was reported having died from an SAE (including the 90-day safety follow-up period). The cause of death was unknown for 12 (8.9%) patients.

Table 8-8 Number of deaths during the entire study period and cause of death (AP)

	N	%
Total number of patients, N	*216*	
Total number of deaths during the study, N	135	100
Cause of death, n, %		
Neoplastic disease[1]	119	88.1
Comorbidity	1	0.7
Other	3	2.2
Unknown[2]	12	8.9
Specification of "other" reason[3], n, %		
Extremely rapid progression of AML	1	0.7
Multiple organ failure	1	0.7
SAE	1	0.7

[Source: Herceptin_Abschlussanalyse_Tables; Table 19.3, Table 19.4].
AML = Acute myeloid leukemia; AP = Analysis population; N/n = Number; SAE = Serious adverse event
[1]For one patient (pat ID 1004001), the fatal SAE was assigned to pulmonary embolism; however, the cause of death was tumor progression (for further details, please refer to Discrepancy Between the Safety Database and Clinical Database (Annex 2); section 9.1.8.1).
[2]This category contains 2 patients, for whom a query was generated and a fatal SAE (death; unknown cause) was recorded (pat IDs 407001 and 859001).
[3]Free-text entries extracted from the EDC and translated into English.

However, of the 135 patients having died during the study, 9 (4.2%) patients were reported with fatal SAEs and/or fatal SADRs; 8 patients with fatal SAEs not related to Herceptin treatment (Table 8-93 ; Table 8-100) and 2 patients (4 cases in total) with fatal SADRs (Table 8-93; Table 8-107). One patient (pat ID 223001) was documented with both related and non-related fatal SAEs.

The 8 fatal SAEs not related to Herceptin corresponded to the following patients:

- death (n=2; pat IDs 407001 and 859001)
    - pat ID 407001: patient aged 50.3 years at baseline, Herceptin re-therapy from 19 November 2009 to 30 December 2009, date of death: 5 January 2010, cause of death: unknown. This patient was previously reported with

diarrhea of CTCAE grade 2 lasting for one day, which was not flagged as serious and assessed as not related to Herceptin.

- pat ID 859001: patient aged 53.2 years at baseline, Herceptin re-therapy from 19 February 2010 to 23 April 2010, date of death: 2 May 2010, cause of death: unknown. This patient was reported with a prior event of dyspnea of CTCAE grade 1 lasting for two days, which was flagged as serious but not attributable to Herceptin.

- dyspnea (n=1; pat ID 223001):
  - patient aged 48.7 years at baseline, Herceptin re-therapy from 12 October 2010 to 3 November 2010, the event (dyspnea) started on 8 November 2010 (after discontinuation of Herceptin re-therapy) and lasted until time of death (18 November 2010). However, the reported cause of death was neoplastic disease. This patient was reported with gastritis erosive and oesophageal candidiasis (both events were of CTCAE grade 1), which were not flagged as serious and not assessed as related to Herceptin. Both events started on same date as the onset of dyspnea. The outcome of the events is unknown.

- general physical health deterioration (n=3; pat IDs 659006, 701002 and 973004)
  - pat ID 659006: patient aged 62.1 years at baseline, Herceptin re-therapy from 28 October 2011 to 25 January 2012, the event (general physical health deterioration) started on 2 February 2012 (after discontinuation of Herceptin re-therapy) and lasted until time of death (5 February 2012). However, the reported cause of death was neoplastic disease. No other AEs were reported for this patient.
  - pat ID 701002: patient aged 54.2 years at baseline, Herceptin re-therapy from 16 November 2010 to 1 March 2011, the event (general physical health deterioration) started on 9 April 2011 (after discontinuation of Herceptin re-therapy), which was also the reported date of death. However, the reported cause of death was neoplastic disease. No other AEs were reported for this patient.
  - pat ID 973004: patient aged 71.8 years at baseline, Herceptin re-therapy from 28 June 2012 to 14 July 2012, the event (general physical health

deterioration) started on 20 July 2012 (after discontinuation of Herceptin re-therapy) and lasted until date of death (22 July 2012). However, the reported cause of death was neoplastic disease. No other AEs were reported for this patient.

- malignant neoplasm progression (n=1; pat ID 888002):
    - patient aged 49.7 years at baseline, Herceptin re-therapy from 17 January 2011 to 11 October 2011, the event (tumor progression) started on 14 October 2011 (after discontinuation of Herceptin re-therapy) and lasted until time of death (4 December 2011). This patient was reported with 4 previous events of leukopenia (CTCAE grade 3: n=2; CTCAE grade 4: n=2), none was flagged as serious and none was assessed as related to Herceptin. All leukopenia events were resolved.

- toxic epidermal necrolysis (n=1; pat ID 860001):
    - patient aged 42.3 years at baseline, Herceptin re-therapy from 31 March 2010 to 7 July 2010, the event (toxic epidermal necrolysis) started on 13 July 2010 (after discontinuation of Herceptin re-therapy) and lasted until date of death (28 July 2010). However, the reported cause of death was neoplastic disease. No other AE was reported for this patient.

The 4 fatal SADR cases corresponded to the following 2 patients:

- general physical health deterioration, pleural effusion and pneumonia (all 3 related, fatal events were reported for pat ID 223001):
    - patient aged 48.7 years at baseline, Herceptin re-therapy from 12 October 2010 to 3 November 2010, the events started on 8 November 2010 (general physical health deterioration) or on 16 November 2010 (pleural effusion and pneumonia) and lasted until time of death (18 November 2010). All 3 events started after permanent discontinuation of Herceptin re-therapy (3 November 2010), but were however assessed by treating physician as being related to Herceptin treatment. However, the reported cause of death was neoplastic disease. This patient was reported with previous AEs including thrombocytopenia (mild), pyrexia (mild), cough (moderate), leukopenia (moderate) and anemia (serious), all of which were

assessed as possibly related to Herceptin. Anemia, leukopenia and pyrexia were resolved, whereas thrombocytopenia and cough were reported as unresolved.

- multiple organ dysfunction syndrome (pat ID 507005):
    - patient aged 78.4 years at baseline, start and end date of Herceptin re-therapy reported for the same day (18 May 2011), the event (multiple organ dysfunction syndrome) had its onset on 3 June 2011 and lasted until time of death (21 June 2011). The suspected causal link with Herceptin was unknown (however, considered related to Herceptin in the final analysis). However, the reported cause of death was neoplastic disease. This patient was reported with prior AEs related to Herceptin including chills (moderate), dyspnea (moderate) and vomiting (mild), none was however flagged as serious and all were reported as resolved.

For further details on the fatal events (SAE/SADR), please refer to Patient Listings 23.1 and 23.2.

This contrasts with the information presented in Table 8-8 (only one patient documented with a fatal SAE, however, reported as *"other reason"*; aneurysm; pat ID 698003). The two other patients falling into the category "other" correspond to pat IDs 388002 (extremely rapid progression of AML) and 859004 (multiple organ failure). Further information on these three fatal events was not documented. For the patient reported with a fatal comorbidity (pat ID 614004), further information specifying the fatal comorbidity was not recorded (only dementia was documented as comorbidity in the anamnesis). With regards to the 9 patients *reported* with fatal SAEs/SADRs,, 2 of the 9 patients fall into the category "Unknown" (n=12; Table 8-8), for whom a query was generated and a fatal SAE (death; unknown cause) was recorded (pat IDs 407001 and 859001). Regarding the other 7 patients with fatal SAEs/SADRs, the reported cause of death was "neoplastic disease" (pat IDs 223001, 507005, 659006, 701002, 860001 and 973004) or "malignant neoplasm progression" (pat ID 888002).

As aforementioned, 2 of the 12 patients in the "Unknown" category were recorded with a fatal SAE. Regarding the other 10 patients with unknown cause of death, follow-up queries were generated with the following patient IDs and responses:

- Pat ID 01003: Response: Correct entry. No SAE documented
- Pat ID 1496002: Response: No information on the cause of death. No SAE documented
- Pat ID 338005: Response: Unfortunately, died elsewhere. No information available. No SAE documented
- Pat ID 40001: Response: Reviewed: it is not trackable where and from what the patient died, with high probability of the underlying disease. No SAE documented
- Pat ID 450005: The query was not responded to.
- Pat ID 534003: The query was not responded to.
- Pat ID 543001: Response: The cause of death is unknown. No SAE documented
- Pat ID 726002: No query was generated because of the following information in the comment field: the patient is no longer in our treatment. No SAE documented
- Pat ID 859002: Response: The patient was transferred on 8 October 2010 in a reduced general condition to a palliative care unit of another hospital. The cause of death is unknown. No SAE documented (12-month documentation period)
- Pat ID 859008: Response: The cause of death is unknown. No SAE documented

8.2 DESCRIPTIVE DATA

8.2.1 Demographic and Other Characteristics of Patients at Baseline

In the AP (N=216), the median age of patients at time of initiation of Herceptin re-therapy was 56.1 years. All patients had HER2-positive BC, whereas HR-positive tumors were reported in 54.6% of patients. Two patients were documented with tumors of stage 0 at initial diagnosis (Tis N0 M0). Most patients were reported with invasive ductal carcinoma (88.0%) and tumors of grade G3 (59.3%). For the majority of patients a R0 resection (87.5%) resulted from surgical intervention. At least one comorbidity was documented in 50% of patients. The main characteristics of the patients at baseline are further detailed in Table 8-9 for the total population (AP) as well as for the subgroups of patients having received Herceptin re-therapy as monotherapy and patients having received combination therapy together with Herceptin re-therapy.

Table 8-9 Demographic and other characteristics of patients at baseline (AP)

Parameter	Total	Herceptin mono re-therapy	Taxanes	Endocrine therapy	Other CTx	CTx and endocrine therapy
Total number of patients, N	*216*	*36*	*51*	*35*	*74*	*20*
Age[1] (years)						
N	216	36	51	35	74	20
Median	56.1	57.4	58.0	49.0	57.4	55.1
Min	22.3	32.5	36.5	31.4	29.0	22.3
Max	85.3	85.3	79.5	78.2	83.4	75.8
BMI[2] (kg/m^2)						
N	215	35	51	35	74	20
Median	25.8	25.0	25.9	25.7	26.1	27.1
Min	16.3	16.7	19.0	19.6	16.3	19.3
Max	45.6	43.7	36.7	42.2	44.6	45.6
Comorbidities						
≥1 comorbidity, n (%)	108 (50.0)	15 (41.7)	31 (60.8)	16 (45.7)	37 (50.0)	9 (45.0)
The 3 most common comorbidities, n (%)						
Hypertension	62 (28.7)	11 (30.6)	20 (39.2)	9 (25.7)	18 (24.3)	4 (20.0)
Diabetes mellitus (without end organ damage)	21 (9.7)	6 (16.7)	2 (3.9)	4 (11.4)	7 (9.5)	2 (10.0)
Thyroid gland disorders	17 (7.9)	3 (8.3)	3 (5.9)	1 (2.9)	9 (12.2)	1 (5.0)
Charlson comorbidity index, n (%)						
0	169 (78.2)	25 (69.4)	44 (86.3)	30 (85.7)	54 (73.0)	16 (80.0)
1	27 (12.5)	7 (19.4)	6 (11.8)	3 (8.6)	9 (12.2)	2 (10.0)
2	14 (6.5)	3 (8.3)	1 (2.0)	2 (5.7)	7 (9.5)	1 (5.0)
3	5 (2.3)	1 (2.8)	0	0	3 (4.1)	1 (5.0)
4	1 (0.5)	0	0	0	1 (1.4)	0
Location of the primary tumor, n (%)						
Left	111 (51.4)	17 (47.2)	23 (45.1)	23 (65.7)	42 (56.8)	6 (30.0)
Right	98 (45.4)	16 (44.4)	27 (52.9)	11 (31.4)	32 (43.2)	12 (60.0)
Bilateral	7 (3.2)	3 (8.3)	1 (2.0)	1 (2.9)	0	2 (10.0)
Missing	0	0	0	0	0	0
Tumor histology at initial diagnosis,						

Parameter	Total	Herceptin mono re-therapy	Taxanes	Endocrine therapy	Other CTx	CTx and endocrine therapy
n (%)						
Invasive ductal	190 (88.0)	30 (83.3)	46 (90.2)	30 (85.7)	65 (87.8)	19 (95.0)
Invasive lobular	6 (2.8)	0	0	3 (8.6)	3 (4.1)	0
Inflammatory breast cancer	9 (4.2)	5 (13.9)	1 (2.0)	0	2 (2.7)	1 (5.0)
Other	11 (5.1)	1 (2.8)	4 (7.8)	2 (5.7)	4 (5.4)	0
Missing	0	0	0	0	0	0
Invasive ductal carcinoma with DCIS component, n (%)						
Yes	78 (36.1)	10 (27.8)	21 (41.2)	9 (25.7)	29 (39.2)	9 (45.0)
No	112 (51.9)	20 (55.6)	25 (49.0)	21 (60.0)	36 (48.6)	10 (50.0)
Missing	0	0	0	0	0	0
No invasive ductal carcinoma	26 (12.0)	6 (16.7)	5 (9.8)	5 (14.3)	9 (12.2)	1 (5.0)
Invasive lobular carcinoma with LCIS component, n (%)						
Yes	2 (0.9)	0	0	1 (2.9)	1 (1.4)	0
No	4 (1.9)	0	0	2 (5.7)	2 (2.7)	0
Missing	0	0	0	0	0	0
No invasive lobular carcinoma	210 (97.2)	36 (100.0)	51 (100.0)	32 (91.4)	71 (95.9)	20 (100.0)
Lymph node resection (n)						
Number of lymph nodes removed						
N	207	34	50	32	71	20
Median	15.0	15.0	15.5	15.0	16.0	13.0
Min	0.0	2.0	1.0	0.0	1.0	1.0
Max	59.0	59.0	35.0	33.0	38.0	31.0
Number of metastatic lymph nodes						
N	206	34	50	32	70	20
Median	2.0	1.0	1.0	2.0	4.0	1.5
Min	0.0	0.0	0.0	0.0	0.0	0.0
Max	36.0	15.0	28.0	26.0	36.0	21.0
Patients with sentinel node involvement, n (%)						
Involved sentinel nodes	33 (15.3)	3 (8.3)	11 (21.6)	6 (17.1)	11 (14.9)	2 (10.0)

Parameter	Total	Herceptin mono re-therapy	Taxanes	Endocrine therapy	Other CTx	CTx and endocrine therapy
No sentinel node involvement	78 (36.1)	16 (44.4)	16 (31.4)	16 (45.7)	22 (29.7)	8 (40.0)
Unknown	105 (48.6)	17 (47.2)	24 (47.1)	13 (37.1)	41 (55.4)	10 (50.0)
Missing	0	0	0	0	0	0
Tumor stage at initial diagnosis, n (%)						
Stage 0	2 (0.9)	1 (2.8)	0	0	1 (1.4)	0
Stage I[3]	39 (18.1)	10 (27.8)	11 (21.6)	6 (17.1)	8 (10.8)	4 (20.0)
Stage IIA	33 (15.3)	5 (13.9)	10 (19.6)	4 (11.4)	9 (12.2)	5 (25.0)
Stage IIB	33 (15.3)	3 (8.3)	8 (15.7)	8 (22.9)	11 (14.9)	3 (15.0)
Stage IIIA	37 (17.1)	6 (16.7)	8 (15.7)	4 (11.4)	17 (23.0)	2 (10.0)
Stage IIIB	14 (6.5)	4 (11.1)	3 (5.9)	2 (5.7)	3 (4.1)	2 (10.0)
Stage IIIC	37 (17.1)	1 (2.8)	8 (15.7)	7 (20.0)	18 (24.3)	3 (15.0)
Stage IV	3 (1.4)	2 (5.6)	0	1 (2.9)	0	0
Missing	18 (8.3)	4 (11.1)	3 (5.9)	3 (8.6)	7 (9.5)	1 (5.0)
Grade at initial diagnosis, n (%)						
G1	1 (0.5)	0	1 (2.0)	0	0	0
G2	81 (37.5)	13 (36.1)	15 (29.4)	18 (51.4)	25 (33.8)	10 (50.0)
G3	128 (59.3)	22 (61.1)	34 (66.7)	15 (42.9)	47 (63.5)	10 (50.0)
G4	1 (0.5)	0	0	0	1 (1.4)	0
GX	5 (2.3)	1 (2.8)	1 (2.0)	2 (5.7)	1 (1.4)	0
Missing	0	0	0	0	0	0
Resection outcome, n (%)						
R0	189 (87.5)	33 (91.7)	46 (90.2)	30 (85.7)	63 (85.1)	17 (85.0)
R1	15 (6.9)	2 (5.6)	2 (3.9)	3 (8.6)	5 (6.8)	3 (15.0)
RX	12 (5.6)	1 (2.8)	3 (5.9)	2 (5.7)	6 (8.1)	0
Missing	0	0	0	0	0	0
HER2 status, n (%)						
Positive	216 (100.0)	36 (100.0)	51 (100.0)	35 (100.0)	74 (100.0)	20 (100.0)
Negative	0	0	0	0	0	0
Missing	0	0	0	0	0	0
Estrogen receptor status, n (%)						
Positive	109 (50.5)	10 (27.8)	20 (39.2)	31 (88.6)	31 (41.9)	17 (85.0)

Parameter	Total	Herceptin mono re-therapy	Taxanes	Endocrine therapy	Other CTx	CTx and endocrine therapy
Negative	106 (49.1)	25 (69.4)	31 (60.8)	4 (11.4)	43 (58.1)	3 (15.0)
Unknown	1 (0.5)	1 (2.8)	0	0	0	0
Missing	0	0	0	0	0	0
Progesterone receptor status, n (%)						
Positive	85 (39.4)	10 (27.8)	14 (27.5)	21 (60.0)	29 (39.2)	11 (55.0)
Negative	130 (60.2)	25 (69.4)	37 (72.5)	14 (40.0)	45 (60.8)	9 (45.0)
Unknown	1 (0.5)	1 (2.8)	0	0	0	0
Missing	0	0	0	0	0	0
Hormone receptor status[4], n (%)						
Positive	118 (54.6)	13 (36.1)	22 (43.1)	32 (91.4)	34 (45.9)	17 (85.0)
Negative	97 (44.9)	22 (61.1)	29 (56.9)	3 (8.6)	40 (54.1)	3 (15.0)
Unknown	1 (0.5)	1 (2.8)	0	0	0	0
Missing	0	0	0	0	0	0

[Source: Herceptin_Abschlussanalyse_Tables; Table 2.1-a, Table 2.1-b, Table 2.2-a, Table 2.2-b, Table 3.1-a, Table 3.1-b, Table 3.3-a, Table 3.3-b, Table 4.2-a, Table 4.2-b, Table 4.6-a, Table 4.6-b, Table 4.7-a, Table 4.7-b, Table 4.8-a, Table 4.8-b, Table 5.1-a, Table 5.1-b, Table 5.2-a, Table 5.2-b, Table 5.3-a, Table 5.3-b, Table 5.4-a, Table 5.4-b, Table 5.5-a, Table 5.5-b, Table 5.6-a, Table 5.6-b, Table 5.7-a, Table 5.7-b, Table 5.8-a, Table 5.8-b, Table 5.9-a, Table 5.9-b].
AP = Analysis population; BMI = Body mass index; CTx = Chemotherapy; DCIS = Ductal carcinoma in situ; HER2 = Human epidermal growth factor receptor 2; LCIS = Lobular carcinoma in situ; Max = Maximum; Min = Minimum; N/n = Number
Herceptin mono re-therapy: Patients who did not receive any combination therapy (neither chemo-/immunotherapy nor endocrine therapy) with their Herceptin re-therapy.
Taxanes: Patients receiving a taxane in combination with their Herceptin re-therapy (but no endocrine therapy).
Endocrine therapy: Patients receiving endocrine therapy in combination with their Herceptin re-therapy (but no chemo-/immunotherapy).
Other CTx: Patients receiving chemo-/immunotherapy other than taxanes in combination with their Herceptin re-therapy (but no endocrine therapy).
CTx and endocrine therapy: Patients receiving any chemo-/immunotherapy (taxanes or other CTx) and endocrine therapy in combination with their Herceptin re-therapy.
[1]Age at initiation of Herceptin re-therapy. [2]BMI at time of inclusion into the study. The BMI for one patient with Herceptin mono re-therapy could not be determined due to missing values.
[3]N1 micro-metastases were not recorded separately, therefore, there is no differentiation between Stages IA and IB. [4]Hormone receptor status is defined as positive, if estrogen or progesterone receptor status, or both, are positive. If both estrogen and progesterone receptor status are negative, then the hormone receptor status is defined as negative.

8.2.2 Prior Treatments

8.2.2.1 Prior Surgery

All patients (N=216) were reported having been subjected to prior surgery (Table 8-10). Most patients (>20%) had been subjected to breast-conserving surgery (n=115; 53.2%), total mastectomy (n=71; 32.9%) and mastectomy (n=52; 24.1%).

Table 8-10 Surgeries (AP)

	N	%
Total number of patients, N	*216*	*100*
Surgeries[1], n, %		
Breast-conserving surgery	115	53.2
Mastectomy	52	24.1
Total mastectomy	71	32.9
Re-resection	22	10.2
Other	54	25.0
No surgery	0	0.0
Missing	0	0.0

[Source: Herceptin_Abschlussanalyse_Tables; Table 4.3-a].
AP = Analysis population; N/n = Number
[1]More than one entry per patient possible. Biopsies were not considered a surgical procedure.

8.2.2.2 Prior Radiation Therapy

Most patients (n=186; 86.1%) were documented with prior radiation therapy (Table 8-11).

Table 8-11 Radiation therapy[1] (AP)

	N	%
Total number of patients, N	*216*	*100*
Radiation therapy, n, %		
Yes	186	86.1
No	29	13.4
Unknown	1	0.5

[Source: Herceptin_Abschlussanalyse_Tables; Table 6.4.1].
AP = Analysis population; N/n = Number
[1]This table shows the number of patients who received radiation therapy before enrolment into this study.

8.2.2.3 Prior Endocrine Therapy

8.2.2.3.1 Neoadjuvant Endocrine Therapy

In total, 3 (1.4%) patients were reported having been subjected to neoadjuvant endocrine therapy receiving anastrozole alone (n=1), a combination with goserelin and tamoxifen (n=1) or leuprorelin alone (n=1) as summarized in Table 8-12.

Table 8-12 Neoadjuvant endocrine therapy (AP)

	N	%
Total number of patients, N	*216*	*100*
Neoadjuvant endocrine therapy, n, %		
Yes	3	1.4
No	213	98.6
Drug combination[1], n, %		
Anastrozole	1	0.5
Goserelin; Tamoxifen	1	0.5
Leuprorelin	1	0.5

[Source: Herceptin_Abschlussanalyse_Tables; Table 6.1.4, Table 6.1.5].
AP = Analysis population; N/n = Number
[1]This table displays all drugs administered for adjuvant endocrine treatment in a patient, respectively. Drugs are displayed in alphabetical order.

8.2.2.3.1.1 Duration of Neoadjuvant Endocrine Therapy

The median duration (min – max) of neoadjuvant endocrine therapy was 15.8 months (6.5 – 36.8 months; Table 8-13).

Table 8-13 Duration of neoadjuvant endocrine therapy (AP)

	N	Mean	STD	Median	25% quartile	75% quartile	Min	Max
Duration of neoadjuvant endocrine therapy (months)	3	19.7	15.51	15.8	6.5	36.8	6.5	36.8

[Source: Herceptin_Abschlussanalyse_Tables; Table 6.1.6].
AP = Analysis population; Min = Minimum; Max = Maximum; N = Number; STD = Standard deviation

8.2.2.3.2 Adjuvant Endocrine Therapy

In total, 106 (49.1%) patients were reported having been subjected to adjuvant endocrine therapy and the most common treatments given were tamoxifen alone (n=25; 11.6%), anastrozole alone (n=19; 8.8%), letrozole alone (n=16; 7.4%), a combination with goserelin and tamoxifen (n=15; 6.9%), and a combination with anastrozole and tamoxifen (n=10; 4.6%) as summarized in Table 8-14.

Table 8-14 Adjuvant endocrine therapy (AP)

	N	%
Total number of patients, N	*216*	*100*
Adjuvant endocrine therapy, n, %		
Yes	106	49.1
No	110	50.9
Drug combination[1], n, %		
Tamoxifen	25	11.6
Anastrozole	19	8.8

	N	%
Letrozole	16	7.4
Goserelin; Tamoxifen	15	6.9
Anastrozole; Tamoxifen	10	4.6
Letrozole; Tamoxifen	5	2.3
Exemestane	4	1.9
Leuprorelin; Tamoxifen	3	1.4
Exemestane; Letrozole	2	0.9
Exemestane; Tamoxifen	2	0.9
Anastrozole; Exemestane	1	0.5
Anastrozole; Exemestane; Goserelin; Tamoxifen	1	0.5
Anastrozole; Exemestane; Tamoxifen	1	0.5
Exemestane; Letrozole; Tamoxifen	1	0.5
Goserelin; Letrozole; Tamoxifen	1	0.5

[Source: Herceptin_Abschlussanalyse_Tables; Table 6.1.1, Table 6.1.2].
AP = Analysis population; N/n = Number
[1]This table displays all drugs administered for adjuvant endocrine treatment in a patient, respectively. Drugs are displayed in alphabetical order. The drug combinations were not necessarily given simultaneously, but sometimes also sequential or even with years between administrations.

8.2.2.3.2.1 Duration of Adjuvant Endocrine Therapy

The median duration (min – max) of adjuvant endocrine therapy overall was 32.2 months (0.0 – 89.1 months; Table 8-15). Among the most common treatments administered, the shortest median duration of adjuvant endocrine therapy was with tamoxifen alone (26.0 months (3.5 – 75.7 months)), whereas the longest duration of adjuvant endocrine therapy was treatment with anastrozole and tamoxifen in combination (39.6 months (10.5 – 57.1 months)).

Table 8-15 Duration of adjuvant endocrine therapy overall and by most frequent treatments (AP)

Duration of adjuvant endocrine therapy (months)	N	Mean	STD	Median	25% quartile	75% quartile	Min	Max
Total	94	36.4	19.40	32.2	22.8	50.2	0.0	89.1
Tamoxifen	22	30.1	17.52	26.0	18.1	41.9	3.5	75.7
Anastrozole	19	33.5	18.83	30.8	22.2	53.0	0.0	60.1
Letrozole	15	30.1	16.06	29.3	15.6	42.9	6.7	58.1
Goserelin; Tamoxifen	14	35.2	12.97	31.1	25.7	42.4	21.4	66.3
Anastrozole; Tamoxifen	8	38.9	16.18	39.6	29.4	52.9	10.5	57.1

[Source: Herceptin_Abschlussanalyse_Table; Table 6.1.3].
AP = Analysis population; N = Number
This analysis comprises data of patients with documented begin and end of endocrine therapy and with end date later than begin date. In total, 106 patients received adjuvant endocrine therapy.

8.2.2.4 Prior Chemotherapy

8.2.2.4.1 Neoadjuvant Chemotherapy

In total, 70 (32.4%) patients were documented with neoadjuvant chemotherapy with cyclophosphamide (n=64; 29.6%), epirubicin (n=53; 24.5%) and docetaxel (n=52; 24.1%) being the most commonly used drugs in first neoadjuvant chemotherapy (Table 8-16). Only one (0.5%) patient was reported with second neoadjuvant chemotherapy (vinorelbine).

Table 8-16 Drugs used in first and second neoadjuvant chemotherapy (AP)

	N	%
Total number of patients, N	*216*	*100*
Neoadjuvant chemotherapy, n, %		
Yes	70	32.4
No	146	67.6
First neoadjuvant chemotherapy[1], n, %	70	32.4
Cyclophosphamide	64	29.6
Epirubicin	53	24.5
Docetaxel	52	24.1
Doxorubicin	16	7.4
Fluorouracil	14	6.5
Paclitaxel	11	5.1
Carboplatin	3	1.4
Capecitabine	1	0.5
Second neoadjuvant chemotherapy, n, %	1	0.5
Vinorelbine	1	0.5

[Source: Herceptin_Abschlussanalyse_Table; Table 6.2.7, Table 6.2.8].
AP = Analysis population; N/n = Number
[1]Multiple entries per patient possible.

8.2.2.4.1.1 Drug Combinations Used in Neoadjuvant Chemotherapy

The drug combinations used in patients receiving neoadjuvant chemotherapy overall (N=70) are summarized in Table 8-17. The most frequently used drug combination in first neoadjuvant chemotherapy was cyclophosphamide, docetaxel, and epirubicin (n=26; 12.0%). Only one patient (0.5%) was reported having been subjected to two neoadjuvant chemotherapies (first neoadjuvant chemotherapy: epirubicin, paclitaxel; second neoadjuvant chemotherapy: vinorelbine).

Table 8-17 Drug combinations used in neoadjuvant chemotherapy (AP)

	N	%
Total number of patients, N	*216*	*100*
Patients with neoadjuvant chemotherapy, n, %	70	32.4

	N	%
Drug combination, n, %		
Cyclophosphamide, Docetaxel, Epirubicin	26	12.0
Cyclophosphamide, Docetaxel, Doxorubicin	12	5.6
Cyclophosphamide, Docetaxel, Epirubicin, Fluorouracil	7	3.2
Cyclophosphamide, Epirubicin, Paclitaxel	7	3.2
Cyclophosphamide, Epirubicin, Fluorouracil	3	1.4
Cyclophosphamide, Epirubicin	2	0.9
Cyclophosphamide, Epirubicin, Fluorouracil, Paclitaxel	2	0.9
Capecitabine, Cyclophosphamide, Docetaxel, Epirubicin	1	0.5
Carboplatin, Docetaxel	1	0.5
Carboplatin, Docetaxel, Epirubicin	1	0.5
Carboplatin, Paclitaxel	1	0.5
Cyclophosphamide, Docetaxel, Doxorubicin, Epirubicin	1	0.5
Cyclophosphamide, Docetaxel, Doxorubicin, Fluorouracil	1	0.5
Cyclophosphamide, Doxorubicin	1	0.5
Cyclophosphamide, Doxorubicin, Epirubicin, Fluorouracil	1	0.5
Docetaxel	1	0.5
Docetaxel, Epirubicin	1	0.5
Epirubicin, Paclitaxel -> Vinorelbine	1	0.5

[Source: Herceptin_Abschlussanalyse_Table; Table 6.2.9].
AP = Analysis population; N/n = Number
Substances used within one treatment are separated by comma. Different neoadjuvant treatments are separated by the symbol "-->". In total 70 patients received a neoadjuvant chemotherapy. Of these, one patient had received two neoadjuvant chemotherapies.

8.2.2.4.1.1.1 Drug Combinations Used in Neoadjuvant Chemotherapy – Subgroup "Herceptin Mono Re-Therapy" (*Post-Hoc* Analysis)

In total, 14 (38.9%) patients of all the patients having received Herceptin mono re-therapy (N=36) were documented with neoadjuvant chemotherapy (Table 8-18). The most commonly used neoadjuvant chemotherapy was a combination of cyclophosphamide, docetaxel, and epirubicin (n=3; 8.3%).

Table 8-18 Drug combinations used in neoadjuvant chemotherapy – subgroup "Herceptin mono re-therapy" (AP)

	N	%
Total number of patients, N	*216*	
Total number of patients with Herceptin mono re-therapy, N	36	100
Patients with neoadjuvant chemotherapy, n, %	14	38.9
Drug combination, n, %		
Cyclophosphamide, Docetaxel, Epirubicin	3	8.3
Cyclophosphamide, Docetaxel, Doxorubicin	2	5.6

	N	%
Cyclophosphamide, Epirubicin, Paclitaxel	2	5.6
Carboplatin, Docetaxel	1	2.8
Carboplatin, Docetaxel, Epirubicin	1	2.8
Cyclophosphamide, Docetaxel, Epirubicin, Fluorouracil	1	2.8
Cyclophosphamide, Doxorubicin, Epirubicin, Fluorouracil	1	2.8
Cyclophosphamide, Epirubicin	1	2.8
Cyclophosphamide, Epirubicin, Fluorouracil	1	2.8
Cyclophosphamide, Epirubicin, Fluorouracil, Paclitaxel	1	2.8

[Source: Herceptin_Abschlussanalyse_Table; Table 22.4-a].
AP = Analysis population; N/n = Number
Herceptin mono re-therapy: Patients who did not receive any combination therapy (neither chemo-/immunotherapy nor endocrine therapy) with their Herceptin re-therapy.

8.2.2.4.1.1.2 Drug Combinations Used in Neoadjuvant Chemotherapy – Subgroup "Taxanes Combined with Herceptin Re-Therapy" (*Post-Hoc* Analysis)

In total, 10 (19.6%) patients of all the patients having received taxanes combined with Herceptin re-therapy (N=51) were documented with neoadjuvant chemotherapy (Table 8-19). The most frequently used drug combination comprised cyclophosphamide, docetaxel, and epirubicin (n=4; 7.8%).

Table 8-19 Drug combinations used in neoadjuvant chemotherapy – subgroup "taxanes combined with Herceptin re-therapy" (AP)

	N	%
Total number of patients, N	*216*	
Total number of patients with therapy with taxanes combined with Herceptin re-therapy, N	51	100
Patients with neoadjuvant chemotherapy, n, %	10	19.6
Drug combination, n, %		
Cyclophosphamide, Docetaxel, Epirubicin	4	7.8
Cyclophosphamide, Docetaxel, Doxorubicin	3	5.9
Cyclophosphamide, Epirubicin, Paclitaxel	2	3.9
Cyclophosphamide, Epirubicin, Fluorouracil	1	2.0

[Source: Herceptin_Abschlussanalyse_Table; Table 22.4-b].
AP = Analysis population; N/n = Number
Subgroup "Taxanes": Patients receiving a taxane in combination with their Herceptin re-therapy (but no endocrine therapy).

8.2.2.4.1.1.3 Drug Combinations Used in Neoadjuvant Chemotherapy – Subgroup "Endocrine Therapy Combined with Herceptin Re-Therapy" (*Post-Hoc* Analysis)

In total, 9 (25.7%) patients of all the patients with endocrine therapy combined with Herceptin re-therapy (N=35) were documented with neoadjuvant chemotherapy (Table

8-20). The most commonly used drug combination comprised cyclophosphamide, docetaxel, and epirubicin (n=4; 11.4%).

Table 8-20 Drug combinations used in neoadjuvant chemotherapy – subgroup "endocrine therapy combined with Herceptin re-therapy" (AP)

	N	%
Total number of patients, N	*216*	
Total number of patients with endocrine therapy combined with Herceptin re-therapy, N	35	100
Patients with neoadjuvant chemotherapy, n, %	9	25.7
Drug combination, n, %		
Cyclophosphamide, Docetaxel, Epirubicin	4	11.4
Capecitabine, Cyclophosphamide, Docetaxel, Epirubicin	1	2.9
Cyclophosphamide, Docetaxel, Doxorubicin	1	2.9
Cyclophosphamide, Docetaxel, Epirubicin, Fluorouracil	1	2.9
Cyclophosphamide, Epirubicin	1	2.9
Cyclophosphamide, Epirubicin, Paclitaxel	1	2.9

[Source: Herceptin_Abschlussanalyse_Table; Table 22.4-c].
AP = Analysis population; N/n = Number
Subgroup "Endocrine therapy": Patients receiving endocrine therapy in combination with their Herceptin re-therapy (but no chemo-/immunotherapy).

8.2.2.4.1.1.4 Drug Combinations Used in Neoadjuvant Chemotherapy – Subgroup "Chemotherapy other than Taxanes Combined with Herceptin Re-Therapy" (*Post-Hoc* Analysis)

In total, 27 (36.5%) patients of all the patients having received chemotherapy other than taxanes combined with Herceptin re-therapy (N=74) were documented with neoadjuvant chemotherapy (Table 8-21). The most frequently used drug combination comprised cyclophosphamide, docetaxel, and epirubicin (n=12; 16.2%).

Table 8-21 Drug combinations used in neoadjuvant chemotherapy – subgroup "chemotherapy other than taxanes combined with Herceptin re-therapy" (AP)

	N	%
Total number of patients, N	*216*	
Total number of patients with chemotherapy other than taxanes combined with Herceptin re-therapy, N	74	100
Patients with neoadjuvant chemotherapy, n, %	27	36.5
Drug combination, n, %		
Cyclophosphamide, Docetaxel, Epirubicin	12	16.2
Cyclophosphamide, Docetaxel, Doxorubicin	5	6.8
Cyclophosphamide, Docetaxel, Epirubicin, Fluorouracil	2	2.7
Carboplatin, Paclitaxel	1	1.4
Cyclophosphamide, Docetaxel, Doxorubicin, Epirubicin	1	1.4

	N	%
Cyclophosphamide, Docetaxel, Doxorubicin, Fluorouracil	1	1.4
Cyclophosphamide, Doxorubicin	1	1.4
Cyclophosphamide, Epirubicin, Fluorouracil, Paclitaxel	1	1.4
Docetaxel	1	1.4
Docetaxel, Epirubicin	1	1.4
Epirubicin, Paclitaxel -> Vinorelbine	1	1.4

[Source: Herceptin_Abschlussanalyse_Table; Table 22.4-d].
AP = Analysis population; N/n = Number
Substances used within one treatment are separated by comma. Different neoadjuvant treatments are separated by the symbol "-->".
Subgroup "Other chemotherapy than taxanes": Patients receiving chemo-/immunotherapy other than taxanes in combination with their Herceptin re-therapy (but no endocrine therapy).

8.2.2.4.1.1.5 Drug Combinations Used in Neoadjuvant Chemotherapy – Subgroup "Chemotherapy and Endocrine Therapy Combined with Herceptin Re-Therapy" (*Post-Hoc* Analysis)

In total, 10 (50.0%) patients of all the patients having received chemotherapy and endocrine therapy combined with Herceptin re-therapy (N=20) were documented with neoadjuvant chemotherapy (Table 8-22). The most commonly used drug combinations comprised cyclophosphamide, docetaxel, and epirubicin (n=3; 15.0%) and cyclophosphamide, docetaxel, epirubicin, and fluorouracil (n=3; 15.0%).

Table 8-22 Drug combinations used in neoadjuvant chemotherapy – subgroup "chemotherapy and endocrine therapy combined with Herceptin re-therapy" (AP)

	N	%
Total number of patients, N	*216*	
Total number of patients with chemotherapy and endocrine therapy combined with Herceptin re-therapy, N	20	100
Patients with neoadjuvant chemotherapy, n, %	10	50.0
Drug combination, n, %		
Cyclophosphamide, Docetaxel, Epirubicin	3	15.0
Cyclophosphamide, Docetaxel, Epirubicin, Fluorouracil	3	15.0
Cyclophosphamide, Epirubicin, Paclitaxel	2	10.0
Cyclophosphamide, Docetaxel, Doxorubicin	1	5.0
Cyclophosphamide, Epirubicin, Fluorouracil	1	5.0

[Source: Herceptin_Abschlussanalyse_Table; Table 22.4-e].
AP = Analysis population; N/n = Number
Subgroup "Chemotherapy and endocrine therapy": Patients receiving any chemo-/immunotherapy (taxanes or other chemotherapy) and endocrine therapy in combination with their Herceptin re-therapy.

8.2.2.4.1.2 Combination of Anthracycline / Taxane Used in Neoadjuvant Chemotherapy

Most of the patients (n=60; 85.7%) with neoadjuvant chemotherapy (N=70) were reported having received a combination of anthracycline and taxane (Table 8-23).

Table 8-23 Combination of anthracycline / taxane used in neoadjuvant chemotherapy (AP)

	N	%
Total number of patients, N	*216*	
Total number of patients with neoadjuvant chemotherapy, N	70	100
Patients with anthracycline and taxane, n, %		
Anthracycline and taxane	60	85.7
Anthracycline	7	10.0
Taxane	3	4.3
Others	0	0.0

[Source: Herceptin_Abschlussanalyse_Table; Table 6.2.10].
AP = Analysis population; N/n = Number
Anthracycline: Patients receiving an anthracycline-based regimen in combination with adjuvant Herceptin therapy (but no taxanes)
Taxane: Patients receiving a taxane-based regimen in combination with adjuvant Herceptin therapy (but no anthracycline)
Anthracycline and Taxane: Patients receiving anthracycline and taxane-based regimen in combination with adjuvant Herceptin therapy
Other: patients receiving a regimen not containing an anthracycline or taxane in combination with adjuvant Herceptin therapy

8.2.2.4.1.3 Duration of Neoadjuvant Chemotherapy

The median duration (min – max) of first and second neoadjuvant chemotherapy was 4.8 months (0.7 – 7.0 months) and 0.3 months (0.3 – 0.3 months), respectively (Table 8-24).

Table 8-24 Duration of first and second neoadjuvant chemotherapy (AP)

	N	Mean	STD	Median	25% quartile	75% quartile	Min	Max
Duration of first neoadjuvant therapy (months)	64	4.1	1.27	4.8	3.5	4.9	0.7	7.0
Duration of second neoadjuvant therapy (months)	1	0.3		0.3	0.3	0.3	0.3	0.3

[Source: Herceptin_Abschlussanalyse_Table; Table 6.2.12].
AP = Analysis population; Min = Minimum; Max = Maximum; N = Number; STD = Standard deviation
The duration of neoadjuvant therapy was calculated only when sufficient information was available on the start and end date (month and year known at least). This explains why the number of patients in this analysis (column "N") differs from the total number of patients receiving neoadjuvant chemotherapy (N=70). Of these, one patient had received two neoadjuvant chemotherapies. One patient was documented having received neoadjuvant therapy from December 2006 to April 2017. This patient's data were excluded from the calculation of treatment duration on the grounds of implausibility.

8.2.2.4.2 Adjuvant Chemotherapy

In total, 141 (65.3%) patients were documented with adjuvant chemotherapy (Table 8-25). The most commonly (>20%) used medications in first adjuvant chemotherapy were cyclophosphamide (n=117; 54.2%), epirubicin (n=111; 51.4%), fluorouracil (n=78; 36.1%), and docetaxel (n=64; 29.6%). Ten (4.6%) patients were reported having received second adjuvant chemotherapy where the main drug used was cyclophosphamide (n=8; 3,7%).

Table 8-25 Drugs used in first and second adjuvant chemotherapy (AP)

	N	%
Total number of patients, N	*216*	*100*
Adjuvant chemotherapy, n, %		
Yes	141	65.3
No	75	34.7
First adjuvant chemotherapy[1], n, %	141	65.3
Cyclophosphamide	117	54.2
Epirubicin	111	51.4
Fluorouracil	78	36.1
Docetaxel	64	29.6
Paclitaxel	34	15.7
Doxorubicin	15	6.9
Carboplatin	9	4.2
Capecitabine	7	3.2
Gemcitabine	4	1.9
Vinorelbine	1	0.5
Second adjuvant chemotherapy[1], n, %	10	4.6
Cyclophosphamide	8	3.7
Capecitabine	2	0.9
Fluorouracil	2	0.9
Doxorubicin	1	0.5
Epirubicin	1	0.5

Source: Herceptin_Abschlussanalyse_Table; Table 6.2.1, Table 6.2.2].
AP = Analysis population; N/n = Number
[1]Multiple entries per patient possible.

8.2.2.4.2.1 Drug Combinations Used in Adjuvant Chemotherapy

The drug combinations used in patients receiving adjuvant chemotherapy overall (N=141) are shown in Table 8-26. The most frequently used drug combination in adjuvant chemotherapy was cyclophosphamide, epirubicin, and fluorouracil (n=36; 16.7%; first adjuvant chemotherapy).

Table 8-26 Drug combinations used in adjuvant chemotherapy (AP)

	N	%
Total number of patients, N	*216*	*100*
Patients with adjuvant chemotherapy, n, %	141	65.3
Drug combination, n, %		
Cyclophosphamide, Epirubicin, Fluorouracil	36	16.7
Cyclophosphamide, Docetaxel, Epirubicin, Fluorouracil	31	14.4
Cyclophosphamide, Epirubicin, Paclitaxel	11	5.1

	N	%
Cyclophosphamide, Docetaxel, Doxorubicin	9	4.2
Cyclophosphamide, Docetaxel, Epirubicin	9	4.2
Epirubicin, Paclitaxel -> Cyclophosphamide	6	2.8
Capecitabine, Cyclophosphamide, Epirubicin, Paclitaxel	5	2.3
Carboplatin, Docetaxel	5	2.3
Cyclophosphamide, Docetaxel, Epirubicin, Fluorouracil, Gemcitabine	4	1.9
Cyclophosphamide, Doxorubicin, Paclitaxel	4	1.9
Docetaxel	3	1.4
Carboplatin, Paclitaxel	2	0.9
Cyclophosphamide, Epirubicin, Fluorouracil, Paclitaxel	2	0.9
Capecitabine	1	0.5
Capecitabine, Epirubicin, Paclitaxel	1	0.5
Carboplatin	1	0.5
Carboplatin, Epirubicin, Fluorouracil	1	0.5
Cyclophosphamide, Docetaxel	1	0.5
Cyclophosphamide, Docetaxel, Epirubicin -> Cyclophosphamide, Epirubicin, Fluorouracil	1	0.5
Cyclophosphamide, Doxorubicin, Fluorouracil	1	0.5
Cyclophosphamide, Doxorubicin, Fluorouracil, Paclitaxel	1	0.5
Cyclophosphamide, Epirubicin	1	0.5
Cyclophosphamide, Epirubicin, Fluorouracil -> Capecitabine	1	0.5
Docetaxel, Epirubicin -> Cyclophosphamide, Doxorubicin, Fluorouracil	1	0.5
Epirubicin, Paclitaxel -> Capecitabine	1	0.5
Fluorouracil, Vinorelbine	1	0.5
Paclitaxel	1	0.5

[Source: Herceptin_Abschlussanalyse_Table; Table 6.2.3].
AP = Analysis population; N/n = Number
Substances used within one treatment are separated by comma. Different adjuvant treatments are separated by the symbol "-->".

8.2.2.4.2.1.1 Drug Combinations Used in Adjuvant Chemotherapy – Subgroup "Herceptin Mono Re-Therapy" (*Post-Hoc* Analysis)

In total, 20 (55.6%) patients of all the patients having received Herceptin mono re-therapy (N=36) were documented with adjuvant chemotherapy (Table 8-27). The most commonly used drug combinations were cyclophosphamide, docetaxel, epirubicin, and fluorouracil (n=5; 13.9%; first adjuvant chemotherapy) and cyclophosphamide, epirubicin, and fluorouracil (n=5; 13.9%; first adjuvant chemotherapy).

Table 8-27 Drug combinations used in adjuvant chemotherapy – subgroup "Herceptin mono re-therapy" (AP)

	N	%
Total number of patients, N	*216*	
Total number of patients with Herceptin mono re-therapy, N	36	100
Patients with adjuvant chemotherapy, n, %	20	55.6
Drug combination, n, %		
Cyclophosphamide, Docetaxel, Epirubicin, Fluorouracil	5	13.9
Cyclophosphamide, Epirubicin, Fluorouracil	5	13.9
Cyclophosphamide, Docetaxel, Doxorubicin	2	5.6
Carboplatin, Docetaxel	1	2.8
Cyclophosphamide, Docetaxel, Epirubicin -> Cyclophosphamide, Epirubicin, Fluorouracil	1	2.8
Cyclophosphamide, Doxorubicin, Paclitaxel	1	2.8
Cyclophosphamide, Epirubicin, Fluorouracil -> Capecitabine	1	2.8
Cyclophosphamide, Epirubicin, Paclitaxel	1	2.8
Docetaxel	1	2.8
Epirubicin, Paclitaxel -> Cyclophosphamide	1	2.8
Fluorouracil, Vinorelbine	1	2.8

[Source: Herceptin_Abschlussanalyse_Table; Table 22.3-a].
AP = Analysis population; N/n = Number
Substances used within one treatment are separated by comma. Different adjuvant treatments are separated by the symbol "-->".
Herceptin mono re-therapy: Patients who did not receive any combination therapy (neither chemo-/immunotherapy nor endocrine therapy) with their Herceptin re-therapy.

8.2.2.4.2.1.2 Drug Combinations Used in Adjuvant Chemotherapy – Subgroup "Taxanes Combined with Herceptin Re-Therapy" (*Post-Hoc* Analysis)

In total, 39 (76.5%) patients of all the patients having received taxanes in combination with Herceptin re-therapy (N=51) were documented with adjuvant chemotherapy (Table 8-28). The most frequently used drug combination was cyclophosphamide, epirubicin, and fluorouracil (n=16; 31.4%; first adjuvant chemotherapy).

Table 8-28 Drug combinations used in adjuvant chemotherapy – subgroup "taxanes combined with Herceptin re-therapy" (AP)

	N	%
Total number of patients, N	*216*	
Total number of patients with taxanes combined with Herceptin re-therapy, N	51	100
Patients with adjuvant chemotherapy, n, %	39	76.5
Drug combination, n, %		
Cyclophosphamide, Epirubicin, Fluorouracil	16	31.4
Cyclophosphamide, Docetaxel, Epirubicin, Fluorouracil	7	13.7
Cyclophosphamide, Epirubicin, Paclitaxel	3	5.9
Cyclophosphamide, Doxorubicin, Paclitaxel	2	3.9

	N	%
Capecitabine	1	2.0
Capecitabine, Cyclophosphamide, Epirubicin, Paclitaxel	1	2.0
Carboplatin, Docetaxel	1	2.0
Cyclophosphamide, Docetaxel, Doxorubicin	1	2.0
Cyclophosphamide, Docetaxel, Epirubicin	1	2.0
Cyclophosphamide, Docetaxel, Epirubicin, Fluorouracil, Gemcitabine	1	2.0
Cyclophosphamide, Doxorubicin, Fluorouracil	1	2.0
Cyclophosphamide, Epirubicin	1	2.0
Cyclophosphamide, Epirubicin, Fluorouracil, Paclitaxel	1	2.0
Epirubicin, Paclitaxel -> Capecitabine	1	2.0
Epirubicin, Paclitaxel -> Cyclophosphamide	1	2.0

[Source: Herceptin_Abschlussanalyse_Table; Table 22.3-b].
AP = Analysis population; N/n = Number
Substances used within one treatment are separated by comma. Different adjuvant treatments are separated by the symbol "-->".
Subgroup "Taxanes": Patients receiving a taxane in combination with their Herceptin re-therapy (but no endocrine therapy).

8.2.2.4.2.1.3 Drug Combinations Used in Adjuvant Chemotherapy – Subgroup "Endocrine Therapy Combined with Herceptin Re-Therapy" (*Post-Hoc* Analysis)

In total, 24 (68.6%) patients of all the patients having received endocrine therapy in combination with Herceptin re-therapy (N=35) were documented with adjuvant chemotherapy (

Table 8-29). The most commonly used drug combination was cyclophosphamide, docetaxel, epirubicin, and fluorouracil (n=8; 22.9%; first adjuvant chemotherapy). No patients were reported with second adjuvant chemotherapy.

Table 8-29 Drug combinations used in adjuvant therapy – subgroup "endocrine therapy combined with Herceptin re-therapy" (AP)

	N	%
Total number of patients, N	*216*	
Total number of patients with endocrine therapy combined with Herceptin re-therapy, N	35	100
Patients with adjuvant chemotherapy, n, %	24	68.6
Drug combination, n, %		
Cyclophosphamide, Docetaxel, Epirubicin, Fluorouracil	8	22.9
Cyclophosphamide, Epirubicin, Fluorouracil	5	14.3
Cyclophosphamide, Epirubicin, Paclitaxel	3	8.6
Carboplatin, Docetaxel	2	5.7
Cyclophosphamide, Docetaxel, Epirubicin, Fluorouracil, Gemcitabine	2	5.7
Capecitabine, Cyclophosphamide, Epirubicin, Paclitaxel	1	2.9

	N	%
Cyclophosphamide, Docetaxel	1	2.9
Cyclophosphamide, Docetaxel, Doxorubicin	1	2.9
Cyclophosphamide, Doxorubicin, Fluorouracil, Paclitaxel	1	2.9

[Source: Herceptin_Abschlussanalyse_Table; Table 22.3-c].
AP = Analysis population; N/n = Number
Substances used within one treatment are separated by comma. Different adjuvant treatments are separated by the symbol "-->".
Subgroup "Endocrine therapy": Patients receiving endocrine therapy in combination with their Herceptin re-therapy (but no chemo-/immunotherapy).

8.2.2.4.2.1.4 Drug Combinations Used in Adjuvant Chemotherapy – Subgroup "Chemotherapy other than Taxanes Combined with Herceptin Re-Therapy" *(Post-Hoc* Analysis)

In total, 48 (64.9%) patients of all the patients having received chemotherapy other than taxanes in combination with Herceptin re-therapy (N=74) were documented with adjuvant chemotherapy (Table 8-30). The most common drug combination was cyclophosphamide, docetaxel, epirubicin, and fluorouracil (n=11; 14.9%; first adjuvant chemotherapy).

Table 8-30 Drug combinations used in adjuvant therapy – subgroup "chemotherapy other than taxanes combined with Herceptin re-therapy" (AP)

	N	%
Total number of patients, N	*216*	
Total number of patients with chemotherapy other than taxanes combined with Herceptin re-therapy, N	74	100
Patients with adjuvant chemotherapy, n, %	48	64.9
Drug combination, n, %		
Cyclophosphamide, Docetaxel, Epirubicin, Fluorouracil	11	14.9
Cyclophosphamide, Docetaxel, Epirubicin	8	10.8
Cyclophosphamide, Docetaxel, Doxorubicin	4	5.4
Cyclophosphamide, Epirubicin, Fluorouracil	4	5.4
Cyclophosphamide, Epirubicin, Paclitaxel	4	5.4
Epirubicin, Paclitaxel -> Cyclophosphamide	4	5.4
Capecitabine, Cyclophosphamide, Epirubicin, Paclitaxel	3	4.1
Carboplatin, Paclitaxel	2	2.7
Docetaxel	2	2.7
Capecitabine, Epirubicin, Paclitaxel	1	1.4
Carboplatin	1	1.4
Carboplatin, Docetaxel	1	1.4
Cyclophosphamide, Doxorubicin, Paclitaxel	1	1.4
Cyclophosphamide, Epirubicin, Fluorouracil, Paclitaxel	1	1.4
Paclitaxel	1	1.4

[Source: Herceptin_Abschlussanalyse_Table; Table 22.3-d].
AP = Analysis population; N/n = Number

Substances used within one treatment are separated by comma. Different adjuvant treatments are separated by the symbol "-->".
Subgroup "Other chemotherapy than taxanes": Patients receiving chemo-/immunotherapy other than taxanes in combination with their Herceptin re-therapy (but no endocrine therapy).

8.2.2.4.2.1.5 Drug Combinations Used in Adjuvant Chemotherapy – Subgroup "Chemotherapy and Endocrine Therapy Combined with Herceptin Re-Therapy" (*Post-Hoc* Analysis)

In total, 10 (50.0%) patients of all the patients having received chemotherapy and endocrine therapy in combination with Herceptin re-therapy (N=20) were documented with adjuvant chemotherapy (Table 8-31). The most frequent drug combination was cyclophosphamide, epirubicin, and fluorouracil (n=6; 30.0%; first adjuvant chemotherapy).

Table 8-31 Drug combinations used in adjuvant therapy – subgroup "chemotherapy and endocrine therapy combined with Herceptin re-therapy" (AP)

	N	%
Total number of patients, N	*216*	
Total number of patients with chemotherapy and endocrine therapy combined with Herceptin re-therapy, N	20	100
Patients with adjuvant chemotherapy, n, %	10	50.0
Drug combination, n, %		
Cyclophosphamide, Epirubicin, Fluorouracil	6	30.0
Carboplatin, Epirubicin, Fluorouracil	1	5.0
Cyclophosphamide, Docetaxel, Doxorubicin	1	5.0
Cyclophosphamide, Docetaxel, Epirubicin, Fluorouracil, Gemcitabine	1	5.0
Docetaxel, Epirubicin -> Cyclophosphamide, Doxorubicin, Fluorouracil	1	5.0

[Source: Herceptin_Abschlussanalyse_Table; Table 22.3-e].
AP = Analysis population; N/n = Number
Substances used within one treatment are separated by comma. Different adjuvant treatments are separated by the symbol "-->".
Subgroup "Chemotherapy and endocrine therapy": Patients receiving any chemo-/immunotherapy (taxanes or other chemotherapy) and endocrine therapy in combination with their Herceptin re-therapy.

8.2.2.4.2.2 Combination of Anthracycline / Taxane Used in Adjuvant Chemotherapy

Most of the patients (n=86; 61.0%) with adjuvant chemotherapy (N=141) were reported having received a combination of anthracycline and taxane (Table 8-32).

Table 8-32 Combination of anthracycline / taxane used in adjuvant chemotherapy (AP)

	N	%
Total number of patients, N	*216*	
Total number of patients with adjuvant chemotherapy, N	141	100.0
Patients with anthracycline / taxane, n, %		
Anthracycline and taxane	86	61.0
Anthracycline	40	28.4

Taxane	12	8.5
Other	3	2.1

[Source: Herceptin_Abschlussanalyse_Table; Table 6.2.4].
AP = Analysis population; N/n = Number
Anthracycline: Patients receiving an anthracycline-based regimen in combination with adjuvant Herceptin therapy (but no taxanes)
Taxane: Patients receiving a taxane-based regimen in combination with adjuvant Herceptin therapy (but no anthracycline)
Anthracycline and Taxane: Patients receiving anthracycline and taxane-based regimen in combination with adjuvant Herceptin therapy
Other: patients receiving a regimen not containing an anthracycline or taxane in combination with adjuvant Herceptin therapy.

8.2.2.4.2.3 Duration of Adjuvant Chemotherapy

The median duration (min – max) of first and second adjuvant chemotherapy was 3.6 months (0.0 – 15.5 months) and 1.1 months (0.7 – 11.6 months), respectively (Table 8-33).

Table 8-33 Duration of first and second adjuvant chemotherapy (AP)

	N	Mean	STD	Median	25% quartile	75% quartile	Min	Max
Duration of first adjuvant chemotherapy (months)	134	4.0	1.84	3.6	3.5	4.5	0.0	15.5
Duration of second adjuvant chemotherapy (months)	10	2.4	3.30	1.1	1.0	2.0	0.7	11.6

[Source: Herceptin_Abschlussanalyse_Table; Table 6.2.6].
AP = Analysis population; Min = Minimum; Max = Maximum; N = Number; STD = Standard deviation
The duration of adjuvant therapy was calculated only when sufficient information was available on the start and end date (month and year known at least). This explains why the number of patients in this analysis (column "N") differs from the total number of patients receiving adjuvant chemotherapy. A total of 141 patients received adjuvant chemotherapy. Of these, 10 patients had received two adjuvant chemotherapies.

8.2.2.5 Prior Anti-HER2 Therapy

8.2.2.5.1 Neoadjuvant and Adjuvant Anti-HER2 Therapy

Overall, 32 (14.8%) patients were documented with neoadjuvant anti-HER2 therapy (Herceptin therapy: n=30; 13.9%) and 205 (94.9%) patients with adjuvant anti-HER2 therapy (all received Herceptin therapy) as detailed in Table 8-34.

Table 8-34 Drugs used in neoadjuvant and adjuvant anti-HER2 therapy (AP)

		N	%
Total number of patients, N		*216*	*100*
Neoadjuvant anti-HER2 therapy[1], n, %		32	14.8
	Herceptin	30	13.9
	Lapatinib	2	0.9
Adjuvant anti-HER2 therapy[1], n, %		205	94.9
	Herceptin	205	94.9
	Lapatinib	5	2.3

[Source: Herceptin_Abschlussanalyse_Table; Table 6.3.1].
AP = Analysis population; HER2 = Human epidermal growth factor receptor 2; N/n = Number
[1]More than one entry per patient possible.

8.2.2.5.2 Duration of Neoadjuvant Anti-HER2 Therapy

The median duration (min – max) of neoadjuvant anti-HER2 therapy was 4.9 months (0.0 – 15.1 months; Table 8-35).

Table 8-35 Duration of neoadjuvant anti-HER2 therapy (AP)

	N	Mean	STD	Median	25% quartile	75% quartile	Min	Max
Duration of neoadjuvant anti-HER2 therapy (months)	31	6.7	4.64	4.9	2.8	11.9	0.0	15.1

[Source: Herceptin_Abschlussanalyse_Table; Table 6.3.3].
AP = Analysis population; HER2 = Human epidermal growth factor receptor 2; Min = Minimum; Max = Maximum; N = Number; STD = Standard deviation
The duration of therapy is shown for patients for whom the start and end dates of neoadjuvant anti-HER2 therapy is documented. This explains why the number of patients in this analysis (column "N") differs from the total number of patients who received neoadjuvant anti-HER therapy (N=32).

8.2.2.5.3 Duration of Adjuvant Anti-HER2 Therapy

The median duration (min – max) of adjuvant anti-HER2 therapy was 11.8 months (2.0 – 28.8 months; Table 8-36).

Table 8-36 Duration of adjuvant anti-HER2 therapy (AP)

	N	Mean	STD	Median	25% quartile	75% quartile	Min	Max
Duration of adjuvant anti-HER2 therapy (months)	196	11.7	2.51	11.8	11.5	12.2	2.0	28.8

[Source: Herceptin_Abschlussanalyse_Table; Table 6.3.2].
AP = Analysis population; HER2 = Human epidermal growth factor receptor 2; Min = Minimum; Max = Maximum; N = Number; STD = Standard deviation
The duration is shown for patients for whom the start and end date of adjuvant anti-HER2 therapy is documented. This explains why the number of patients in this analysis (column "N") differs from the total number of patients who received adjuvant anti-HER therapy (N=205).

8.2.2.5.4 Number of Cycles by Active Substance in Neoadjuvant and Adjuvant Anti-HER2 Therapy

The patients documented with neoadjuvant anti-HER2 therapy had received a median (min – max) of 8 cycles (1.0 – 25.0 cycles) of Herceptin therapy and the patients with adjuvant anti-HER2 therapy had received a median of 18 cycles (7.0 – 113.0 cycles) of Herceptin therapy (Table 8-37).

Table 8-37 Number of cycles by active substance in neoadjuvant and adjuvant anti-HER2 therapy (AP)

	N	Mean	STD	Median	25% quartile	75% quartile	Min	Max
Neoadjuvant therapy, n								
Herceptin	29	10.8	6.86	8.0	4.0	18.0	1.0	25.0
Lapatinib	2	30.0	31.11	30.0	8.0	52.0	8.0	52.0
Adjuvant treatment, n								
Herceptin	193	18.8	9.37	18.0	17.0	18.0	7.0	113.0

	N	Mean	STD	Median	25% quartile	75% quartile	Min	Max
Lapatinib	4	187.0	204.96	187.5	9.5	364.5	8.0	365.0

[Source: Herceptin_Abschlussanalyse_Table; Table 6.3.4].
AP = Analysis population; HER2 = Human epidermal growth factor receptor 2; Min = Minimum; Max = Maximum; N/n = Number; STD = Standard deviation
The number of cycles is shown for patients for whom the information was available. This explains why the number of patients in this analysis (column "N") differs from the total number of patients who received adjuvant (N=205) or neoadjuvant anti-HER therapy (N=32). The definition of a "cycle" was specified by the documenting study site.

8.2.2.5.5 Cycle Length by Active Substance in Neoadjuvant and Adjuvant Anti-HER2 Therapy

Most of the patients having received neoadjuvant anti-HER2 therapy with Herceptin (n=30; 13.9%) had received Herceptin on a three-weekly schedule as per the first documented cycle (n=26; 12.0%; Table 8-38). The majority of the patients documented with adjuvant anti-HER2 therapy with Herceptin (n=205; 94.9%) were reported having received Herceptin on a three-weekly schedule (first documented cycle; n=180; 83.3%).

Table 8-38 Cycle length by active substance in neoadjuvant and adjuvant anti-HER2 therapy[1] (AP)

	N	%
Total number of patients, N	*216*	*100*
Neoadjuvant anti-HER2 therapy, n, %	32	14.8
Herceptin, n, %	30	13.9
3 qw	26	12.0
1 qw	3	1.4
unknown	1	0.5
Lapatinib, n, %	2	0.9
continuous	2	0.9
Adjuvant anti-HER2 therapy, n, %	205	94.9
Herceptin, n, %	205	94.9
3 qw	180	83.3
1 qw	16	7.4
unknown	9	4.2
Lapatinib, n, %	5	2.3
continuous	5	2.3

[Source: Herceptin_Abschlussanalyse_Table; Table 6.3.5].
AP = Analysis population; HER2 = Human epidermal growth factor receptor 2; N/n = Number
[1]The table shows the first documented cycle length.

8.2.2.5.6 First Documented Planned Dose by Active Substance in Neoadjuvant and Adjuvant Anti-HER2 Therapy

The first documented planned Herceptin dose was 6 mg/kg for most patients (n=14; 6.5%) having received neoadjuvant anti-HER2 therapy with Herceptin (n=30; 13.9%; Table 8-39).

For most patients with adjuvant anti-HER2 therapy with Herceptin (n=205; 94.9%), the first documented planned Herceptin dose was 6 mg/kg (n=115; 53.2%).

Table 8-39 First documented planned dose by active substance in neoadjuvant and adjuvant anti-HER2 therapy[1] (AP)

	N	%
Total number of patients, N	*216*	*100*
Neoadjuvant anti-HER2 therapy, n, %	32	14.8
Herceptin, n, %	30	13.9
6 mg/kg	14	6.5
8 mg/kg	6	2.8
2 mg/kg	4	1.9
4 mg/m²	1	0.5
400 mg/m²	1	0.5
6 mg/m²	1	0.5
unknown	3	1.4
Lapatinib, n, %	2	0.9
1,250 mg/day	1	0.5
1,500 mg/day	1	0.5
Adjuvant anti-HER2 therapy, n, %	205	94.9
Herceptin, n, %	205	94.9
6 mg/kg	115	53.2
8 mg/kg	26	12.0
6 mg/m²	13	6.0
2 mg/kg	8	3.7
4 mg/kg	7	3.2
100 mg/m²	1	0.5
110 mg/kg	1	0.5
138 mg/day	1	0.5
14 mg/m²	1	0.5
150 mg/m²	1	0.5
150 mg/day	1	0.5
18 mg/kg	1	0.5
2 mg/m²	1	0.5
300 mg/kg	1	0.5
300 mg/m²	1	0.5
336 mg/kg	1	0.5
340 mg/day	1	0.5
438 mg/day	1	0.5
450 mg/kg	1	0.5
450 mg/day	1	0.5
472 mg/kg	1	0.5
500 mg/day	1	0.5
540 mg/day	1	0.5

		N	%
	570 mg/kg	1	0.5
	6.0 pg/kg	1	0.5
	600 mg/kg	1	0.5
	8 mg/m²	1	0.5
	unknown	14	6.5
Lapatinib, n, %		5	2.3
	1,000 mg/day	2	0.9
	1,500 mg/day	1	0.5
	21,000 mg/day	1	0.5
	2,500 mg/day	1	0.5

[Source: Herceptin_Abschlussanalyse_Table; Table 6.3.6].
AP = Analysis population; HER2 = Human epidermal growth factor receptor 2; N/n = Number
[1]The table shows the first documented planned dose. The data were extracted from the eCRF unchanged. The eCRF may contain documentation errors.

8.2.2.5.7 LVEF Before/After (Neo-) Adjuvant Anti-HER2 Therapy

The median LVEF was 65% both before and after completed (neo-) adjuvant anti-HER2 therapy (Table 8-40).

Table 8-40 LVEF before/after (neo-)adjuvant anti-HER2 therapy (AP)

	N	Mean	STD	Median	25% quartile	75% quartile	Min	Max
LVEF before anti-HER2-therapy (%)	110	65.7	7.31	65.0	60.0	70.0	47.0	83.0
LVEF after anti-HER2 therapy (%)	108	64.4	8.23	65.0	60.0	70.0	25.0	95.0

[Source: Herceptin_Abschlussanalyse_Table; Table 6.3.8].
AP = Analysis population; HER2 = Human epidermal growth factor receptor 2; LVEF = Left ventricular ejection fraction; N = Number
The data are shown for patients for whom the information was available. This explains why the number of patients in this analysis (column "N") differs from the total number of patients who received (neo)adjuvant anti-HER2 therapy (N=216).

8.2.2.5.8 Reasons for Discontinuation of (Neo-)Adjuvant Anti-HER2 Therapy

The main documented reason for discontinuation of (neo-) adjuvant anti-HER2 therapy was "regular end", i.e., after 1 year of treatment (n=208; 96.3%, Table 8-41). For 2 (0.9%) patients, the reason for end of treatment was "cardiac side effects".

Table 8-41 Reason for discontinuation of (neo-) adjuvant anti-HER2 therapy (AP)

	N	%
Total number of patients, N	*216*	*100*
Reasons for end of (neo-) adjuvant anti-HER2 therapy, n, %		
Regular end (after 1 year of treatment)	208	96.3
Cardiac side effects	2	0.9

Other side effects	1	0.5
Investigator's decision	1	0.5
Other	4	1.9

[Source: Herceptin_Abschlussanalyse_Table; Table 6.3.10].
AP = Analysis population; HER2 = Human epidermal growth factor receptor 2; N/n = Number

8.2.3 Recurrence / Distant Metastases After Adjuvant Anti-HER2 Therapy

8.2.3.1 Local Recurrence

Following completion of adjuvant anti-HER2 therapy, 79 (36.6%) patients were documented with local recurrence with 28 (13.0%) patients reported with local recurrence located to the breast (Table 8-42).

Table 8-42 Local findings / local recurrence (AP)

	N	%
Total number of patients, N	*216*	*100*
Patients with local abnormalities[1], n, %	79	36.6
Breast (e.g. inflammatory changes)	28	13.0
Chest wall	27	12.5
Axillary	19	8.8
Supraclavicular	13	6.0
No local abnormalities	137	63.4

[Source: Herceptin_Abschlussanalyse_Tables; Table 7.1].
AP = Analysis population; N/n = Number
[1]More than one entry per patient possible.

8.2.3.2 Distant Metastases

Distant metastases were documented in 173 (80.1%) patients with bone (n=77; 35.6%), liver (n=67; 31.0%) and lung (n=51, 23.6%) being the most frequent (>10%) metastatic sites (Table 8-43).

Table 8-43 Distant metastases (AP)

	N	%
Total number of patients, N	*216*	*100*
Patients with distant metastases[1], n, %	173	80.1
Bone	77	35.6
Liver	67	31.0
Lung	51	23.6
Pleural effusion	14	6.5
CNS	6	2.8
Ascites	1	0.5
Other	45	20.8
No distant metastases	43	19.9

[Source: Herceptin_Abschlussanalyse_Tables; Table 7.2].

AP = Analysis population; N/n = Number
[1]More than one entry per patient possible.

8.2.3.2.1 Type of Metastatic Disease in Subgroups – Combination Therapy (*Post-Hoc* Analysis)

Patients without metastases and patients with non-visceral/visceral disease are detailed in Table 8-44 for the subgroups of patients having received Herceptin re-therapy as monotherapy and patients having received combination therapy together with Herceptin re-therapy. Proportion of patients with visceral metastases (n=36; 70.6%) was highest in the subgroup of patients having received taxanes together with Herceptin re-therapy.

Table 8-44 Type of metastatic disease in the subgroups (combination therapy, AP)

	Herceptin mono re-therapy	Taxanes	Endocrine therapy	Other CTx	CTx and endocrine therapy
Total number of patients: N=216					
Number of patients per subgroup, N	36	51	35	74	20
Type of metastatic disease, n (%)					
No metastases	12 (33.3)	7 (13.7)	7 (20.0)	12 (16.2)	5 (25.0)
Non-visceral metastases only[1]	11 (30.6)	8 (15.7)	23 (65.7)	16 (21.6)	3 (15.0)
Visceral metastases[1]	13 (36.1)	36 (70.6)	5 (14.3)	44 (59.5)	12 (60.0)
Missing[2]	0	0	0	2 (2.7)	0

[Source: Herceptin_Abschlussanalyse_Tables; Table 22.1].
AP = Analysis population; CTx = Chemotherapy; N/n = Number
Herceptin mono re-therapy: Patients who did not receive any combination therapy (neither chemo-/immunotherapy nor endocrine therapy) with their Herceptin re-therapy.
Taxanes: Patients receiving a taxane in combination with their Herceptin re-therapy (but no endocrine therapy).
Endocrine therapy: Patients receiving endocrine therapy in combination with their Herceptin re-therapy (but no chemo-/immunotherapy).
Other CTx: Patients receiving chemo-/immunotherapy other than taxanes in combination with their Herceptin re-therapy (but no endocrine therapy).
CTx and endocrine therapy: Patients receiving any chemo-/immunotherapy (taxanes or other CTx) and endocrine therapy in combination with their Herceptin re-therapy.
[1]Definition of non-visceral/visceral disease is provided in Table 7-5 (section 7.7.4.7 Subgroup Analyses). [2]The metastatic situation of two patients (IDs 1014007 and 497003) could not be classified. Neither of the patients demonstrated local recurrence and the only available information relating to metastases was “secondary malignancy, contralateral” and “elevated tumor marker”, respectively.

8.2.4 Effectiveness of Prior (Neo-) Adjuvant Anti-HER2 Therapy

8.2.4.1 Tumor Response to Neoadjuvant Anti-HER2 Therapy

Most of the patients having received neoadjuvant anti-HER2 therapy (n=32; 14.8%) were reported with a PR (n=18; 56.3%; Table 8-45). One (3.1%) patient was documented with a CR and 3 (9.4%) patients with a pathologic CR.

Table 8-45 Tumor response to neoadjuvant anti-HER2 therapy (AP)

	N	%
Total number of patients, N	*216*	
Patients with neoadjuvant anti-HER2 therapy, n, %	32	100

	N	%
Clinical response[1], n, %		
CR	1	3.1
pCR	3	9.4
PR	18	56.3
NC (SD)	2	6.3
Unknown	8	25.0

[Source: Herceptin_Abschlussanalyse_Tables; Table 9.1].
AP = Analysis population; CI = Confidence interval; CR = Complete remission; HER2 = Human epidermal growth factor receptor 2; N/n = Number; NC = No change; pCR = Pathologic complete remission; PR = Partial remission; SD = Stable disease
[1]Entries selected from a dropdown menu in EDC where multiple answers per patient was not possible.

8.2.4.2 Time From Initial Diagnosis to First Recurrence / Distant Metastases

The median time (min – max) from initial diagnosis to first documented local recurrence/distant metastasis was 37.4 months (7.0 – 142.3 months; Table 8-46).

Table 8-46 Time from initial diagnosis to first recurrence/distant metastasis (AP)

	N	Mean	STD	Median	25% quartile	75% quartile	Min	Max
Time from initial diagnosis to first recurrence/(distant) metastasis (months)	215	41.5	18.85	37.4	29.2	50.7	7.0	142.3

[Source: Herceptin_Abschlussanalyse_Tables; Table 9.2].
AP = Analysis population; Min = Minimum; Max = Maximum; N = Number; STD = Standard deviation
For one patient, the exact date of recurrence was unknown, therefore, this case was excluded from the calculation.

8.2.4.3 Time Span Between End of Adjuvant Anti-HER2 Therapy and Initiation of Herceptin Re-Therapy

The median time span (min – max) between completed adjuvant anti-HER2 therapy and initiation of Herceptin re-therapy was 21.1 months (0.6 – 98.3 months; Table 8-47).

Table 8-47 Time span between end of adjuvant anti-HER2 therapy and initiation of Herceptin re-therapy (AP)

	N	Mean	STD	Median	25% quartile	75% quartile	Min	Max
Time span between end of adjuvant anti-HER2 therapy and initiation of Herceptin re-therapy (months)	208	23.7	15.39	21.1	12.7	32.0	0.6	98.3

[Source: Herceptin_Abschlussanalyse_Tables; Table 9.3].
AP = Analysis population; HER2 = Human epidermal growth factor receptor 2; Min = Minimum; Max = Maximum; N = Number; STD = Standard deviation
For 8 patients, the end date of adjuvant therapy was either not or only partially known (only the year); these 8 cases were therefore excluded from the calculation.

8.2.4.4 Time From Initial Tumor Resection to Start of Herceptin Re-Therapy – Subgroups: Combination Therapy (*Post-Hoc* Analysis)

The time from initial tumor resection to start of Herceptin re-therapy in the subgroups of patients having received Herceptin re-therapy as monotherapy and patients having received combination therapy together with Herceptin re-therapy is summarized in Table 8-48. The median time (min – max) from initial tumor resection to start of Herceptin re-therapy was shortest for patients having received Herceptin mono re-therapy (31.1 months (8.2 – 106.1 months)), whereas it was longest for patients having received endocrine therapy together with Herceptin re-therapy (45.1 months (20.4 – 136.4 months)).

Table 8-48 Time from initial tumor resection to start to Herceptin re-therapy – subgroups: combination therapy (AP)

	N	Mean	STD	Median	25% quartile	75% quartile	Min	Max
Time from initial tumor resection to start of Herceptin re-therapy (months)								
Herceptin mono re-therapy	36	37.0	20.41	31.1	24.5	43.3	8.2	106.1
Taxanes	51	42.3	15.25	38.6	31.5	53.7	18.9	79.3
Endocrine therapy	35	46.1	20.96	45.1	30.4	53.0	20.4	136.4
Other CTx	74	38.8	17.38	36.7	26.9	49.3	8.8	97.7
CTx and endocrine therapy	20	43.5	12.55	41.9	34.7	49.8	23.5	67.2

Source: Herceptin_Abschlussanalyse_Tables; Table 22.2].
AP = Analysis population; CTx = Chemotherapy; Min = Minimum; Max = Maximum; N = Number; STD = Standard deviation
Herceptin mono re-therapy: Patients who did not receive any combination therapy (neither chemo-/immunotherapy nor endocrine therapy) with their Herceptin re-therapy.
Taxanes: Patients receiving a taxane in combination with their Herceptin re-therapy (but no endocrine therapy).
Endocrine therapy: Patients receiving endocrine therapy in combination with their Herceptin re-therapy (but no chemo-/immunotherapy).
Other CTx: Patients receiving chemo-/immunotherapy other than taxanes in combination with their Herceptin re-therapy (but no endocrine therapy).
CTx and endocrine therapy: Patients receiving any chemo-/immunotherapy (taxanes or other CTx) and endocrine therapy in combination with their Herceptin re-therapy.

8.2.4.5 Disease-Free Survival

DFS was defined as the time from initial tumor resection to the onset of the first local recurrence / (distant) metastasis which led to the initiation of Herceptin re-therapy. The DFS overall and by prior chemotherapy is summarized in Table 8-49. The median (min – max) DFS overall was 36.5 months (8.0 – 135.1 months). Patients having received prior therapy with taxanes and possibly other chemotherapeutic agents other than anthracyclines had the shortest median DFS (28.6 months (15.4 – 46.3 months)), whereas the longest median DFS were observed in patients with prior therapy with anthracyclines and possibly other chemotherapeutic agents other than taxanes (39.7 months (8.0 – 96.7 months)).

Table 8-49 Disease-free survival (DFS) overall and by prior chemotherapy (AP)

	N	Mean	STD	Median	25% quartile	75% quartile	Min	Max
DFS (months)								
Total	214	39.0	17.61	36.5	26.5	48.6	8.0	135.1
Anthracycline	45	41.6	16.92	39.7	29.7	50.6	8.0	96.7
Taxane	13	31.9	10.72	28.6	24.1	43.5	15.4	46.3
Anthracycline and taxane	145	39.4	18.65	36.3	26.3	49.1	8.1	135.1
Other chemotherapy	2	30.0	11.75	30.0	21.7	38.3	21.7	38.3
No (neo-) adjuvant chemotherapy	9	33.0	6.94	32.2	27.9	39.3	24.3	42.2

Source: Herceptin_Abschlussanalyse_Tables; Table 9.4-a].
AP = Analysis population; DFS = Disease-free survival; Min = Minimum; Max = Maximum; N = Number; STD = Standard deviation
DFS was defined as the time from initial tumor resection to the onset of the first recurrence/(distant) metastasis which led to the initiation of Herceptin re-therapy.
For two patients, the DFS could not be determined:

- For one patient (who received adjuvant chemotherapy with anthracycline), the DFS could not be determined because the exact date of the recurrence was unknown. This patient (ID 343002) underwent initial tumor resection in July 2005 and the recurrence occurred in 2010.
- For the other patient (ID 1552002), the initial tumor resection was documented in February 2005 while the onset of recurrence was dated 1 September 2004, i.e. before the initial tumor resection. This patient received (neo-) adjuvant chemotherapy with anthracyclines and taxanes. However, this patient was included in the final analysis.

Prior chemotherapy ((neo-) adjuvant therapy) was separated into the following subgroups:

- Anthracycline: Patients receiving an anthracycline-based regimen in combination with adjuvant Herceptin therapy (but no taxanes)
- Taxane: Patients receiving a taxane-based regimen in combination with adjuvant Herceptin therapy (but no anthracyclines)
- Anthracycline and Taxane: Patients receiving anthracycline and taxane-based regimen in combination with adjuvant Herceptin therapy
- Other: patients receiving a regimen not containing an anthracycline or taxane in combination with adjuvant Herceptin therapy

8.3 OUTCOME DATA

The final analyses were performed with a dataset of 216 patients (AP)and 49 patients (SmPC-population). Please refer to Table 7-5 and Table 8-1 for definition of subgroups and number of patients in each subgroup, respectively.

Outcome data were:

Description of effectiveness and safety of re-therapy with Herceptin in routine clinical practice in patients with HER2-positive BC having relapsed following completed (neo-) adjuvant anti-HER2-therapy with Herceptin for HER2-positive EBC

- Herceptin re-therapy: duration of therapy, dosage, number of cycles, cycle length
- Combination therapy: Drug combination and duration of therapy

- Reasons for treatment modification and discontinuation of Herceptin re-therapy / combination therapy
- Criteria for choice of Herceptin re-therapy / combination therapy
- Type of second-line and further-line therapy (following end of Herceptin re-therapy
- Effectiveness of Herceptin re-therapy: PFS, OS, OS-2, ORR, and manifestation of new metastases in organ systems not affected at enrollment (course of neoplastic disease)
- Incidence and severity of AEs, SAEs, ADRs, and SADRs
- Cardiac monitoring: LVEF during the study

8.4 MAIN RESULTS

8.4.1 Herceptin Re-Therapy

8.4.1.1 LVEF at Initiation of Herceptin Re-Therapy

In total, 113 (52.3%) patients were documented with a LVEF >60% at time of initiation of Herceptin re-therapy (Table 8-50).

Table 8-50 LVEF at initiation of Herceptin re-therapy (AP)

	N	%
Total number of patients, N	*216*	*100*
Level of LVEF, n, %		
≤60%	59	27.3
>60%	113	52.3
Missing	44	20.4

[Source: Herceptin_Abschlussanalyse_Tables; Table 13.1].
AP = Analysis population; LVEF = Left ventricular ejection fraction; N/n = Number

8.4.1.2 Initial Dose of Herceptin Re-Therapy

Most patients were documented with an initial dose of Herceptin of 8 mg/kg (n=111; 51.4%) or 4 mg/kg (n=76; 35.2%; Table 8-51).

Table 8-51 Initial dose of Herceptin re-therapy (AP)

	N	%
Total number of patients, N	*216*	*100*
Initial dose of Herceptin[1], n, %		

	N	%
8 mg/kg	111	51.4
4 mg/kg	76	35.2
6 mg/kg	22	10.2
2 mg/kg	6	2.8
12 mg/kg	1	0.5

[Source: Herceptin_Abschlussanalyse_Tables; Table 13.3].
AP = Analysis population; N/n = Number
[1]Data on the initial dose of Herceptin re-therapy extracted from the eCRF unchanged.

8.4.1.3 Duration of Herceptin Re-Therapy

The median duration (min – max) of Herceptin re-therapy was 9.0 months (0.0- 74.7 months; Table 8-52).

Table 8-52 Duration of Herceptin re-therapy (AP)

	N	Mean	STD	Median	25% quartile	75% quartile	Min	Max
Duration of Herceptin re-therapy (months)	214	11.9	12.65	9.0	3.7	13.7	0.0	74.7

[Source: Herceptin_Abschlussanalyse_Tables; Table 13.4].
AP = Analysis population; Min = Minimum; Max = Maximum; N = Number; STD = Standard deviation
For two patients, the information on the end date of Herceptin re-therapy was insufficient. The data of these two patients were therefore not included in the analysis.

8.4.1.4 Number of Cycles of Herceptin Re-Therapy

Patients received a median (min – max) of 16 cycles (1.0 – 565.0 cycles) of Herceptin re-therapy (Table 8-53).

Table 8-53 Number of cycles of Herceptin re-therapy (AP)

	N	Mean	STD	Median	25% quartile	75% quartile	Min	Max
Number of cycles	209	24.2	45.68	16.0	8.0	24.0	1.0	565.0

[Source: Herceptin_Abschlussanalyse_Tables; Table 13.5].
AP = Analysis population; Min = Minimum; Max = Maximum; N = Number; STD = Standard deviation
For 7 patients, the number of cycles of Herceptin re-therapy was not documented. The data of these patients were therefore not included in the analysis.

8.4.1.4.1 Cycle Length (Herceptin Re-Therapy)

Most patients were reported having received Herceptin re-therapy on a three-weekly schedule (n=151; 69.9%), whereas 56 (25.9%) patients were documented with a weekly schedule (first documented cycle length; Table 8-54).

Table 8-54 Cycle length – Herceptin re-therapy (AP)

	N	%
Total number of patients, N	*216*	*100*
Cycle length[1], n, %		

	N	%
3 qw	151	69.9
1 qw	56	25.9
4 qw	4	1.9
2 qw	2	0.9
6 qw	1	0.5
Unknown	2	0.9

[Source: Herceptin_Abschlussanalyse_Tables; Table 13.7].
AP = Analysis population; N = number
[1]The table shows the first documented cycle length. Changes that occurred during treatment were not included in the analysis.

8.4.1.5 Modifications of Herceptin Re-Therapy

At least one therapy modification was documented in 82 (38.0%) patients during Herceptin re-therapy (Table 8-55). The most common therapy modification was dose modification (n=57; 26.4%).

Table 8-55 Proportion of patients with modifications of Herceptin re-therapy (AP)

	N	%
Total number of patients, N	*216*	*100*
Patients with ≥1 therapy modification, n, %	82	38.0
Type of therapy modification[1], n, %		
≥1 dose modification	57	26.4
≥1 therapy delay	25	11.6
≥1 therapy interruption	23	10.6

[Source: Herceptin_Abschlussanalyse_Tables; Table 13.8].
AP = Analysis population; N/n = Number
[1]Multiple entries per patient possible.

8.4.1.5.1 Reasons for Modification of Herceptin Re-Therapy

The most common reasons for dose modification were treating physician's decision (n=33; 15.3%) and change in body weight (n=28; 13.0%; Table 8-56). Treating physician's decision and patient's request were the most frequent reasons both for therapy delay (n= 13 (6.0%); n=11 (5.1%)) and therapy interruption (n=15 (6.9%); n=6 (2.8%)), respectively.

Table 8-56 Reasons for modification of Herceptin re-therapy (AP)

	N	%
Total number of patients, N	*216*	*100*
Patients with ≥1 dose modification, n, %	57	26.4
Reasons[1], n, %		
Treating physician's decision	33	15.3
Change in body weight	28	13.0
Patient's request	4	1.9

	N	%
Re-escalation	4	1.9
Missing	2	0.9
Patients with ≥1 therapy delay, n, %	25	11.6
Reasons[1], n, %		
Treating physician's decision	13	6.0
Patient's request	11	5.1
Toxicity	2	0.9
Re-escalation	1	0.5
Patients with ≥1 therapy interruption, n, %	23	10.6
Reasons[1], n, %		
Treating physician's decision	15	6.9
Patient's request	6	2.8
Toxicity	3	1.4
Re-escalation	1	0.5

[Source: Herceptin_Abschlussanalyse_Tables; Table 13.9].
AP = Analysis population; N/n = Number
[1]Multiple entries per patient possible.

8.4.1.6 Reasons for Discontinuation of Herceptin Re-Therapy

The main reason for discontinuation of Herceptin re-therapy was disease progression (local recurrence/metastases) as documented in 111 (51.4%) patients (Table 8-57). Herceptin re-therapy was discontinued due to patient death in 22 (10.2%) patients and due to cardiac side effects in 8 (3.7%) patients.

Table 8-57 Reasons for discontinuation of Herceptin re-therapy (AP)

	N	%
Total number of patients, N	*216*	*100*
Reason for discontinuation of Herceptin re-therapy, n, %		
Disease progression[1]	111	51.4
Patient death	22	10.2
Treating physician's decision[2]	21	9.7
Patient's request[2]	13	6.0
Cardiac side effects	8	3.7
Other side effects	3	1.4
Other[2]	34	15.7
Missing	4	1.9

[Source: Herceptin_Abschlussanalyse_Tables; Table 13.10].
AP = Analysis population; N/n = Number
[1]Disease progression includes local recurrence / metastasis.
[2]For specification of reasons, please refer to Appendices, Table 1.

8.4.2 Concomitant Treatments With Herceptin Re-Therapy

8.4.2.1 Concomitant Endocrine Therapy With Herceptin Re-Therapy

In total, 69 (31.9%) patients were documented with endocrine therapy concurrent with Herceptin re-therapy (Table 8-58). The most common (>5% of patients) drugs used were exemestane (n=19; 8.8%), fulvestrant (n=18; 8.3%), tamoxifen (n=18; 8.3%), anastrozole (n=16; 7.4%) and letrozole (n=16; 7.4%).

Table 8-58 Concomitant endocrine therapy with Herceptin re-therapy (AP)

	N	%
Total number of patients, N	*216*	*100*
Concomitant endocrine therapy, n, %		
Yes	69	31.9
No	147	68.1
Drugs[1], n, %		
Exemestane	19	8.8
Fulvestrant	18	8.3
Tamoxifen	18	8.3
Anastrozole	16	7.4
Letrozole	16	7.4
Goserelin	10	4.6
Leuprorelin	2	0.9
MPA	1	0.5

[Source: Herceptin_Abschlussanalyse_Tables; Table 12.1, Table 12.2].
AP = Analysis population; MPA = Medroxyprogesterone acetate; N/n = Number
[1]Multiple entries per patient possible.

8.4.2.1.1 Drug Combinations Used in Concomitant Endocrine Therapy

The documented drug combinations used in concomitant endocrine therapy are detailed in Table 8-59. The most common (>3% of patients) endocrine therapies administered were exemestane (n=10; 4.6%), anastrozole (n=9; 4.2%), tamoxifen (n=9; 4.2%), letrozole (n=8; 3.7%) and fulvestrant (n=7; 3.2%).

Table 8-59 Drug combinations used in concomitant endocrine therapy (AP)

	N	%
Total number of patients, N	*216*	*100*
Patients with concomitant endocrine therapy, n, %	69	31.9
Drug combination, n, %		

	N	%
Exemestane	10	4.6
Anastrozole	9	4.2
Tamoxifen	9	4.2
Letrozole	8	3.7
Fulvestrant	7	3.2
Anastrozole, Fulvestrant	2	0.9
Exemestane, Fulvestrant	2	0.9
Exemestane, Goserelin	2	0.9
Goserelin	2	0.9
Anastrozole, Exemestane	1	0.5
Anastrozole, Exemestane, Fulvestrant, Tamoxifen	1	0.5
Anastrozole, Goserelin	1	0.5
Anastrozole, Goserelin, Tamoxifen	1	0.5
Anastrozole, Letrozole	1	0.5
Exemestane, Fulvestrant, Tamoxifen	1	0.5
Exemestane, Letrozole	1	0.5
Exemestane, Tamoxifen	1	0.5
Fulvestrant, Goserelin, Letrozole	1	0.5
Fulvestrant, Goserelin, Tamoxifen	1	0.5
Fulvestrant, Letrozole	1	0.5
Fulvestrant, MPA	1	0.5
Fulvestrant, Tamoxifen	1	0.5
Goserelin, Letrozole	1	0.5
Goserelin, Tamoxifen	1	0.5
Letrozole, Leuprorelin	1	0.5
Letrozole, Leuprorelin, Tamoxifen	1	0.5
Letrozole, Tamoxifen	1	0.5

[Source: Herceptin_Abschlussanalyse_Tables; Table 12.4].
AP = Analysis population; MPA = Medroxyprogesterone acetate; N/n = Number

8.4.2.1.2 Duration of Endocrine Therapy

The median duration (min – max) of concomitant endocrine therapy was 10.9 months (0.6 – 87.2 months; Table 8-60).

Table 8-60 Duration of concomitant endocrine therapy (AP)

	N	Mean	STD	Median	25% quartile	75% quartile	Min	Max
Duration of concomitant endocrine therapy (months)	57	18.0	17.91	10.9	4.2	29.5	0.6	87.2

[Source: Herceptin_Abschlussanalyse_Tables; Table 12.8].
AP = Analysis population; Min = Minimum; Max = Maximum; N = Number; STD = Standard deviation

The duration of therapy was calculated for patients for whom the start and end dates of concomitant endocrine therapy were available. A total of 69 patients had received endocrine therapy in addition to Herceptin re-therapy.

8.4.2.1.3 Modifications of Concomitant Endocrine Therapy

Only one patient (1.4%) was documented with ≥1 modification of concomitant endocrine therapy (Table 8-61). This patient had been subjected to ≥1 therapy delay (treating physician's decision).

Table 8-61 Modifications of concomitant endocrine therapy (AP)

	N	%
Total number of patients, N	*216*	
Total number of patients with concomitant endocrine therapy, N	69	100
Patients with ≥1 therapy modification, n, %	1	1.4
Type of therapy modification, n, %		
≥1 therapy delay	1	1.4
Reason for modification, n, %		
Treating physician's decision	1	1.4

[Source: Herceptin_Abschlussanalyse_Tables; Table 12.6, Table 12.7].
AP = Analysis population; N/n = Number

8.4.2.1.4 Reasons for Discontinuation of Concomitant Endocrine Therapy

Most patients (n=35; 50.7%) were reported having discontinued the concomitant endocrine therapy due to progression (Table 8-62). For 7 (10.1%) patients, the therapy was discontinued due to death.

Table 8-62 Reasons for discontinuation of concomitant endocrine therapy (AP)

	N	%
Total number of patients, N	*216*	
Total number of patients with concomitant endocrine therapy, N	69	100
Reasons for discontinuation of concomitant endocrine therapy, n, %		
Progression	35	50.7
Death	7	10.1
Patient's request	4	5.8
Treating physician's decision	2	2.9
CR	1	1.4
PR	1	1.4
Toxicity	1	1.4
Other	13	18.8
Missing	5	7.2

[Source: Herceptin_Abschlussanalyse_Tables; Table 12.9].
AP = Analysis population; CR = Complete remission; N/n = Number; PR = Partial remission

8.4.2.2 Concomitant Combination Chemotherapy With Herceptin Re-Therapy

In total, 145 (67.1%) patients were reported having received concomitant combination chemotherapy with Herceptin re-therapy (Table 8-63). The most common (>10% of patients) drugs used in the first line of concomitant combination chemotherapy (treatment 1) with Herceptin re-therapy were paclitaxel (n=53; 24.5%), vinorelbine (n=40; 18.5%), capecitabine (n=31; 14.4%) and docetaxel (n=23; 10.6%). Table 8-63 also details the drugs used in the second (treatment 2; n=9) and third (treatment 3; n=1) line of concomitant combination chemotherapy with Herceptin re-therapy.

Table 8-63 Concomitant combination chemotherapy with Herceptin re-therapy (AP)

	N	%
Total number of patients, N	*216*	*100*
Patients with concomitant combination chemotherapy, n, %		
Yes	145	67.1
No	71	32.9
Drugs[1], n, %		
Treatment 1	145	67.1
Paclitaxel	53	24.5
Vinorelbine	40	18.5
Capecitabine	31	14.4
Docetaxel	23	10.6
Carboplatin	11	5.1
Bevacizumab	3	1.4
Doxorubicin	2	0.9
Cyclophosphamide	1	0.5
Fluorouracil	1	0.5
Lapatinib	1	0.5
Pertuzumab	1	0.5
Treatment 2	9	4.2
Capecitabine	4	1.9
Paclitaxel	2	0.9
Vinorelbine	2	0.9
Fluorouracil	1	0.5
Na-Folinat	1	0.5
Oxaliplatin	1	0.5
Treatment 3	1	0.5
Carboplatin	1	0.5
Gemcitabine	1	0.5

[Source: Herceptin_Abschlussanalyse_Tables; Table 11.1, Table 11.2].

AP = Analysis population; eCRF = Electronic case report form; N/n = Number
[1]Multiple entries per patient possible.
This table displays all treatments documented in the eCRF form "Concomitant chemotherapy" and which were given in combination with Herceptin re-therapy. Changes in the concomitant chemotherapy are represented by the categories "Treatment 1", "Treatment 2" und "Treatment 3". Categorization was done medical experts of iOMEDICO AG.
For 11 patients, subsequent chemotherapies (starting after end of Herceptin re-therapy) were documented in this form by mistake. These are

- 1494002: Vinorelbine
- 44001: Capecitabine
- 44002: Paclitaxel
- 450002: Vinorelbine
- 474003: Vinorelbine
- 687003: Lapatinib -> Trastuzumab
- 764004: Paclitaxel -> Capecitabine -> Trastuzumab
- 810001: Paclitaxel
- 859002: Capecitabine
- 888001: Capecitabine
- 948002: Capecitabine

8.4.2.2.1 Drug Combinations Used in Concomitant Chemotherapy

The documented drug combinations used in concomitant combination chemotherapy are detailed in Table 8-64. The most frequently (>10% of patients) concomitant combination chemotherapy given was monotherapy with paclitaxel (n=43; 29.7%), vinorelbine (n=31; 21.4%), capecitabine (n=23; 15.9%), and docetaxel (n=17; 11.7%).

Table 8-64 Drug combinations used in concomitant chemotherapy (AP)

	N	%
Total number of patients, N	*216*	
Total number of patients with concomitant combination chemotherapy, N	145	100
Drug combination, n, %		
Paclitaxel	43	29.7
Vinorelbine	31	21.4
Capecitabine	23	15.9
Docetaxel	17	11.7
Capecitabine, Vinorelbine	4	2.8
Carboplatin, Docetaxel	4	2.8
Carboplatin, Paclitaxel	3	2.1
Bevacizumab, Capecitabine	2	1.4
Carboplatin	2	1.4
Paclitaxel -> Vinorelbine	2	1.4
Bevacizumab, Paclitaxel -> Capecitabine	1	0.7
Capecitabine -> Fluorouracil, Na-Folinat, Oxaliplatin	1	0.7
Capecitabine -> Paclitaxel	1	0.7
Carboplatin, Lapatinib, Paclitaxel	1	0.7
Carboplatin, Paclitaxel -> Capecitabine	1	0.7
Cyclophosphamide, Doxorubicin	1	0.7

	N	%
Docetaxel, Paclitaxel	1	0.7
Docetaxel, Vinorelbine	1	0.7
Doxorubicin	1	0.7
Fluorouracil, Vinorelbine	1	0.7
Paclitaxel, Pertuzumab	1	0.7
Vinorelbine -> Capecitabine	1	0.7
Vinorelbine -> Capecitabine -> Carboplatin, Gemcitabine	1	0.7
Vinorelbine -> Paclitaxel	1	0.7

[Source: Herceptin_Abschlussanalyse_Tables; Table 11.3].
AP = Analysis population; eCRF = Electronic case report form; N/n = Number
This table displays all treatments documented in the eCRF form "Concomitant chemotherapy" and which were given in combination with Herceptin re-therapy. Changes in the concomitant chemotherapy are represented by the symbol "->". Categorization was done medical experts of iOMEDICO AG. For 11 patients, subsequent chemotherapies (starting after end of Herceptin re-therapy) were documented in this form by mistake. These are

- 1494002: Vinorelbine
- 44001: Capecitabine
- 44002: Paclitaxel
- 450002: Vinorelbine
- 474003: Vinorelbine
- 687003: Lapatinib -> Trastuzumab
- 764004: Paclitaxel -> Capecitabine -> Trastuzumab
- 810001: Paclitaxel
- 859002: Capecitabine
- 888001: Capecitabine
- 948002: Capecitabine

8.4.2.2.2 Duration of Concomitant Chemotherapy

The median duration (min – max) of concomitant combination chemotherapy was 3.6 months (0.0 – 25.0 months; Treatment 1), 4.8 months (2.8 – 9.6 months; Treatment 2) and 5.5 months (5.5 – 5.5 months, Treatment 3) as displayed in Table 8-65.

Table 8-65 Duration of concomitant chemotherapy (AP)

Duration of concomitant chemotherapy (months)	N	Mean	STD	Median	25% quartile	75% quartile	Min	Max
Treatment 1	141	4.6	3.54	3.6	2.6	5.3	0.0	25.0
Treatment 2	9	5.5	2.47	4.8	3.9	6.3	2.8	9.6
Treatment 3	1	5.5		5.5	5.5	5.5	5.5	5.5

[Source: Herceptin_Abschlussanalyse_Tables; Table 11.4].
AP = Analysis population; eCRF = Electronic case report form; Min = Minimum; Max = Maximum; N = Number; STD = Standard deviation
Data include all treatments recorded as "Concomitant chemotherapy" in the eCRF and co-administered with Herceptin re-therapy. Changes in concomitant chemotherapy are reflected by classification into "Treatment 1", "Treatment 2" and "Treatment 3". The classification was carried out by medical staff of iOMEDICO AG. The duration was calculated for all cases for which sufficient information was available on treatment start and end dates.

8.4.2.2.3 Modifications of Concomitant Chemotherapy

In total, 38 (26.2%) patients were documented with ≥1 modification of concomitant chemotherapy (Table 8-66). The most frequent modification of chemotherapy was dose reduction (n=25; 17.2%).

Table 8-66 Modifications of concomitant chemotherapy (AP)

	N	%
Total number of patients, N	*216*	
Total number of patients with concomitant chemotherapy, N	145	100
Patients with ≥1 therapy modification[1], n, %	38	26.2
Type of therapy modification, n, %		
≥1 dose reduction	25	17.2
≥1 therapy delay	15	10.3
≥1 dose increase	6	4.1

[Source: Herceptin_Abschlussanalyse_Tables; Table 11.8].
AP = Analysis population; eCRF = Electronic case report form; N/n = Number
[1]Multiple entries per patient possible. Data include all treatment modifications concerning chemotherapeutic treatment recorded as "Concomitant chemotherapy" in the eCRF and co-administered with Herceptin re-therapy.

8.4.2.2.3.1 Reasons for Modification of Chemotherapy

The most common reasons for dose reduction were toxicity (n=14; 9.7%) and treating physician's decision (n=10; 6.9%; Table 8-67). The most frequent reason for therapy delay and dose increase was toxicity (n=8; 5.5%) and change in body weight (n=3; 2.1%), respectively.

Table 8-67 Reasons for modification of chemotherapy (AP)

	N	%
Total number of patients, N	*216*	
Total number of patients with concomitant chemotherapy, N	145	100
Patients with ≥1 dose reduction, n, %	25	17.2
Reasons[1], n, %		
Toxicity	14	9.7
Treating physician's decision	10	6.9
Patient's request	2	1.4
Change in body weight	1	0.7
Patients with ≥1 therapy delay, n, %	15	10.3
Reasons[1], n, %		
Toxicity	8	5.5
Treating physician's decision	6	4.1
Patient's request	3	2.1
Patients with ≥1 dose increase, n, %	6	4.1
Reasons[1], n, %		
Change in body weight	3	2.1
Treating physician's decision	2	1.4
Re-escalation	1	0.7

[Source: Herceptin_Abschlussanalyse_Tables; Table 11.9].
AP = Analysis population; eCRF = Electronic case report form; N/n = Number

[1]Multiple entries per patient possible. Data include all treatments recorded as "Concomitant chemotherapy" in the eCRF and co-administered with Herceptin re-therapy.

8.4.2.2.4 Reasons for Discontinuation of Concomitant Combination Chemotherapy

The most frequent (>10% of patients) reasons for discontinuation of concomitant chemotherapy were progression (n=39; 26.9%), treating physician's decision (n=23; 15.9%) and PR (n=16; 11.0%; Table 8-68). Concomitant chemotherapy was discontinued due to CR in 10 patients (6.9%) and due to death in 10 patients (6.9%).

Table 8-68 Reasons for discontinuation of concomitant chemotherapy (AP)

	N	%
Total number of patients, N	*216*	
Total number of patients with concomitant chemotherapy, N	145	100
Reasons for discontinuation of concomitant chemotherapy, n, %		
Progression	39	26.9
Treating physician's decision	23	15.9
PR	16	11.0
CR	10	6.9
Death	10	6.9
Toxicity	9	6.2
Patient's request	8	5.5
Other	29	20.0
Missing	1	0.7

[Source: Herceptin_Abschlussanalyse_Tables; Table 11.10].
AP = Analysis population; CR = Complete remission; N/n = Number; PR = Partial remission

8.4.3 Palliative Surgeries

In total, 60 (27.8%) patients were documented with palliative surgery during the study with local recurrence (n=24; 11.1%) and lymph nodes (n=15; 6.9%) being the most frequent sites subjected to surgery (Table 8-69).

Table 8-69 Palliative surgeries (AP)

	N	%
Total number of patients, N	*216*	*100*
Palliative surgery, n, %		
Yes	60	27.8
No	156	72.2
Organ systems subjected to surgery[1], n, %		
Local recurrence	24	11.1
Lymph nodes	15	6.9

	N	%
Lung	5	2.3
Liver	5	2.3
Bone	4	1.9
Other	24	11.1

[Source: Herceptin_Abschlussanalyse_Tables; Table 14.1, Table 14.2].
AP = Analysis population; N/n = Number
[1]Multiple entries per patient possible.

8.4.4 Cardiac Monitoring

8.4.4.1 LVEF Documentation Period

The median duration (min – max) of the LVEF documentation period was 15.2 months (-1.8 – 62.0 months) comprising data from start of Herceptin re-therapy and the last documented LVEF measurement during the study including the 4-year follow-up period per patient (Table 8-70).

Table 8-70 LVEF documentation period (AP)

	N	Mean	STD	Median	25% quartile	75% quartile	Min	Max
Duration of the LVEF documentation period (months)	170	22.0	19.59	15.2	5.2	35.7	-1.8	62.0

[Source: Herceptin_Abschlussanalyse_Tables; Table 15.1].
AP = Analysis population; LVEF = Left ventricular ejection fraction; Min = Minimum; Max = Maximum; N = Number; STD = Standard deviation
This table shows the period from the start of Herceptin re-therapy and the last documented LVEF measurement for the entire study (including the follow-up documentation and the period after discontinuation of Herceptin re-therapy). The analysis included data from patients with at least one documented LVEF measurement. A negative value means that the last documented measurement took place before treatment started.

8.4.4.2 Time to LVEF Nadir

The median (min – max) time to LVEF nadir was 10.7 months (1.2 – 55.6 months; Table 8-71).

Table 8-71 Time to LVEF nadir (AP)

	N	Mean	STD	Median	25% quartile	75% quartile	Min	Max
Time to LVEF nadir (months)	129	15.1	13.21	10.7	4.6	20.3	1.2	55.6

[Source: Herceptin_Abschlussanalyse_Tables; Table 15.4].
AP = Analysis population; LVEF = Left ventricular ejection fraction; Min = Minimum; Max = Maximum; N = Number; STD = Standard deviation
The nadir was defined as the lowest post-baseline LVEF documented over the course of the study (including follow-up documentation and the period after discontinuation of Herceptin re-therapy). The analysis includes data from patients with at least one documented post-baseline LVEF measurement.

8.4.4.3 LVEF <50% During Study

During the study, 14 (10.9%) patients were reported with a LVEF <50% (Table 8-72).

Table 8-72 LVEF <50% during treatment (AP)

	N	%
Total number of patients, N	*216*	
Number of patients with ≥1 documented post-baseline LVEF measurement, N	129	100
Lowest post-baseline LVEF <50%, n, %	14	10.9
Lowest post-baseline LVEF ≥50%, n, %	115	89.1

[Source: Herceptin_Abschlussanalyse_Tables; Table 15.5].
AP = Analysis population; LVEF = Left ventricular ejection fraction; N/n = Number
The analysis includes data from patients with at least one documented post-baseline LVEF measurement over the course of the study (including follow-up documentation and the period after discontinuation of Herceptin re-therapy). The following nadir levels <50% were documented: 30% (pat ID 423001), 32% (pat ID 482001), 38% (pat ID 859004), 40% (n=5; pat IDs 511001, 548003, 687003, 726005 and 888002), 42% (pat ID 1108002), 45% (n=2; pat IDs 696001 and 859005), 48% (pat ID 1000001), 49% (n=2; pat IDs 189001 and 450002).
However, in cases where LVEF <45% or LVEF drop >10%, a corresponding AE had not been reported in all affected patients. The following (S)AEs related to LVEF were reported, however not corresponding to the LVEF nadir values above for patient IDs 423001, 482001 and 859004 as the SAE was reported for a LVEF value > LVEF nadir:

- Pat ID 423001: SAE with onset on 16 September 2009: LVEF drop; LVEF 35%
- Pat ID 482001: SAE with onset on 19 October 2010: Ventricular dysfunction; LVEF 47%
- Pat ID 859004: SAE with onset on 11 October 2011: Reduced LV function; Numerical estimate of LVEF not stated
- Pat ID 548003: AE with onset on 10 February 2011: Worsened LVEF function; LVEF 40%
- Pat ID 687003: SAE with onset on 3 February 2012: Ejection fraction decreased; LVEF 40%
- Pat ID 726005: AE with onset on 5 August 2014: LVEF drop to 40%; LVEF 40%
- Pat ID 888002: AE with onset on 11 October 2011: Congestive heart insufficiency; LVEF 40%

8.4.4.3.1 Time to First LVEF <50%

The median time (min – max) until first LVEF <50% was 7.4 months (1.3 – 44.8 months; Table 8-73).

Table 8-73 Time to first LVEF <50% (AP)

	N	Mean	STD	Median	25% quartile	75% quartile	Min	Max
Time to first LVEF value <50% (months)	14	11.2	12.15	7.4	3.1	11.7	1.3	44.8

[Source: Herceptin_Abschlussanalyse_Tables; Table 15.7].
AP = Analysis population; LVEF = Left ventricular ejection fraction; Min = Minimum; Max = Maximum; N = Number; STD = Standard deviation
This table shows the time span between initiation of Herceptin re-therapy and the first LVEF value <50% (post-baseline) measured over the course of the study (including follow-up documentation and the period after discontinuation of Herceptin re-therapy).

8.4.4.4 LVEF Decrease >10% Compared to Baseline

Overall, there were 84 patients with a documented baseline LVEF measurement and ≥1 post-baseline LVEF measurement (Table 8-74), of these, 30 (35.7%) patients were reported with a LVEF nadir >10% lower than the baseline value.

Table 8-74 LVEF Decrease >10% Compared to Baseline

	AP (N=216)
Number of patients with a documented baseline LVEF measurement and ≥1 post-baseline LVEF measurement, N (%)	84 (100)[1]

	AP (N=216)
LVEF nadir at least 10% lower than the baseline value, n (%)	30 (35.7)
Difference in LVEF nadir of less than 10% versus baseline (or nadir greater than baseline value), n (%)	54 (64.3)

[Source: Herceptin_Abschlussanalyse_Tables; Table 15.6].
AP = Analysis population; LVEF = Left ventricular ejection fraction; N/n = Number
[1]The analysis included data from patients with a documented baseline LVEF (4 weeks before or after initiation of re-therapy with Herceptin) and at least one post-baseline LVEF measurement over the course of the study.
The nadir was defined as the lowest post-baseline LVEF documented over the course of the study (including follow-up documentation and the period after discontinuation of Herceptin re-therapy). However, in cases where LVEF <45% or LVEF drop >10%, a corresponding AE had not been reported in all affected patients.

8.4.5 Development of Secondary Carcinoma

Overall, 10 patients developed secondary carcinoma during the study (total population), of these, 3 patients were reported with a secondary carcinoma (breast (pat ID 492001), cholangiocellular carcinoma (pat ID 497003), and contralateral invasive lobular breast carcinoma (pat ID 828001), respectively) which had metastasized. For further details, please refer to Patient Listing 23.6.

8.4.6 Effectiveness Analysis

8.4.6.1 Manifestation of Metastases in New Organ Systems During the Study

The number of patients with manifestation of metastases in new organ systems not affected at time of enrollment is depicted in Table 8-75. The most frequently (>5% of patients) affected organ systems were lung (n=24; 11.1%), bone (n=23; 10.6%), liver (n=20; 9.3%), CNS (n=17; 7.9%) and pleural effusion (n=14; 6.5%).

Table 8-75 Manifestation of metastases in new organ systems during the study[1] (AP)

	N	%
Total number of patients, N	*216*	*100*
New organ systems affected by metastases[2], n, %		
Lung	24	11.1
Bone	23	10.6
Liver	20	9.3
CNS	17	7.9
Pleural effusion	14	6.5
Peritoneum	5	2.3
Other	41	19.0

[Source: Herceptin_Abschlussanalyse_Tables; Table 8.1].
AP = Analysis population; CNS = Central nervous system; N/n = Number
[1]The table shows the first time that new metastases were documented in organ systems not yet affected at baseline. For example, a patient who had lung metastases at the time of enrolment into the study (i.e., before starting Herceptin re-therapy) and later developed liver metastases during the study (during treatment or after discontinuation) would fall into the organ class "Liver". [2]Multiple entries per patient possible.

8.4.6.1.1 Time to First Emergence of Metastases in New Organ Systems

The median time (min – max) to first emergence of metastases in new organ systems not affected at time of enrollment is detailed in Table 8-76. The median time to first emergence of metastases was shortest for peritoneum (4.2 months (0.4 – 11.7 months)), whereas it was longest for pleural effusion (13.8 months (0.2 – 30.9 months)).

Table 8-76 Time to first emergence of metastases in new organ systems (AP)

Time to first emergence of metastases (months)	N	Mean	STD	Median	25% quartile	75% quartile	Min	Max
Lung	24	7.6	7.02	5.3	0.7	12.5	0.1	21.8
Bone	23	9.8	11.55	8.3	1.6	12.7	0.0	54.2
Liver	20	9.5	9.58	6.1	4.0	11.1	0.4	32.5
CNS	17	10.8	8.02	8.0	6.3	13.5	0.1	29.7
Pleural effusion	14	13.4	9.97	13.8	4.4	17.7	0.2	30.9
Peritoneum	5	4.5	4.59	4.2	0.8	5.4	0.4	11.7
Other	41	11.1	11.40	9.7	1.2	19.4	0.1	55.5

[Source: Herceptin_Abschlussanalyse_Tables; Table 8.2].
AP = Analysis population; CNS = Central nervous system; Min = Minimum; Max = Maximum; N = Number; STD = Standard deviation
The table shows the first time that new metastases were documented in organ systems not yet affected at baseline. The metastases considered relevant were those that appeared either during or after discontinuation of Herceptin re-therapy.

8.4.6.2 Progression-Free Survival

PFS was estimated by using the Kaplan-Meier method. Progression-free survival was defined as the time from diagnosis of local recurrent tumor / distant metastasis, which led to the initiation of anti-HER2 re-therapy with Herceptin to progression or death due to any cause. In total, 166 patients (76.9%) in the AP experienced an event (PD or death) during Herceptin re-therapy. The median PFS in the AP was 12.7 months (10.5 – 14.8 months) with an estimated 6-month and 12-month PFS rate at 82.0% and 52.8%, respectively (Table 8-77; Figure 8-2). In the SmPC-population, 45 patients (91.8%) had experienced an event. The median PFS in the SmPC-population was 9.8 months (7.9 – 12.7 months; Table 8-77; Figure 8-3).

Table 8-77 Progression-free survival (AP/SmPC-population)

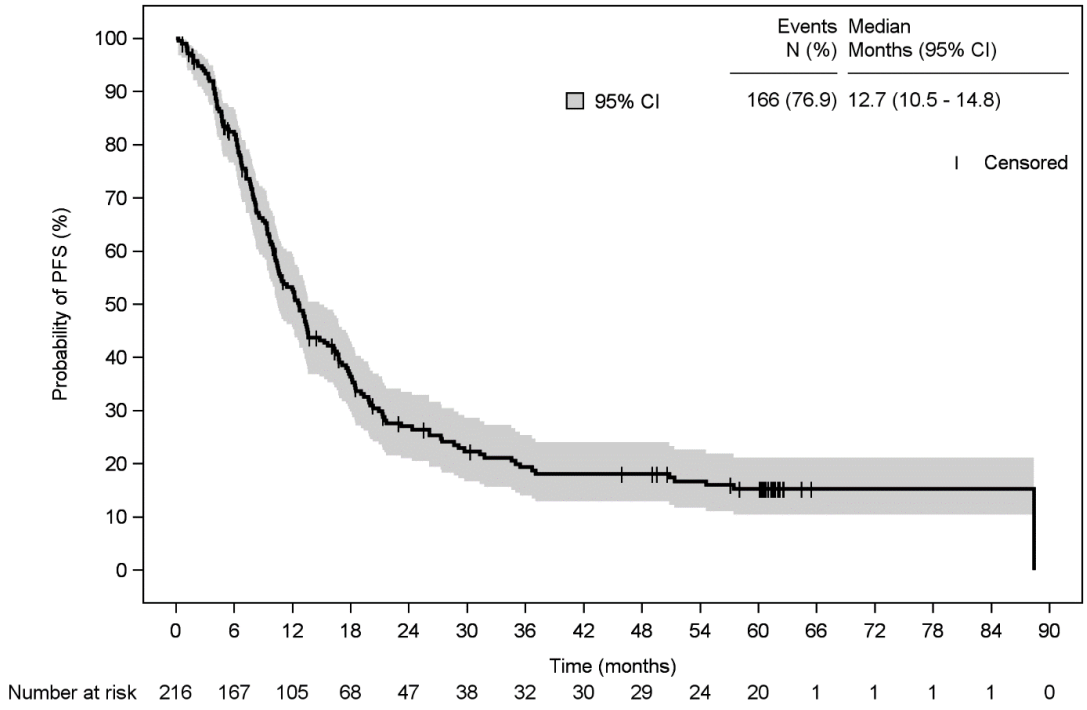
	Total population (AP)	SmPC-population[1]
Total number of patients, N	*216*	*49*
Events, n (%)	166 (76.9)	45 (91.8)
Quartiles (months)		
25% quantile [95% CI]	7.2 (6.3 - 8.1)	6.6 (3.3 - 7.9)
50% quantile [95% CI] (Median)	12.7 (10.5 - 14.8)	9.8 (7.9 - 12.7)
75% quantile [95% CI]	27.3 (20.0 - 36.7)	17.9 (11.4 - 29.7)
PFS rates (%) [95% CI]		
6-month	82.0% (76.1% - 86.5%)	77.6% (63.1% - 86.9%)
12-month	52.8% (45.7% - 59.4%)	38.3% (24.8% - 51.7%)

[Source: Herceptin_Abschlussanalyse_Tables; Table 21.1-a, Table 23.1-a].
AP = Analysis population; CI = Confidence interval; N/n = Number; PFS = Progression-free survival; SmPC = Summary of Product Characteristics
[1]The SmPC-population was defined *post-hoc*.
Progression-free survival was estimated by using the Kaplan-Meier method.
Progression-free survival was defined as the time from diagnosis of local recurrent tumor / distant metastasis, which led to the initiation of anti-HER2 re-therapy with Herceptin to progression or death due to any cause. Patients without an event (progression or death) before change of therapy or at end of study participation were censored using the earliest date of one of the following:

- Date of change of therapy (start of second-line therapy)
- Date of last patient contact

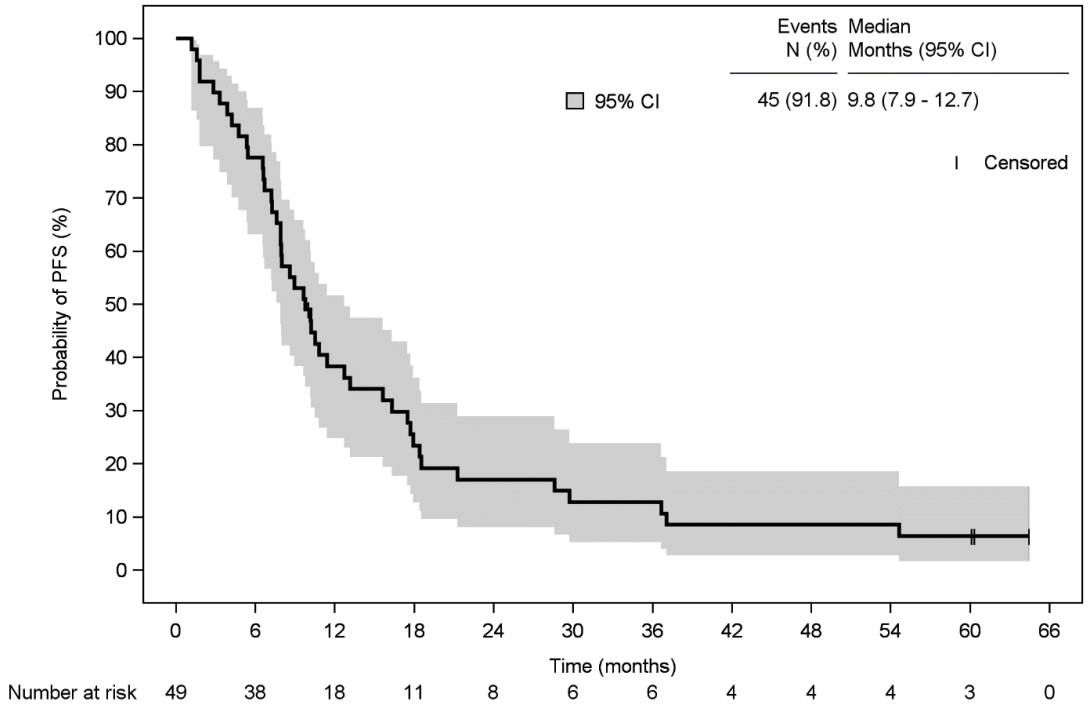
If none of the above dates was available, the date of last documented dose of Herceptin was used for the censored case.

Figure 8-2 Progression-free survival (AP)



[Source: Herceptin_Abschlussanalyse_Figures; Figure 22.1-a].
AP = Analysis population; CI = Confidence interval; N = Number; PFS = Progression-free survival
Progression-free survival was estimated by using the Kaplan-Meier method.
Progression-free survival was defined as the time from diagnosis of local recurrent tumor / distant metastasis, which led to the initiation of anti-HER2 re-therapy with Herceptin to progression or death due to any cause.

Figure 8-3 Progression-free survival (SmPC-population[1])



[Source: Herceptin_Abschlussanalyse_Figures; Figure 22.4-a].
CI = Confidence interval; N = Number; PFS = Progression-free survival; SmPC = Summary of Product Characteristics
[1]The SmPC-population was defined *post-hoc*.
Progression-free survival was estimated by using the Kaplan-Meier method.
Progression-free survival was defined as the time from diagnosis of local recurrent tumor / distant metastasis, which led to the initiation of anti-HER2 re-therapy with Herceptin to progression or death due to any cause.

8.4.6.2.1 Progression-Free Survival – Subgroup "Metastases"

The PFS was estimated in subgroups of patients with no metastases (local recurrence only), patients with non-visceral metastases (± local recurrence, no visceral metastases) and patients with visceral metastases (± non-visceral metastases ± local recurrence) at start of Herceptin re-therapy. In the AP, the median PFS was shortest in the subgroup of patients with visceral metastases (10.2 months (8.0 – 11.4 months)), whereas the longest median PFS was observed in patients with no metastases (26.1 months (12.7 months – not reached)) as further detailed in Table 8-78 and Figure 8-4. The lowest 6-month (75.7%) and 12-month (40.4%) PFS rates were seen in the subgroup of patients with visceral metastases.

Similar data was observed in the SmPC-population (Table 8-78; Figure 8-5) with a less favorable outcome (median PFS and survival rates) in patients with visceral metastases.

Table 8-78 Progression-free survival – subgroup "metastases / local recurrence only" (AP/SmPC-population)

	No metastases (local recurrence only)	Non-visceral	Visceral
Analysis population (AP): Total N=216			
Total number of patients (subgroups)[1], N	*43*	*61*	*110*
Events, n (%)	24 (55.8)	44 (72.1)	97 (88.2)
Quartiles (months)			
25% quantile [95% CI]	11.9 (6.4 - 15.3)	8.1 (4.8 - 9.6)	6.2 (4.2 - 7.2)
50% quantile [95% CI] (Median)	26.1 (12.7 - NA)	16.3 (9.6 - 21.5)	10.2 (8.0 - 11.4)
75% quantile [95% CI]	NA	57.4 (21.5 - 88.4)	17.7 (13.5 - 19.9)
PFS rates (%) [95% CI]			
6-month	92.9% (79.5% - 97.6%)	84.9% (72.9% - 91.8%)	75.7% (66.5% - 82.8%)
12-month	72.8% (56.2% - 83.9%)	59.3% (45.7% - 70.6%)	40.4% (30.8% - 49.6%)
SmPC-population[2]: Total N=49			
Total number of patients (subgroups), N	*6*	*8*	*35*
Events, n (%)	4 (66.7)	6 (75.0)	35 (100)
Quartiles (months)			
25% quantile [95% CI]	21.3 (10.2 - 37.1)	10.9 (3.3 - 18.4)	5.3 (1.8 - 7.2)
50% quantile [95% CI] (Median)	36.9 (10.2 - NA)	17.5 (3.3 - 18.6)	7.9 (6.6 - 9.8)
75% quantile [95% CI]	NA	18.6 (13.2 - NA)	11.4 (8.9 - 17.7)
PFS rates (%) [95% CI]			
6-month	100.0% (100.0% - 100.0%)	87.5% (38.7% - 98.1%)	71.4% (53.4% - 83.5%)
12-month	83.3% (27.3% - 97.5%)	75.0% (31.5% - 93.1%)	22.9% (10.8% - 37.6%)

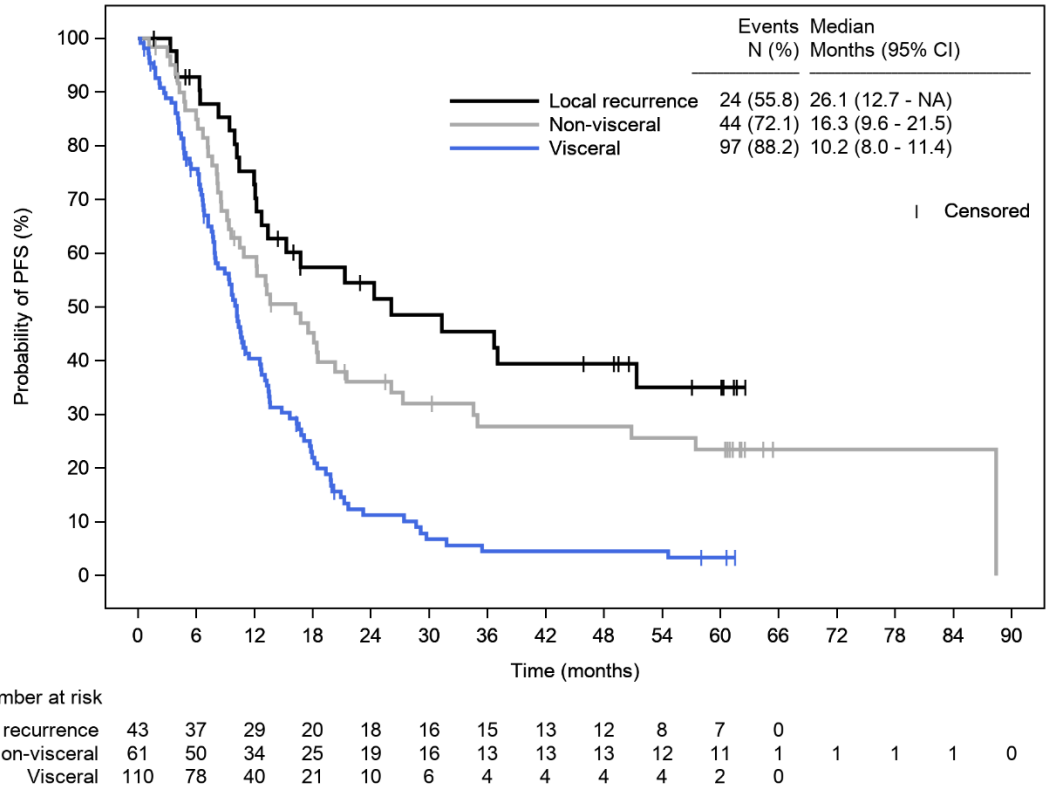
[Source: Herceptin_Abschlussanalyse_Tables; Table 21.1-b, Table 23.1-b].
AP = Analysis population; CI = Confidence interval; N/n = Number; NA = Not reached; PFS = Progression-free survival; SmPC = Summary of Product Characteristics
[1]The metastatic status of 2 patients could not be classified as only the free-text entries "secondary contralateral carcinoma" and "increased tumor marker" were recorded in the eCRF, respectively.
[2]The SmPC-population was defined *post-hoc*.
No metastases: Patients without metastases at start of Herceptin re-therapy (local recurrence only)

Non-visceral: Patients with non-visceral metastases only, i.e. bone, skin, lymph node and soft tissue metastases (± local recurrence, no visceral metastases)
Visceral: Patients with visceral metastases, i.e. lung, liver, CNS, pleural effusion, ascites, and other metastases (free-text entries) coded as visceral by medical experts (± non-visceral metastases ± local recurrence). This group comprises all patients with visceral metastases including those having additional non-visceral metastases.
Progression-free survival was estimated by using the Kaplan-Meier method.
Progression-free survival was defined as the time from diagnosis of local recurrent tumor / distant metastasis, which led to the initiation of anti-HER2 re-therapy with Herceptin to progression or death due to any cause. Patients without an event (progression or death) before change of therapy or at end of study participation were censored using the earliest date of one of the following:

- Date of change of therapy (start of second-line therapy)
- Date of last patient contact

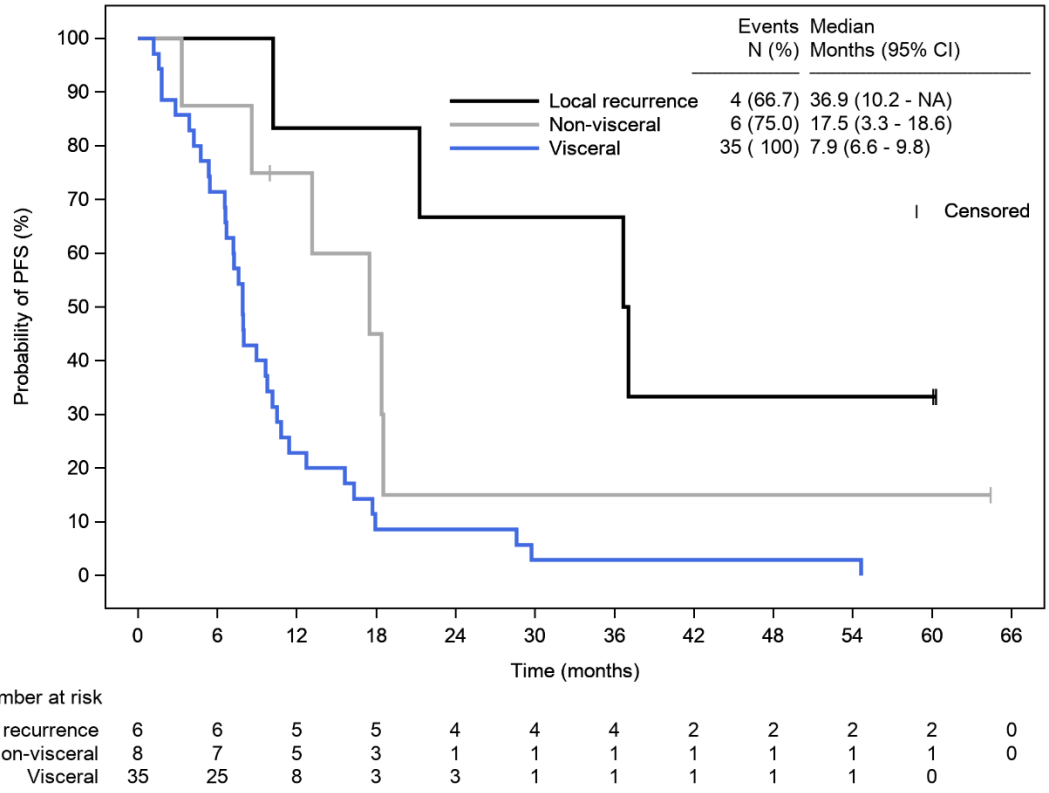
If none of the above dates was available, the date of last documented dose of Herceptin was used for the censored case.

Figure 8-4 Progression-free survival – subgroup "metastases / local recurrence only" (AP)



[Source: Herceptin_Abschlussanalyse_Figures; Figure 22.1-b].
AP = Analysis population; CI = Confidence interval; N = Number; NA = Not reached; PFS = Progression-free survival
Local recurrence: Patients without metastases at start of Herceptin re-therapy (local recurrence only)
Non-visceral: Patients with non-visceral metastases only, i.e. bone, skin, lymph node and soft tissue metastases (± local recurrence, no visceral metastases)
Visceral: Patients with visceral metastases, i.e. lung, liver, CNS, pleural effusion, ascites, and other metastases (free-text entries) coded as visceral by medical experts (± non-visceral metastases ± local recurrence). This group comprises all patients with visceral metastases including those having additional non-visceral metastases.
Progression-free survival was estimated by using the Kaplan-Meier method.
Progression-free survival was defined as the time from diagnosis of local recurrent tumor / distant metastasis, which led to the initiation of anti-HER2 re-therapy with Herceptin to progression or death due to any cause.

Figure 8-5 Progression-free survival – subgroup "metastases / local recurrence only" (SmPC-population[1])



[Source: Herceptin_Abschlussanalyse_Figures; Figure 22.4-b].
CI = Confidence interval; N = Number; NA = Not reached; PFS = Progression-free survival; SmPC-Population = Summary of Product Characteristics
[1]The SmPC-population was defined *post-hoc*.
Local recurrence: Patients without metastases at start of Herceptin re-therapy (local recurrence only)
Non-visceral: Patients with non-visceral metastases only, i.e. bone, skin, lymph node and soft tissue metastases (± local recurrence, no visceral metastases)
Visceral: Patients with visceral metastases, i.e. lung, liver, CNS, pleural effusion, ascites, and other metastases (free-text entries) coded as visceral by medical experts (± non-visceral metastases ± local recurrence). This group comprises all patients with visceral metastases including those having additional non-visceral metastases.
Progression-free survival was estimated by using the Kaplan-Meier method.
Progression-free survival was defined as the time from diagnosis of local recurrent tumor / distant metastasis, which led to the initiation of anti-HER2 re-therapy with Herceptin to progression or death due to any cause.

8.4.6.2.2 Progression-Free Survival – Subgroup "Combination Therapy"

The PFS was estimated in subgroups of patients having received Herceptin mono re-therapy and in subgroups of patients having received combination therapy (chemotherapy/endocrine therapy) with Herceptin re-therapy. In the AP, the shortest median PFS was observed in the subgroup of patients having received a taxane in combination with Herceptin re-therapy (8.9 months (7.2 – 10.3 months)), whereas the

longest median PFS was seen in the subgroup of patients having received any chemo-/immunotherapy (taxanes or other CTx) and endocrine therapy in combination with Herceptin re-therapy (19.9 months (12.7 – 54.6 months)) as further detailed in

. The lowest 6-month (78.4%) and 12-month (29.4%) PFS rates were seen in the subgroup of patients having received a taxane in combination with Herceptin re-therapy.

Table 8-79 Progression-free survival – subgroup "combination therapy" (AP)

	Herceptin mono re-therapy	Taxanes	Endocrine therapy	Other CTx	CTx and endocrine therapy
Analysis population (AP): Total N=216					
Total number of patients (subgroups), N	*36*	*51*	*35*	*74*	*20*
Events, n (%)	22 (61.1)	49 (96.1)	26 (74.3)	56 (75.7)	13 (65.0)
Quartiles (months)					
25% quantile [95% CI]	8.3 (4.0 - 13.6)	6.3 (3.9 - 7.6)	6.7 (4.1 - 10.0)	6.8 (4.2 - 10.0)	12.7 (4.7 - 17.9)
50% quantile [95% CI] (Median)	18.2 (10.4 - 35.0)	8.9 (7.2 - 10.3)	12.2 (8.3 - 27.3)	13.4 (10.2 - 16.6)	19.9 (12.7 - 54.6)
75% quantile [95% CI]	NA	13.3 (10.2 - 18.4)	51.3 (20.3 - 88.4)	21.6 (16.7 - 31.8)	54.6 (19.9 - NA)
PFS rates (%) [95% CI]					
6-month	82.5% (65.1% - 91.7%)	78.4% (64.4% - 87.4%)	80.0% (62.6% - 89.9%)	81.9% (70.9% - 89.1%)	94.7% (68.1% - 99.2%)
12-month	63.3% (44.4% - 77.3%)	29.4% (17.7% - 42.1%)	57.1% (39.3% - 71.5%)	56.2% (43.6% - 67.1%)	78.6% (52.5% - 91.4%)

[Source: Herceptin_Abschlussanalyse_Tables; Table 21.1-c].
AP = Analysis population; CI = Confidence interval; CTx = Chemotherapy; N/n = Number; NA = Not reached; PFS = Progression-free survival
Herceptin mono re-therapy: Patients who did not receive any combination therapy (neither chemo-/immunotherapy nor endocrine therapy) with their Herceptin re-therapy.
Taxanes: Patients receiving a taxane in combination with their Herceptin re-therapy (but no endocrine therapy).
Endocrine therapy: Patients receiving endocrine therapy in combination with their Herceptin re-therapy (but no chemo-/immunotherapy).
Other CTx: Patients receiving chemo-/immunotherapy other than taxanes in combination with their Herceptin re-therapy (but no endocrine therapy).
CTx and endocrine therapy: Patients receiving any chemo-/immunotherapy (taxanes or other CTx) and endocrine therapy in combination with their Herceptin re-therapy.

Progression-free survival was estimated by using the Kaplan-Meier method.
Progression-free survival was defined as the time from diagnosis of local recurrent tumor / distant metastasis, which led to the initiation of anti-HER2 re-therapy with Herceptin to progression or death due to any cause. Patients without an event

(progression or death) before change of therapy or at end of study participation were censored using the earliest date of one of the following:

- Date of change of therapy (start of second-line therapy)
- Date of last patient contact

If none of the above dates was available, the date of last documented dose of Herceptin was used for the censored case.

8.4.6.2.3 Progression-Free Survival – Subgroup "Chemotherapy"

The PFS was estimated in subgroups of patients having received mono-chemotherapy (no endocrine therapy) in combination with Herceptin re-therapy (Table 8-80). In the AP, the shortest median PFS was observed in the subgroup of patients having received monotherapy with a taxane in combination with Herceptin re-therapy (8.9 months (7.2 – 10.3 months)) versus patients with monotherapy with vinorelbine (12.1 months (9.3 – 31.3 months)) or capecitabine (12.5 months (6.4 – 17.1 months)) in combination with Herceptin re-therapy. In the taxane subgroup, the 6-month and 12-month PFS rates were 78.4% and 29.4%, respectively.

Table 8-80 Progression-free survival – subgroup "chemotherapy" (AP)

	Taxane	Vinorelbine	Capecitabine
Analysis population (AP): Total N=216			
Total number of patients (subgroups), N	*51*	*27*	*23*
Events, n (%)	49 (96.1)	18 (66.7)	16 (69.6)
Quartiles (months)			
25% quantile [95% CI]	6.3 (3.9 - 7.6)	9.3 (3.0 - 10.4)	6.4 (2.2 - 10.2)
50% quantile [95% CI] (Median)	8.9 (7.2 - 10.3)	12.1 (9.3 - 31.3)	12.5 (6.4 - 17.1)
75% quantile [95% CI]	13.3 (10.2 - 18.4)	31.8 (13.1 - NA)	24.3 (12.5 - NA)
PFS rates (%) [95% CI]			
6-month	78.4% (64.4% - 87.4%)	84.4% (63.6% - 93.9%)	77.3% (53.7% - 89.8%)
12-month	29.4% (17.7% - 42.1%)	53.5% (31.7% - 71.1%)	51.5% (28.5% - 70.5%)

[Source: Herceptin_Abschlussanalyse_Tables; Table 21.1-d].
AP = Analysis population; CI = Confidence interval; N/n = Number; NA = Not reached; PFS = Progression-free survival
Taxane: Patients receiving a taxane in combination with their Herceptin re-therapy (no other chemotherapy and no endocrine therapy)
Vinorelbine: Patients receiving vinorelbine in combination with their Herceptin re-therapy (no other chemotherapy and no endocrine therapy)
Capecitabine: Patients receiving capecitabine in combination with their Herceptin re-therapy (no other chemotherapy and no endocrine therapy)
Progression-free survival was estimated by using the Kaplan-Meier method.
Progression-free survival was defined as the time from diagnosis of local recurrent tumor / distant metastasis, which led to the initiation of anti-HER2 re-therapy with Herceptin to progression or death due to any cause. Patients without an event (progression or death) before change of therapy or at end of study participation were censored using the earliest date of one of the following:

- Date of change of therapy (start of second-line therapy)
- Date of last patient contact

If none of the above dates was available, the date of last documented dose of Herceptin was used for the censored case.
Due to the small number of patients included, the subgroups "Carboplatin" (n=2) and "Other CTx" (n=1) are not depicted. The PFS of the carboplatin-treated patients was 0.26 months and 6.28 months, respectively; the PFS of the patient treated with other CTx (doxorubicin) was 23.33 months.

8.4.6.2.4 Progression-Free Survival – Cox Regression Analysis

A multivariable Cox regression analysis was performed to identify potential independent factors (baseline demographics and clinical characteristics), which might have an impact on the PFS (Table 8-81). In this analysis including 212 patients (censored: n=49; 23.1%), it was observed that patients with visceral metastases had a worse outcome (PFS) as compared to patients with no metastases (hazard ratio (HR) = 2.89; 95% CI: 1.82 – 4.59; *p*<0.001).

Table 8-81 Cox regression analysis of potential factors influencing the PFS (AP)

	Reference	Hazard ratio (HR)	95% CI (HR)	*p*-value
Analysis population (AP): Total N=216				
Cox regression analysis: N=212 (censored: n=49 (23.1%)				
Parameters				
Age at informed consent	-1 year	1.01	1.00 - 1.02	0.145
BMI	-1 kg/m²	0.98	0.94 - 1.01	0.165
DFS	-1 month	1.00	0.99 - 1.01	0.958
Stage at diagnosis III/IV	0/I/II	1.06	0.76 - 1.47	0.730
Stage at diagnosis unknown	0/I/II	0.52	0.27 - 1.00	0.049*
Hormone receptor status negative	Positive	1.21	0.87 - 1.66	0.255
Non-visceral metastases only	No metastases	1.46	0.88 - 2.45	0.146
Visceral metastases	No metastases	2.89	1.82 - 4.59	<0.001***

[Source: Herceptin_Abschlussanalyse_Tables; Table 21.2].
AP = Analysis population; BMI = Body mass index; CI = Confidence interval; DFS = Disease-free survival; HR = Hazard ratio; N = Number; PFS = Progression-free survival
Global Likelihood Ratio Test *p*-value: <0001
The Efron method was used to check for ties.
For one patient each, the BMI/hormone receptor status was unknown. In addition, the metastasis status of 2 patients could not be determined. The data from these four patients were therefore not included in the model calculations.
Disease-free survival was defined as the time from initial tumor resection to recurrence/(distant) metastases, which led to the initiation of Herceptin re-therapy.
Progression-free survival was defined as the time from diagnosis of local recurrent tumor / distant metastasis, which led to the initiation of anti-HER2 therapy with Herceptin to progression or death due to any cause. Patients without an event (progression or death) before change of therapy or at end of study participation were censored using the earliest date of one of the following:

- Date of change of therapy (start of second-line therapy)
- Date of last patient contact

If none of the above dates was available, the date of last documented dose of Herceptin was used for the censored case.
**p*-value <0.05
***p*-value <0.01
****p*-value <0.001

8.4.6.3 Overall Survival From Initial Tumor Resection (OS)

OS was estimated by using the Kaplan-Meier method. Overall survival was defined as the time from initial tumor resection to death due to any cause. In total, 135 patients (62.5%) died during the study; of these, there were 134 patients (62.0%) with documented date of

death (events). The median OS in the AP was 77.3 months (66.2 – 88.8 months) as depicted in Table 8-82 and Figure 8-6. The 12-month OS rate was 100%, whereas the 24-month, 36-month and 48-month OS rates were 99.5%, 92.9% and 80.3%, respectively.

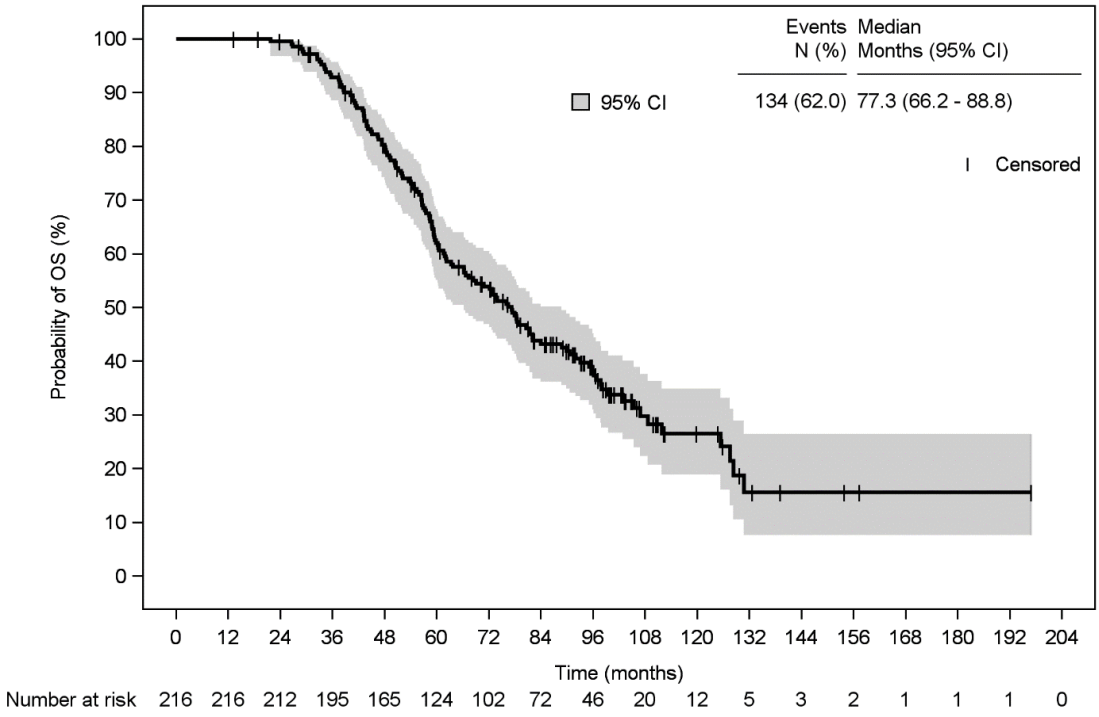
In the SmPC-population (events: n=37; 75.5%), the median OS was 76.4 months (57.6 – 88.8 months; Table 8-82; Figure 8-7).

Table 8-82 Overall survival from initial tumor resection (AP/SmPC-population)

	Total population (AP)	SmPC-population[1]
Total number of patients, N	*216*	*49*
Events, n (%)	134 (62.0)	37 (75.5)
Quartiles (months)		
25% quantile [95% CI]	51.7 (47.4 - 56.6)	48.5 (38.6 - 59.3)
50% quantile [95% CI] (Median)	77.3 (66.2 - 88.8)	76.4 (57.6 - 88.8)
75% quantile [95% CI]	125.4 (105.5 - NA)	96.7 (82.1 - NA)
OS rates (%) [95% CI]		
12-month	100.0% (100.0% - 100.0%)	100.0% (100.0% - 100.0%)
24-month	99.5% (96.7% - 99.9%)	100.0% (100.0% - 100.0%)
36-month	92.9% (88.5% - 95.7%)	91.7% (79.3% - 96.8%)
48-month	80.3% (74.3% - 85.1%)	81.2% (67.1% - 89.8%)

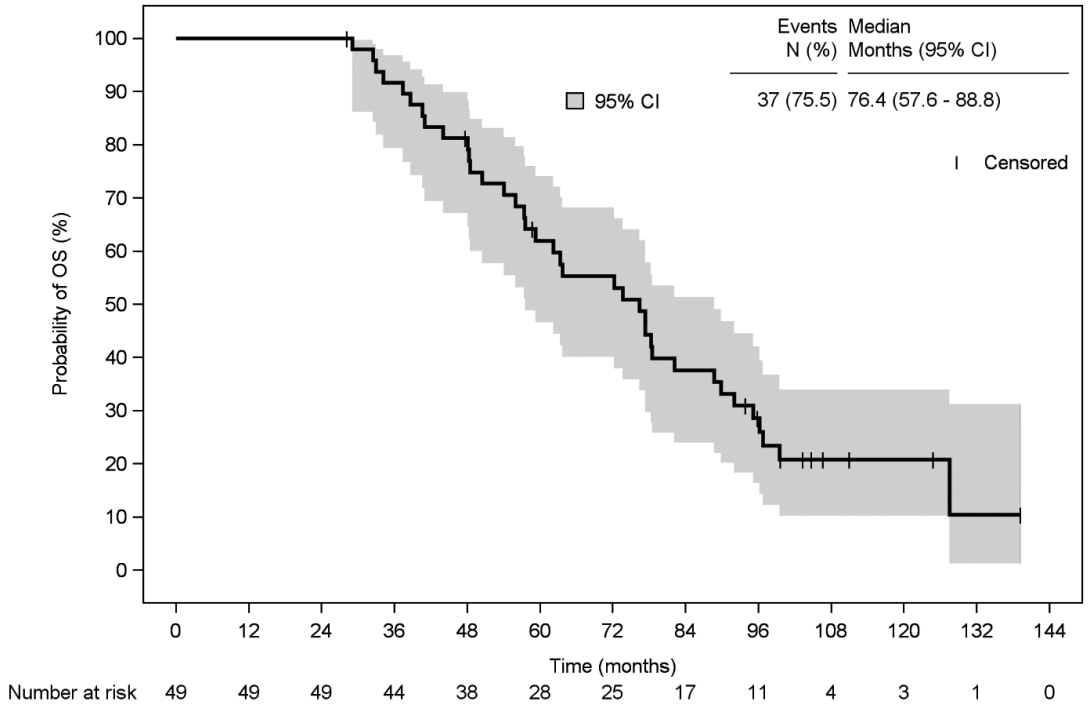
[Source: Herceptin_Abschlussanalyse_Tables; Table 21.3-a, Table 23.2].
AP = Analysis population; CI = Confidence interval; N/n = Number; NA = Not reached; OS = Overall survival;; SmPC = Summary of Product Characteristics
[1]The SmPC-population was defined *post-hoc*.
Overall survival was estimated by using the Kaplan-Meier method.
Overall survival was defined as the time from initial tumor resection to death due to any cause. Patients without documented date of death at the end of study were censored at the last date known to be alive. If this date was not available, the date of the last documented dose of Herceptin was used for the censored case. A total of 135 patients in the AP died during the study. For one patient, the date of death was not available. The overall survival of this patient was therefore included in the analysis as a censored case (date of last contact). A total of 37 patients in the SmPC-population died during the study where the date of death was known for all patients (no death case was censored).

Figure 8-6 Overall survival from initial tumor resection (AP)



[Source: Herceptin_Abschlussanalyse_Figures; Figure 22.2-a].
AP = Analysis population; CI = Confidence interval; N = Number; OS = Overall survival
Overall survival was estimated by using the Kaplan-Meier method.
Overall survival was defined as the time from initial tumor resection to death due to any cause. In total, 135 patients in the AP died during the study. For one patient, date of death was not available. Therefore, the OS of this patient was censored at date of last contact.

Figure 8-7 Overall survival from initial tumor resection (SmPC-population[1])



[Source: Herceptin_Abschlussanalyse_Figures; Figure 22.5].
CI = Confidence interval; N = Number; OS = Overall survival; SmPC = Summary of Product Characteristics
[1]The SmPC-population was defined *post-hoc*.
Overall survival was estimated by using the Kaplan-Meier method.
Overall survival was defined as the time from initial tumor resection to death due to any cause. A total of 37 patients in the SmPC-population died during the study where the date of death was known for all patients (no death case was censored).

8.4.6.4 Overall Survival From Recurrence / Distant Metastases (OS-2)

OS-2 was estimated by using the Kaplan-Meier method. OS-2 was defined as the time from diagnosis of local recurrent tumor / distant metastasis, which led to the initiation of anti-HER2 re-therapy with Herceptin to death due to any cause. The median OS-2 in the AP (events: n=134; 62.0%) was 31.6 months (28.8 – 38.4 months) with estimated OS-2 rates at 82.9% (12 months), 62.9% (24 months), 45.3% (36 months) and 37.1% (48 months) as detailed in Table 8-83 and Figure 8-8.

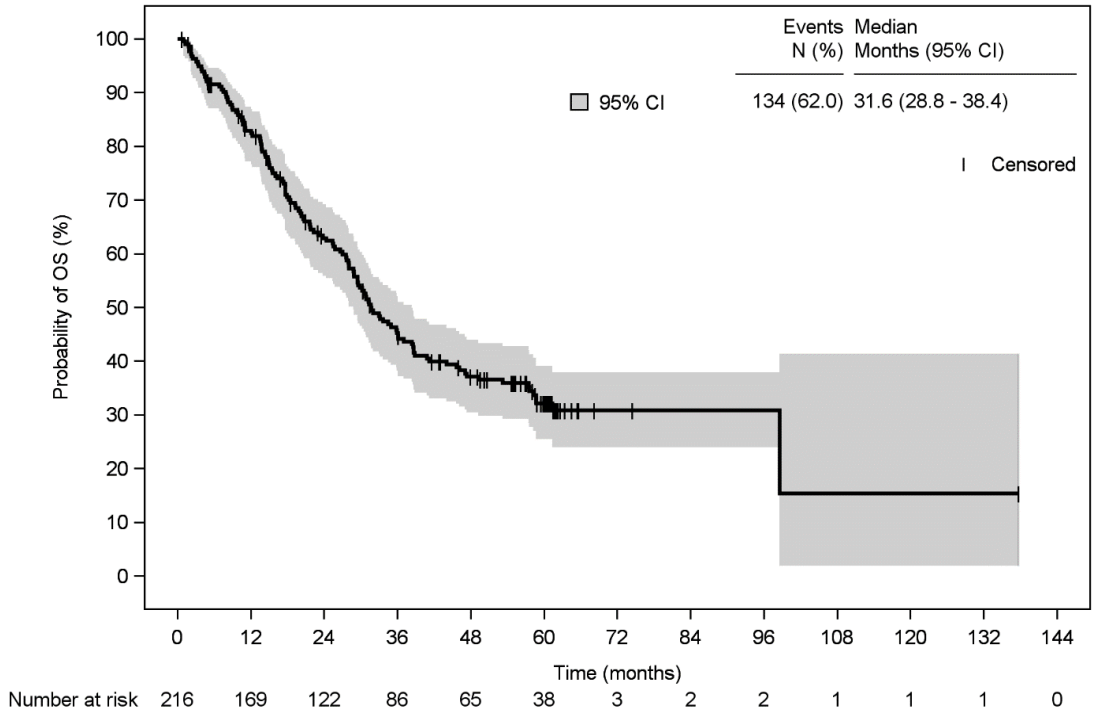
In the SmPC-population (events: n=37; 75.5%), the median OS-2 was 21.8 months (15.0 – 36.1 months; Table 8-83; Figure 8-9).

Table 8-83 Overall survival (OS-2) from recurrence / distant metastases (AP/SmPC-population)

	Total population (AP)	SmPC-population[1]
Total number of patients, N	*216*	*49*
Events, n (%)	134 (62.0)	37 (75.5)
Quartiles (months)		
25% quantile [95% CI]	16.0 (13.5 - 19.3)	10.8 (4.4 - 15.6)
50% quantile [95% CI] (Median)	31.6 (28.8 - 38.4)	21.8 (15.0 - 36.1)
75% quantile [95% CI]	98.6 (61.3 - NA)	57.6 (33.6 - 98.6)
OS-2 rates (%) [95% CI]		
12-month	82.9% (77.1% - 87.4%)	73.4% (58.6% - 83.6%)
24-month	62.9% (55.9% - 69.2%)	48.9% (34.0% - 62.3%)
36-month	45.3% (38.2% - 52.0%)	37.8% (24.0% - 51.5%)
48-month	37.1% (30.4% - 43.9%)	26.7% (14.9% - 39.9%)

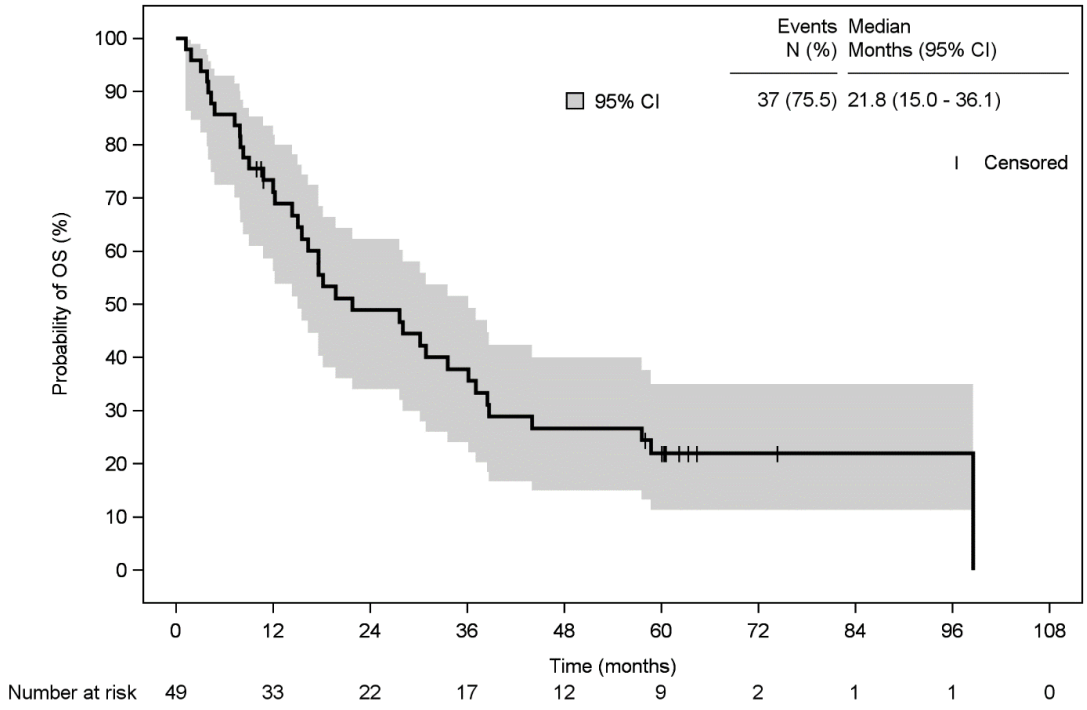
[Source: Herceptin_Abschlussanalyse_Tables; Table 21.4-a, Table 23.3-a].
AP = Analysis population; CI = Confidence interval; N/n = Number; NA = Not reached; OS = Overall survival; SmPC = Summary of Product Characteristics
[1]The SmPC-population was defined *post-hoc*.
Overall survival (OS-2) was estimated by using the Kaplan-Meier method.
OS-2 was defined as the time from diagnosis of local recurrent tumor / distant metastasis, which led to the initiation of anti-HER2 re-therapy with Herceptin to death due to any cause. Patients without documented date of death at the end of study were censored at the last date known to be alive. If this date was not available, the date of the last documented dose of Herceptin was used for the censored case. A total of 135 patients in the AP died during the study. For one patient, the date of death was not available. The overall survival of this patient was therefore included in the analysis as a censored case (date of last contact). A total of 37 patients in the SmPC-population died during the study where the date of death was known for all patients (no death case was censored).

Figure 8-8 Overall survival (OS-2) from recurrence / distant metastases (AP)



[Source: Herceptin_Abschlussanalyse_Figures; Figure 22.3-a].
AP = Analysis population; CI = Confidence interval; N = Number; OS = Overall survival
Overall survival (OS-2) was estimated by using the Kaplan-Meier method.
OS-2 was defined as the time from diagnosis of local recurrent tumor / distant metastasis, which led to the initiation of anti-HER2 re-therapy with Herceptin to death due to any cause. A total of 135 patients in the AP died during the study. For one patient, the date of death was not available. The overall survival of this patient was therefore included in the analysis as a censored case (date of last contact).

Figure 8-9 Overall survival (OS-2) from recurrence/distant metastases (SmPC-population[1])



[Source: Herceptin_Abschlussanalyse_Figures; Figure 22.6-a]
CI = Confidence interval; N = Number; OS = Overall survival; SmPC = Summary of Product Characteristics
[1]The SmPC-population was defined *post-hoc*.
Overall survival (OS-2) was estimated by using the Kaplan-Meier method.
OS-2 was defined as the time from diagnosis of local recurrent tumor / distant metastasis, which led to the initiation of anti-HER2 re-therapy with Herceptin to death due to any cause. A total of 37 patients in the SmPC-Population died during the study where the date of death was known for all patients (no death case was censored).

8.4.6.4.1 Overall Survival (OS-2) – Subgroup "Metastases"

The OS-2 was estimated in subgroups of patients with no metastases (local recurrence only), patients with non-visceral metastases (± local recurrence, no visceral metastases) and patients with visceral metastases (± non-visceral metastases ± local recurrence) at start of Herceptin re-therapy. In the AP, the median OS-2 was shortest in the subgroup of patients with visceral metastases (20.8 months (17.3 – 28.8 months)) versus the median OS-2 in the subgroups of patients with no metastases (not reached) and patients with non-visceral metastases (49.2 months (33.1 months – not reached)) as detailed in Table 8-84 and Figure 8-10. The lowest OS-2 rates were observed in the subgroup of patients with visceral metastases with a 12-month rate at 72.0%, 24-month rate at 46.0%, 36-month rate at 29.6% and 48-month rate at 21.2%.

Similar data were obtained in the SmPC-population (Table 8-84; Figure 8-11) with an inferior outcome (median OS-2 and survival rates) in patients with visceral metastases.

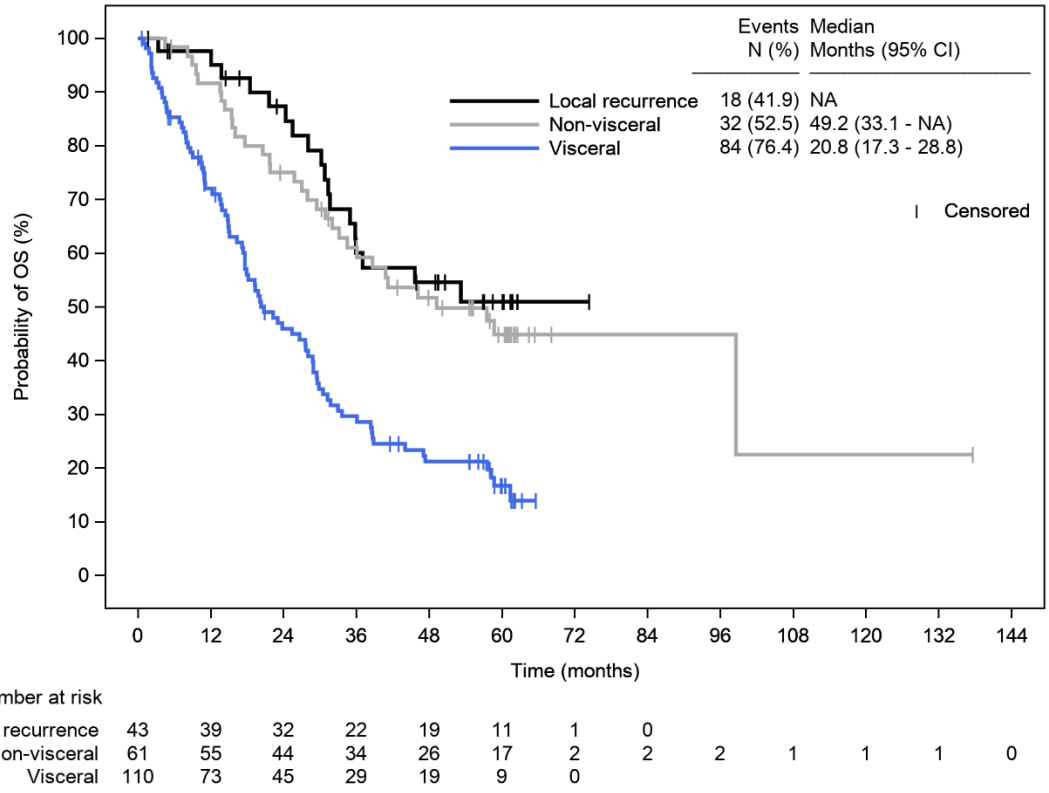
Table 8-84 Overall survival (OS-2) from recurrence / distant metastases – subgroup "metastases / local recurrence only" (AP/SmPC-population)

	No metastases (local recurrence only)	Non-visceral	Visceral
Analysis population (AP): Total N=216			
Total number of patients (subgroups)[1], N	*43*	*61*	*110*
Events, n (%)	18 (41.9)	32 (52.5)	84 (76.4)
Quartiles (months)			
25% quantile [95% CI]	30.8 (21.6 - 35.9)	25.7 (15.4 - 33.1)	10.8 (7.5 - 14.8)
50% quantile [95% CI] (Median)	NA	49.2 (33.1 - NA)	20.8 (17.3 - 28.8)
75% quantile [95% CI]	NA	98.6 (98.6 - NA)	38.8 (30.5 - 61.3)
OS-2 rates (%) [95% CI]			
12-month	97.6% (84.3% - 99.7%)	91.7% (81.2% - 96.5%)	72.0% (62.5% - 79.5%)
24-month	87.3% (72.1% - 94.5%)	75.0% (62.0% - 84.1%)	46.0% (36.1% - 55.3%)
36-month	60.0% (42.6% - 73.7%)	61.1% (47.4% - 72.2%)	29.6% (21.0% - 38.7%)
48-month	54.6% (37.4% - 68.9%)	51.7% (38.1% - 63.7%)	21.2% (13.7% - 29.7%)
SmPC-population[2]: Total N=49			
Total number of patients (subgroups), N	*6*	*8*	*35*
Events, n (%)	3 (50.0)	5 (62.5)	29 (82.9)
Quartiles (months)			
25% quantile [95% CI]	30.2 (12.0 - NA)	26.3 (15.6 - 98.6)	7.9 (3.9 - 12.2)
50% quantile [95% CI] (Median)	NA	67.4 (15.6 - 98.6)	16.3 (9.0 - 27.6)
75% quantile [95% CI]	NA	98.6 (30.9 - 98.6)	38.5 (18.2 - 58.8)
OS-2 rates (%) [95% CI]			
12-month	100.0% (100.0% - 100.0%)	100.0% (100.0% - 100.0%)	62.6% (44.4% - 76.3%)
24-month	83.3% (27.3% - 97.5%)	75.0% (31.5% - 93.1%)	36.2% (20.2% - 52.5%)
36-month	66.7% (19.5% - 90.4%)	62.5% (22.9% - 86.1%)	26.4% (12.6% - 42.4%)

	No metastases (local recurrence only)	Non-visceral	Visceral
48-month	50.0% (11.1% - 80.4%)	50.0% (15.2% - 77.5%)	16.5% (6.1% - 31.3%)

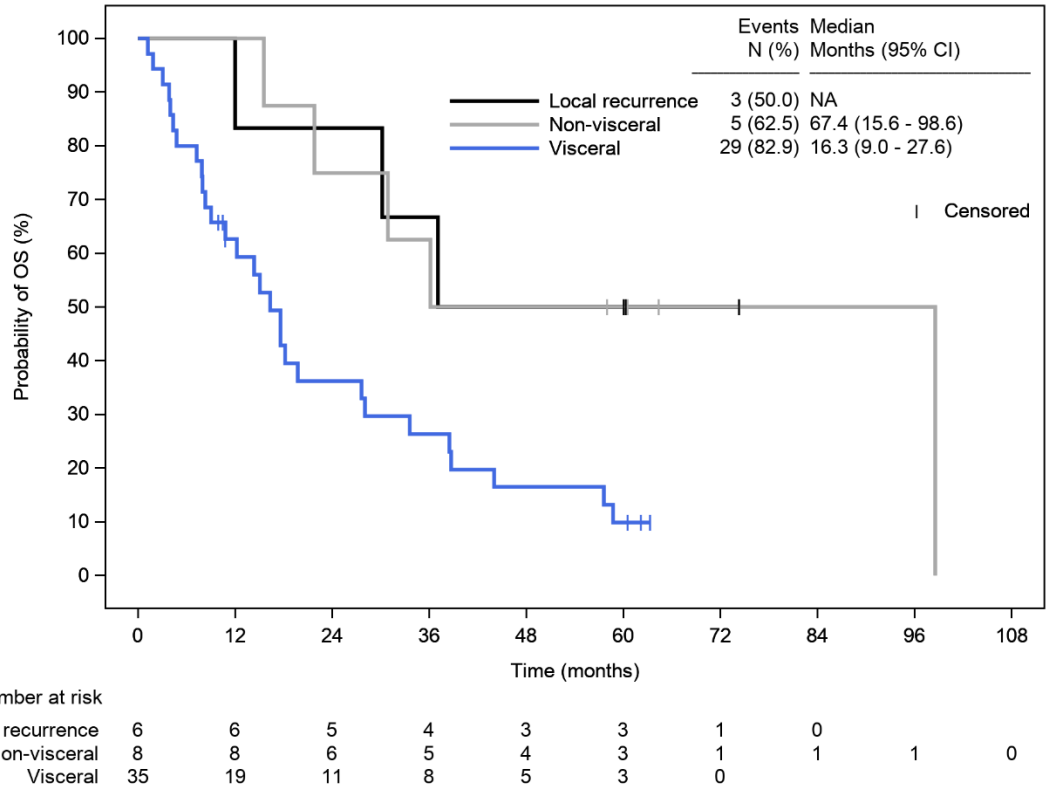
[Source: Herceptin_Abschlussanalyse_Tables; Table 21.4-b, Table 23.3-b].
AP = Analysis population; CI = Confidence interval; N/n = Number; NA = Not reached; OS = Overall survival; SmPC = Summary of Product Characteristics
[1]The metastatic status of 2 patients could not be classified as only the free-text entries “secondary contralateral carcinoma” and “increased tumor marker” were recorded in the eCRF, respectively.
[2]The SmPC-population was defined *post-hoc*.
No metastases: Patients without metastases at start of Herceptin re-therapy (local recurrence only)
Non-visceral: Patients with non-visceral metastases only, i.e. bone, skin, lymph node and soft tissue metastases (± local recurrence, no visceral metastases)
Visceral: Patients with visceral metastases, i.e. lung, liver, CNS, pleural effusion, ascites, and other metastases (free-text entries) coded as visceral by medical experts (± non-visceral metastases ± local recurrence). This group comprises all patients with visceral metastases including those having additional non-visceral metastases.
Overall survival (OS-2) was estimated by using the Kaplan-Meier method.
OS-2 was defined as the time from diagnosis of local recurrent tumor / distant metastasis, which led to the initiation of anti-HER2 re-therapy with Herceptin to death due to any cause. Patients without documented date of death at the end of study were censored at the last date known to be alive. If this date was not available, the date of the last documented dose of Herceptin was used for the censored case.
A total of 33 patients (AP) with exclusively non-visceral metastases died during the study. For one patient, the date of death was not available. The overall survival of this patient was therefore included in the analysis as a censored case (date of last contact).

Figure 8-10 Overall survival (OS-2) from recurrence / distant metastases – subgroup "metastases / local recurrence only" (AP)



[Source: Herceptin_Abschlussanalyse_Figures; Figure 22.3-b].
AP = Analysis population; CI = Confidence interval; N = Number; NA = Not reached; OS = Overall survival
Local recurrence: Patients without metastases at start of Herceptin re-therapy (local recurrence only)
Non-visceral: Patients with non-visceral metastases only, i.e. bone, skin, lymph node and soft tissue metastases (± local recurrence, no visceral metastases)
Visceral: Patients with visceral metastases, i.e. lung, liver, CNS, pleural effusion, ascites, and other metastases (free-text entries) coded as visceral by medical experts (± non-visceral metastases ± local recurrence). This group comprises all patients with visceral metastases including those having additional non-visceral metastases.
Overall survival (OS-2) was estimated by using the Kaplan-Meier method.
OS-2 was defined as the time from diagnosis of local recurrent tumor / distant metastasis, which led to the initiation of anti-HER2 re-therapy with Herceptin to death due to any cause.
For 2 patients eCRF documentation concerning metastases was ambiguous. Data of these patients were excluded from this analysis. In total, 33 patients (AP) with non-visceral metastases only deceased during course of the study. For one patient, date of death was not available. Therefore, OS of this patient is censored at date of last contact.

Figure 8-11 Overall survival (OS-2) from recurrence / distant metastases – subgroup "metastases / local recurrence only" (SmPC-population[1])



[Source: Herceptin_Abschlussanalyse_Figures; Figure 22.6-b].
CI = Confidence interval; N = Number; NA = Not reached; OS = Overall survival; SmPC = Summary of Product Characteristics
[1]The SmPC-population was defined *post-hoc*.
Local recurrence: Patients without metastases at start of Herceptin re-therapy (local recurrence only)
Non-visceral: Patients with non-visceral metastases only, i.e. bone, skin, lymph node and soft tissue metastases (± local recurrence, no visceral metastases)
Visceral: Patients with visceral metastases, i.e. lung, liver, CNS, pleural effusion, ascites, and other metastases (free-text entries) coded as visceral by medical experts (± non-visceral metastases ± local recurrence). This group comprises all patients with visceral metastases including those having additional non-visceral metastases.
Overall survival (OS-2) was estimated by using the Kaplan-Meier method.
OS-2 was defined as the time from diagnosis of local recurrent tumor / distant metastasis, which led to the initiation of anti-HER2 re-therapy with Herceptin to death due to any cause.

8.4.6.4.2 Overall Survival (OS-2) – Subgroup "Combination Therapy"

The OS-2 was estimated in subgroups of patients having received Herceptin mono re-therapy and in subgroups of patients having received combination therapy (chemotherapy/endocrine therapy) with Herceptin re-therapy. In the AP, the shortest median OS-2 was observed in the subgroup of patients having received a taxane in combination with Herceptin re-therapy (18.5 months (15.0 – 27.6 months)), whereas the longest median OS-2 was seen in the subgroup of patients having received Herceptin

mono re-therapy (58.7 months (33.1 months – not reached)) as displayed in Table 8-85. The lowest OS-2 rates were seen in the subgroup of patients having received a taxane in combination with Herceptin re-therapy with a 12-month rate at 72.5%, 24-month rate at 40.6%, 36-month rate at 25.7% and 48-month rate at 15.0%.

Table 8-85 Overall survival (OS-2) from recurrence / distant metastases – subgroup "combination therapy (AP)

	Herceptin mono re-therapy	Taxanes	Endocrine therapy	Other CTx	CTx and endocrine therapy
Analysis population (AP): Total N=216					
Total number of patients (subgroups), N	*36*	*51*	*35*	*74*	*20*
Events, n (%)	16 (44.4)	43 (84.3)	20 (57.1)	44 (59.5)	11 (55.0)
Quartiles (months)					
25% quantile [95% CI]	30.8 (6.8 - 53.2)	9.0 (4.7 - 15.6)	20.3 (8.9 - 32.0)	17.3 (11.0 - 22.3)	21.6 (13.5 - 45.7)
50% quantile [95% CI] (Median)	58.7 (33.1 - NA)	18.5 (15.0 - 27.6)	36.1 (27.0 - NA)	29.6 (25.4 - 47.1)	57.6 (21.6 - NA)
75% quantile [95% CI]	NA	36.1 (26.6 - 58.8)	NA	NA	NA
OS-2 rates (%) [95% CI]					
12-month	85.4% (68.5% - 93.7%)	72.5% (58.0% - 82.7%)	88.6% (72.4% - 95.5%)	81.6% (70.4% - 88.9%)	100.0% (100.0% - 100.0%)
24-month	79.3% (61.5% - 89.6%)	40.6% (26.8% - 54.0%)	68.6% (50.5% - 81.2%)	64.9% (52.2% - 74.9%)	73.7% (47.9% - 88.1%)
36-month	64.1% (45.5% - 77.8%)	25.7% (14.3% - 38.6%)	50.1% (32.4% - 65.4%)	42.1% (29.9% - 53.8%)	63.2% (37.9% - 80.4%)
48-month	60.9% (42.3% - 75.1%)	15.0% (6.6% - 26.5%)	40.7% (24.1% - 56.6%)	35.2% (23.6% - 46.9%)	52.6% (28.7% - 71.9%)

[Source: Herceptin_Abschlussanalyse_Tables; Table 21.4-c].
AP = Analysis population; CI = Confidence interval; N/n = Number; NA = Not reached; OS = Overall survival;
Herceptin mono re-therapy: Patients who did not receive any combination therapy (neither chemo-/immunotherapy nor endocrine therapy) with their Herceptin re-therapy.
Taxanes: Patients receiving a taxane in combination with their Herceptin re-therapy (but no endocrine therapy).
Endocrine therapy: Patients receiving endocrine therapy in combination with their Herceptin re-therapy (but no chemo-/immunotherapy).
Other CTx: Patients receiving chemo-/immunotherapy other than taxanes in combination with their Herceptin re-therapy (but no endocrine therapy).
CTx and endocrine therapy: Patients receiving any chemo-/immunotherapy (taxanes or other CTx) and endocrine therapy in combination with their Herceptin re-therapy.
.
OS-2 was defined as the time from diagnosis of local recurrent tumor / distant metastasis, which led to the initiation of anti-HER2 re-therapy with Herceptin to death due to any cause. Patients without documented date of death at the end of study were censored at the last date known to be alive. If this date was not available, the date of the last documented dose of Herceptin was used for the censored case.
A total of 21 patients (AP) with exclusively endocrine concomitant therapy died during the study. For one patient, the date of death was not available. The overall survival of this patient was therefore included in the analysis as a censored case (date of last contact).

8.4.6.4.3 Overall Survival (OS-2) – Subgroup "Chemotherapy"

The OS-2 was estimated in subgroups of patients having received mono-chemotherapy (no endocrine therapy) in combination with Herceptin re-therapy (Table 8-86). In the AP, the median OS-2 was shortest in the subgroup of patients having received monotherapy with a taxane in combination with Herceptin re-therapy (18.5 months (15.0 – 27.6 months)) versus patients with monotherapy with vinorelbine (29.6 months (17.3 – 49.2 months)) or capecitabine (25.4 months (11.1 months – not reached)) in combination with Herceptin re-therapy. In the taxane subgroup, the 12-month, 24-month, 36-month- and 48-month OS-2 rates were 72.5%, 40.6%, 25.7% and 15.0%, respectively.

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Table 8-86 Overall survival (OS-2) from recurrence / distant metastases – subgroup "chemotherapy" (AP)

	Taxane	Vinorelbine	Capecitabine
Analysis population (AP): Total N=216			
Total number of patients (subgroups), N	*51*	*27*	*23*
Events, n (%)	43 (84.3)	18 (66.7)	12 (52.2)
Quartiles (months)			
25% quantile [95% CI]	9.0 (4.7 - 15.6)	17.1 (8.6 - 29.5)	11.1 (2.2 - 24.3)
50% quantile [95% CI] (Median)	18.5 (15.0 - 27.6)	29.6 (17.3 - 49.2)	25.4 (11.1 - NA)
75% quantile [95% CI]	36.1 (26.6 - 58.8)	NA	NA
OS-2 rates (%) [95% CI]			
12-month	72.5% (58.0% - 82.7%)	84.7% (64.3% - 94.0%)	71.1% (46.5% - 85.9%)
24-month	40.6% (26.8% - 54.0%)	68.9% (47.3% - 83.1%)	60.2% (35.6% - 77.9%)
36-month	25.7% (14.3% - 38.6%)	44.6% (25.0% - 62.5%)	43.8% (21.6% - 64.1%)
48-month	15.0% (6.6% - 26.5%)	35.7% (17.7% - 54.2%)	38.3% (17.5% - 59.0%)

[Source: Herceptin_Abschlussanalyse_Tables; Table 21.4-d].
AP = Analysis population; CI = Confidence interval; N/n = Number; NA = Not reached; OS = Overall survival
Taxane: Patients receiving a taxane in combination with their Herceptin re-therapy (no other chemotherapy and no endocrine therapy)
Vinorelbine: Patients receiving vinorelbine in combination with their Herceptin re-therapy (no other chemotherapy and no endocrine therapy)
Capecitabine: Patients receiving capecitabine in combination with their Herceptin re-therapy (no other chemotherapy and no endocrine therapy)
Overall survival (OS-2) was estimated by using the Kaplan-Meier method.
OS-2 was defined as the time from diagnosis of local recurrent tumor / distant metastasis, which led to the initiation of anti-HER2 re-therapy with Herceptin to death due to any cause. Patients without documented date of death at the end of study were censored at the last date known to be alive. If this date was not available, the date of the last documented dose of Herceptin was used for the censored case.
The subgroups "Carboplatin" (n=2) and "Other Chemotherapy" (n=1) are not displayed due to small sample size. For the two patients treated with carboplatin, the median OS-2 was 2.43 months and. 31.71 months; for the patient treated with other chemotherapy (doxorubicin) the median OS-2 was 31.25 months.

8.4.6.5 Best Tumor Response (ORR)

Best tumor responses (as assessed by the respective treating physician) and the ORR are displayed for the AP and SmPC-Population in Table 8-87. In the AP, the ORR was 35.2% including 20 (9.3%) patients documented with a CR and 56 (25.9%) patients with a PR. The ORR was higher in the SmPC-population (49.0%).

Table 8-87 Best tumor response – (AP /SmPC-population)

	AP population		SmPC-population[1]	
	N	%	N	%
Total number of patients, N	*216*	*100*	*49*	*100*
Best tumor response[2] (ORR), n, %				
CR	20	9.3	6	12.2
PR	56	25.9	18	36.7
ORR	76	35.2	24	49.0
NC (SD)	45	20.8	8	16.3
PD	54	25.0	12	24.5
Unknown	41	19.0	5	10.2

[Source: Herceptin_Abschlussanalyse_Tables; Table 21.5-a Table 23.4].
AP = Analysis population; CR = Complete remission; N/n = Number; NC = No change; ORR = Overall response rate; PD = Progressive disease; PR = Partial remission; SD = Stable disease; SmPC = Summary of Product Characteristics
[1]The SmPC-population was defined *post-hoc*.
[2]As assessed by the respective treating physician.

8.4.6.5.1 Overall Response – Logistic Regression Analysis

A multivariable logistic regression analysis was performed to identify potential independent factors (baseline demographics and clinical characteristics), which might have an impact on the overall response (Table 8-88). In this analysis including 212 patients (responders: n= 74; 34.9%), no factor could be identified having an impact on the overall response (all individual *p*-values >0.1; global likelihood ratio test *p*=0.2977).

Table 8-88 Logistic regression analysis of potential factors influencing the overall response (AP)

	Reference	Odds ratio (OR)	95% CI (OR)	*p*-value
Analysis population (AP): Total N=216				
Logistic regression analysis: n=212 (responders: n=74)				
Parameters				
Intercept		*0.37*		*0.345*
Age at informed consent	-1 year	1.00	0.98 - 1.03	0.722
BMI	-1 kg/m²	1.01	0.95 - 1.06	0.862
DFS	-1 month	1.01	0.99 - 1.03	0.223
Stage at diagnosis III/IV	0/I/II	0.62	0.33 - 1.15	0.130
Stage at diagnosis unknown	0/I/II	1.63	0.56 - 4.71	0.369
Hormone receptor status negative	Positive	1.28	0.70 - 2.34	0.431
Non-visceral metastases only	No metastases	0.60	0.26 - 1.39	0.231
Visceral metastases	No metastases	0.63	0.30 - 1.34	0.229

[Source: Herceptin_Abschlussanalyse_Tables; Table 21.6].
AP = Analysis population; BMI = Body mass index; CI = Confidence interval; DFS = Disease-free survival; N = Number; OR = Odds ratio
Global Likelihood Ratio Test *p*-value: 0.2977
For one patient each, the BMI/hormone receptor status was unknown. In addition, the metastasis status of 2 patients could not be determined. The data from these four patients were therefore not included in the model calculations.
Tumor response modelled (overall response).

8.5 OTHER ANALYSES

8.5.1 Decision Criteria for Choice of Herceptin Re-Therapy

8.5.1.1 Decision-Makers

For half of the patient population (n=108; 50.0%), the decision for Herceptin re-therapy was made by a tumor board, which was the most frequent deciding party (Table 8-89).

Table 8-89 Choice of Herceptin re-therapy – Decision-makers (AP)

	N	%
Total number of patients, N	*216*	*100*
Choice of Herceptin re-therapy – Decision makers, n, %		
Tumor board	108	50.0
NIO (niedergelassener internistischer Onkologe [Resident Internal Oncologist])	52	24.1
Oncology council	24	11.1
Gynecologist	18	8.3
Hospital physician	9	4.2
Other	5	2.3
Missing	0	0.0

[Source: Herceptin_Abschlussanalyse_Tables; Table 10.1].

AP = Analysis population; N/n = Number; NIO= Resident internal oncologist

8.5.1.2 Deciding Factors

HER2 status (n=202; 93.5%) was the most frequent factor reported as a deciding factor for Herceptin re-therapy (Table 8-90). Other common (>30% of patients) deciding factors were “efficacy of (neo-) adjuvant anti-HER2 therapy” (n=102; 47.2%), “tolerability of (neo-) adjuvant anti-HER2 therapy” (n=100; 46.3%), “study results/publications” (n=94; 43.5%) and patient’s performance status (n=73; 33.8%).

Table 8-90 Deciding factors for choice of Herceptin re-therapy (AP)

	N	%
Total number of patients, N	*216*	*100*
Choice of Herceptin re-therapy – Deciding factors[1], n, %		
HER2-status	202	93.5
Efficacy of (neo-) adjuvant anti-HER2 therapy	102	47.2
Tolerability of (neo-) adjuvant anti-HER2 therapy	100	46.3
Study results/publications	94	43.5
Patient’s performance status	73	33.8
Patient age	61	28.2
Hormone receptor status	59	27.3
Intensive treatment required due to life-threatening condition of the patient	26	12.0
Comorbidities	1	0.5
Concomitant medication	0	0.0
Other	1	0.5
Missing	0	0.0

[Source: Herceptin_Abschlussanalyse_Tables; Table 10.3].
AP = Analysis population; HER2 = Human epidermal growth factor receptor 2; N/n = Number
[1]Multiple entries per patient possible.

8.5.2 Decision Criteria for Choice of Chemotherapy in Combination with Herceptin Re-Therapy

The most frequent deciding factor for concomitant chemotherapy in combination with Herceptin re-therapy was “guidelines” (n=105; 48.6%; Table 8-91). Other frequent (>30% of patients) deciding factors were “patient’s performance status” (n=84; 38.9%), “study results/publications” (n=78; 36.1%) and “patient age” (n=71; 32.9%).

Table 8-91 Deciding factors for concomitant chemotherapy (AP)

	N	%
Total number of patients, N	*216*	*100*

	N	%
Choice of concomitant chemotherapy – Deciding factors[1], n, %		
Guidelines	105	48.6
Patient's performance status	84	38.9
Study results/publications	78	36.1
Patient age	71	32.9
Efficacy of (neo)adjuvant chemotherapy	53	24.5
Tolerability of (neo)adjuvant chemotherapy	44	20.4
Intensive treatment required due to life-threatening condition of the patient	38	17.6
Moderate, quality of life-oriented therapy, as no immediate threat to life	24	11.1
Nature of the tumor	7	3.2
Other	27	12.5
Missing	0	0.0
Specification of "nature of the tumor"[2], n, %		
Large carcinoma G3	1	0.5
HER2/new pos.	1	0.5
IHC 3+	1	0.5
Liver metastasis from breast cancer	1	0.5
Only bone metastasis	1	0.5
Pulmonary metastatic spread and LN metastases	1	0.5
Breast cancer recurrence	1	0.5

[Source: Herceptin_Abschlussanalyse_Tables; Table 10.7, Table 10.8].
AP = Analysis population; HER2 = Human epidermal growth factor receptor 2; IHC = Immunohistochemistry; LN = Lymph node; N/n = Number
[1]Multiple entries per patient possible. [2]Free-text entries extracted from the eCRF and translated into English.

8.5.3 Second-Line and Further-Line Palliative Therapy Following end of Herceptin Re-Therapy

In total, 98 (45.4%) patients were documented with second-line therapy following end of Herceptin re-therapy, whereas the number of patients with further-line therapy was 53 (24.5%; third-line), 27 (12.5%; fourth-line) and 13 (6.0%; fifth-line) patients as summarized in Table 8-92, which further details the treatments administered for respective treatment line. In second-line therapy, combination therapy with capecitabine and lapatinib was the most common treatment reported (n=21; 9.7%), whereas the most frequent treatments given in further-line therapy were trastuzumab alone (n=6; 2.8%; third-line), T-DM1 alone (n=6; 2.8%; fourth-line), and combination therapy with capecitabine and lapatinib or doxorubicin alone or trastuzumab alone (all n=2, 0.9%; fifth-line).

Table 8-92 Second-line and further-line therapy (AP)

	N	%
Total number of patients, N	*216*	*100*
Patients with second-line therapy, n, %	98	45.4
Capecitabine, Lapatinib	21	9.7
Trastuzumab	14	6.5
Trastuzumab, vinorelbine	8	3.7
Vinorelbine	7	3.2
Capecitabine, lapatinib, trastuzumab	6	2.8
Capecitabine, trastuzumab	6	2.8
Lapatinib	5	2.3
Lapatinib, trastuzumab	5	2.3
Paclitaxel, trastuzumab	3	1.4
Docetaxel, trastuzumab	2	0.9
Paclitaxel	2	0.9
T-DM1	2	0.9
Bevacizumab, capecitabine	1	0.5
Capecitabine	1	0.5
Capecitabine, docetaxel, pertuzumab, trastuzumab, vinorelbine	1	0.5
Capecitabine, fluorouracil, trastuzumab	1	0.5
Capecitabine, lapatinib, trastuzumab, vinorelbine	1	0.5
Carboplatin	1	0.5
Carboplatin, paclitaxel, trastuzumab	1	0.5
Denosumab, lapatinib, vinorelbine	1	0.5
Docetaxel	1	0.5
Docetaxel, pertuzumab, trastuzumab	1	0.5
Doxorubicin	1	0.5
Doxorubicin, trastuzumab	1	0.5
Eribulin, trastuzumab	1	0.5
Fluorouracil, lapatinib	1	0.5
Fluorouracil, Na-folinate, oxaliplatin	1	0.5
Fulvestrant	1	0.5
Fulvestrant, lapatinib, trastuzumab	1	0.5
Patients with third-line therapy, n, %	53	24.5
Trastuzumab	6	2.8
Capecitabine, Lapatinib	5	2.3
Doxorubicin	4	1.9
Vinorelbine	4	1.9
Capecitabine	3	1.4

		N	%
	Docetaxel, pertuzumab	3	1.4
	Eribulin	3	1.4
	Lapatinib	3	1.4
	T-DM1	3	1.4
	Trastuzumab, vinorelbine	3	1.4
	Capecitabine, trastuzumab	2	0.9
	Paclitaxel, trastuzumab	2	0.9
	Bevacizumab, doxorubicin	1	0.5
	Capecitabine, fluorouracil, trastuzumab	1	0.5
	Carboplatin, paclitaxel, trastuzumab	1	0.5
	Carboplatin, trastuzumab	1	0.5
	Cisplatin, gemcitabine	1	0.5
	Docetaxel	1	0.5
	Docetaxel, pertuzumab, trastuzumab	1	0.5
	Docetaxel, trastuzumab	1	0.5
	Fluorouracil, trastuzumab	1	0.5
	Lapatinib, trastuzumab	1	0.5
	Paclitaxel	1	0.5
	Topotecan	1	0.5
Patients with fourth-line therapy, n, %		27	12.5
	T-DM1	6	2.8
	Paclitaxel, trastuzumab	3	1.4
	Vinorelbine	3	1.4
	Paclitaxel	2	0.9
	Trastuzumab, vinorelbine	2	0.9
	Capecitabine	1	0.5
	Capecitabine, Lapatinib	1	0.5
	Cyclophosphamide	1	0.5
	Docetaxel, trastuzumab	1	0.5
	Doxorubicin	1	0.5
	Eribulin	1	0.5
	Lapatinib, letrozole	1	0.5
	Mitoxantrone	1	0.5
	Nab-paclitaxel	1	0.5
	Nab-paclitaxel, trastuzumab	1	0.5
	Trastuzumab	1	0.5
Patients with fifth-line therapy, n, %		13	6.0
	Capecitabine, Lapatinib	2	0.9
	Doxorubicin	2	0.9

	N	%
Trastuzumab	2	0.9
Bevacizumab, vinorelbine	1	0.5
Epirubicin	1	0.5
Eribulin	1	0.5
T-DM1	1	0.5
Tamoxifen, trastuzumab	1	0.5
Trastuzumab, vinorelbine	1	0.5
Vinorelbine	1	0.5

[Source: Herceptin_Abschlussanalyse_Tables; Table 18.1-a, Table 18.1-b, Table 18.1-c, Table 18.1-d].
AP = Analysis population; N/n = Number; T-DM1 = Trastuzumab-Emtansine

8.6 ADVERSE EVENTS AND ADVERSE REACTIONS

For safety analysis, AEs including AESIs and situations requiring expedited reporting, SAEs, ADRs, SADRs and fatal events (regardless of causality) have been collected. Fatal events can be either fatal SADR (assessed as related to Herceptin treatment) or fatal SAE (assessed as not related to Herceptin). The collection of AEs, SAEs, ADRs and SADRs reflects the real-world situation in which the respective treating physicians with best knowledge of their patients assessed whether an observed event could be related to Herceptin. In this way, this report presents captured safety data that are reflective of the "real-world" setting.

Prior to the amendment to the study protocol (Amendment 3), study sites were requested to only document Herceptin-related events (ADRs), whereas following Amendment 3 study sites were required to document all AEs including all ADRs. This change was implemented in the eCRF on 10 April 2014 and was also applied retroactively until July 2012; hence, also applicable to AEs that had already occurred before Amendment 3 came into effect with a possibility of incomplete data and/or underreporting of AEs. Therefore, the summary tables of AEs assessed as not related to Herceptin treatment are not displayed for the overall AP, but separately as indicated below:

- AEs onset before 10 April 2014
- AEs onset on or after 10 April 2014

The NCI's standardized definitions for CTCAE v4.03 were used for severity grading of all AEs and MedDRA v20.0 for classification of reported terms within respective SOC and PT.

8.6.1 Discrepancies Between Safety Database Roche (SDB) and Clinical Database CRO (CDB) – Final Reconciliation

For a NIS, it is an integral part of Roche´s Safety and Data Quality Management to review all data including free-text entries for possible hidden AEs, to review and re-evaluate seriousness assessments of AEs in terms of need of seriousness upgrade provided by investigators through single case reviews by experienced medical experts in drug safety, and to review all causality assessments. Depending on respective assessment outcomes, discrepancies between the seriousness of AEs as reported by the respective treating physician versus the seriousness as assessed by Roche followed by a company upgrade (i.e. from non-serious to serious) of respective events might occur. Another aspect of review is related to PT coding and SOC allocation of PTs.

Causality assessments might differ in terms of changing “not reported causality” to “unknown causality”, or from “not related” to “related” in terms of sponsor assessment.

Based on all these alternative reasons, altogether 64 differences between CDB and SDB in terms of reported AEs have been identified in this NIS. It also needs to be considered, that discrepancies for one single event might be attributed to several reasons. The differences between the CDB and the company´s SDB for this NIS have been subject of thorough evaluation and scientific discussion. Please refer to Annex 2 for the respective listings and a brief description of the data on the SOC level.

8.6.2 Overview of Adverse Events

With the amendment to the study protocol (Amendment 3), study sites were requested to document all AEs including all ADRs. This change was implemented in the eCRF on 10 April 2014 and was also applied retroactively until July 2012.

An overview of number of patients with reported AEs and SAEs (not related to Herceptin treatment; onset of (S)AEs before / on or after 10 April 2014) as well as number of patients with documented ADRs and SADRs in this NIS is displayed in Table 8-93, specified by number of cases and CTCAE grade 1, CTCAE grade 2, CTCAE grade 3, CTCAE grade 4, CTCAE grade 3/4, and CTCAE grade 5.

Overall, 48 (22.2%) patients were reported with AEs of any CTCAE grade (125 cases) and 22 (10.2%) patients were documented with SAEs (37 cases) where all these (S)AEs were assessed as not related to Herceptin treatment and with onset of the (S)AEs before

10 April 2014. Nineteen (8.8%) patients were documented with AEs of CTCAE grade 3/4 (38 cases). Eight (3.7%) patients were reported with fatal AEs (8 cases).

In total, 3 (1.4%) patients were reported with AEs assessed as not related to Herceptin and with onset of the AEs on or after 10 April 2014 (5 cases; all AEs of CTCAE grade 2). There were no patients reported with SAEs with onset on or after 10 April 2014.

Overall, 52 (24.1%) patients were documented with ADRs (186 cases) and 17 (7.9%) patients with SADRs (27 cases). Eighteen (8.3%) patients were reported with ADRs of CTCAE grade 3 (24 cases; no patients documented with ADRs of grade 4). Two (0.9%) patients were documented with fatal ADRs (4 cases). ADRs (14 cases) leading to discontinuation of Herceptin re-therapy were reported in 10 (4.6%) patients.

Table 8-93 Overview of adverse events (AP)

	N Patients	% Patients	N Cases
Total number of patients, N	*216*	*100*	
Number of patients with reported respective adverse event, n, %, n (cases)			
Patients with AE not related to Herceptin treatment (AE with onset before 10 April 2014)	48	22.2	125
Patients with AE not related to Herceptin treatment (AE with onset on or after 10 April 2014)	3	1.4	5
Patients with adverse drug reactions	52	24.1	186
Patients with serious AE not related to Herceptin treatment (AE with onset before 10 April /2014)	22	10.2	37
Patients with serious AE not related to Herceptin treatment (AE with onset on or after 10 April 2014)	0	0.0	0
Patients with serious adverse drug reactions	17	7.9	27
Patients with AE not related to Herceptin treatment (AE with onset before 10 April 2014)– CTCAE Grade 1	15	6.9	32
Patients with AE not related to Herceptin treatment (AE with onset before 10 April 2014)– CTCAE Grade 2	27	12.5	42
Patients with AE not related to Herceptin treatment (AE with onset before 10 April 2014)– CTCAE Grade 3	16	7.4	33
Patients with AE not related to Herceptin treatment (AE with onset before 10 April 2014)– CTCAE Grade 4	4	1.9	5
Patients with AE not related to Herceptin treatment (AE with onset before 10 April 2014)– CTCAE Grade 5	8	3.7	8
Patients with AE not related to Herceptin treatment (AE with onset before 10 April 2014) – CTCAE Grade 3/4	19	8.8	38
Patients with AE not related to Herceptin treatment (AE with onset before 10 April 2014) that led to discontinuation of Herceptin re-therapy	9	4.2	9
Patients with AE not related to Herceptin treatment (AE with onset on or after 10 April 2014)– CTCAE Grade 1	0	0.0	0
Patients with AE not related to Herceptin treatment (AE with onset on or after 10 April 2014)– CTCAE Grade 2	3	1.4	5
Patients with AE not related to Herceptin treatment (AE with onset on or after 10 April 2014)– CTCAE Grade 3	0	0.0	0
Patients with AE not related to Herceptin treatment (AE with onset on or after 10 April 2014)– CTCAE Grade 4	0	0.0	0
Patients with AE not related to Herceptin treatment (AE with onset on or after 10 April 2014)– CTCAE Grade 5	0	0.0	0
Patients with AE not related to Herceptin treatment (AE with onset on or after 10 April 2014)– CTCAE Grade 3/4	0	0.0	0
Patients with AE not related to Herceptin treatment (AE with onset on or after 10 April 2014) that led to discontinuation of Herceptin re-therapy	0	0.0	0
Patients with adverse drug reactions– CTCAE Grade 1	24	11.1	66

	N Patients	% Patients	N Cases
Patients with adverse drug reactions– CTCAE Grade 2	35	16.2	89
Patients with adverse drug reactions– CTCAE Grade 3	18	8.3	24
Patients with adverse drug reactions– CTCAE Grade 4	0	0.0	0
Patients with adverse drug reactions– CTCAE Grade 5	2	0.9	4
Patients with adverse drug reactions– CTCAE Grade 3/4	18	8.3	24
Patients with adverse drug reactions that led to discontinuation of Herceptin re-therapy	10	4.6	14

[Source: Herceptin_Abschlussanalyse_Tables; Table 16.1].
AE = Adverse event; AP = Analysis population; CTCAE = Common Terminology Criteria for Adverse Events; N = Number
In total, 8 AEs were documented with severity “unknown” or had not been documented (5 AEs not related to Herceptin treatment with onset on or after 10 April 2014; 3 adverse drug reactions).

8.6.3 Adverse Events Not Related to Herceptin Treatment (Onset of AEs Before 10 April 2014) – Preferred Terms

In total, 48 (22.2%) patients were reported with AEs (any CTCAE grade) assessed as not related to Herceptin (125 cases) and with onset of the AEs before 10 April 2014 (Table 8-94). The most frequently reported (>2% of patients) AEs were nausea (n=7; 3.2%), leukopenia (n=6; 2.8%), dyspnea (n=5; 2.3%), general physical health deterioration (n=5; 2.3%), and polyneuropathy (n=5; 2.3%).

Table 8-94 Adverse events (AEs) not related to Herceptin (onset of the AEs before 10 April 2014) – preferred terms (AP)

	N Patients	% Patients	N Cases
Total number of patients, N	*216*	*100*	
Patients with any AE (any CTCAE grade), n, %, n (cases)	48	22.2	125
Gastrointestinal disorders, n, %, n (cases)			
Nausea	7	3.2	8
Vomiting	4	1.9	5
Diarrhea	3	1.4	3
Gastrointestinal pain	2	0.9	2
Abdominal pain	1	0.5	1
Ascites	1	0.5	1
Gastritis hemorrhagic	1	0.5	1
Colitis	1	0.5	1
Gastritis erosive	1	0.5	1
Ileus	1	0.5	1
General disorders and administration site conditions, n, %, n (cases)			
General physical health deterioration	5	2.3	5
Fatigue	2	0.9	2
Death	2	0.9	2
Ulcer hemorrhage	1	0.5	1
Injection site pain	1	0.5	1
Breast complication associated with device	1	0.5	1
Asthenia	1	0.5	1
Nervous system disorders, n, %, n (cases)			
Polyneuropathy	5	2.3	5
Dizziness	3	1.4	4
Paraesthesia	1	0.5	1
Headache	1	0.5	1
Neuropathy peripheral	1	0.5	1
Blood and lymphatic system disorders, n, %, n (cases)			

	N Patients	% Patients	N Cases
Leukopenia	6	2.8	15
Anemia	3	1.4	7
Neutropenia	1	0.5	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps), n, %, n (cases)			
Malignant neoplasm progression	3	1.4	3
Metastases to bone	2	0.9	2
Metastases to central nervous system	1	0.5	1
Cholangiocarcinoma	1	0.5	1
Metastasis	1	0.5	1
Metastases to lung	1	0.5	1
Infections and infestations, n, %, n (cases)			
Urinary tract infection	2	0.9	2
Pneumonia	1	0.5	1
Oesophageal candidiasis	1	0.5	1
Gastroenteritis	1	0.5	1
Appendicitis perforated	1	0.5	1
Respiratory, thoracic and mediastinal disorders, n, %, n (cases)			
Dyspnea	5	2.3	6
Laryngeal pain	1	0.5	1
Bronchial hemorrhage	1	0.5	1
Skin and subcutaneous tissue disorders, n, %, n (cases)			
Palmar-plantar erythrodysaesthesia syndrome	3	1.4	3
Toxic epidermal necrolysis	1	0.5	1
Skin discoloration	1	0.5	1
Dermatitis	1	0.5	1
Skin disorder	1	0.5	1
Erythema	1	0.5	1
Investigations, n, %, n (cases)			
Weight decreased	3	1.4	3
Tumor marker increased	1	0.5	1
Weight increased	1	0.5	1
Prothrombin time prolonged	1	0.5	1
C-reactive protein increased	1	0.5	1
Musculoskeletal and connective tissue disorders, n, %, n (cases)			
Arthralgia	2	0.9	2
Osteoporosis	1	0.5	1
Osteoarthritis	1	0.5	1
Bone pain	1	0.5	1

	N Patients	% Patients	N Cases
Psychiatric disorders, n, %, n (cases)			
Sleep disorder	1	0.5	1
Anxiety	1	0.5	1
Depression	1	0.5	1
Metabolism and nutrition disorders, n, %, n (cases)			
Decreased appetite	1	0.5	1
Hyperglycaemia	1	0.5	1
Injury, poisoning and procedural complications, n, %, n (cases)			
Femoral neck fracture	1	0.5	1
Pregnancy, puerperium and perinatal conditions, n, %, n (cases)			
Pregnancy	1	0.5	1
Renal and urinary disorders, n, %, n (cases)			
Renal failure	1	0.5	1
Reproductive system and breast disorders, n, %, n (cases)			
Menorrhagia	1	0.5	1
Vascular disorders, n, %, n (cases)			
Thrombosis	1	0.5	1

[Source: Herceptin_Abschlussanalyse_Tables; Table 16.2].
AE = Adverse event; AP = Analysis population; CTCAE = Common Terminology Criteria for Adverse Events; N/n = Number
Multiple entries per patient possible.

8.6.3.1 Adverse Events Not Related to Herceptin Treatment (Onset of AEs Before 10 April 2014) – CTCAE Grade 1 (Preferred Terms)

Overall, 15 (6.9%) patients were documented with AEs of CTCAE grade 1 assessed as not related to Herceptin (32 cases) and with onset of the AEs before 10 April 2014 (Table 8-95). The most commonly reported AEs were dizziness, dyspnea, nausea, polyneuropathy, vomiting and weight decreased (2 patients each; 0.9%).

Table 8-95 CTCAE grade 1 adverse events (AEs) not related to Herceptin (onset of the AEs before 10 April 2014) – preferred terms (AP)

	N Patients	% Patients	N Cases
Total number of patients, N	*216*	*100*	
Patients with any AE (CTCAE grade 1), n, %, n (cases)	15	6.9	32
Gastrointestinal disorders, n, %, n (cases)			
Vomiting	2	0.9	3
Nausea	2	0.9	2
Diarrhea	1	0.5	1

	N Patients	% Patients	N Cases
Gastritis erosive	1	0.5	1
Investigations, n, %, n (cases)			
Weight decreased	2	0.9	2
Tumor marker increased	1	0.5	1
Prothrombin time prolonged	1	0.5	1
C-reactive protein increased	1	0.5	1
Nervous system disorders, n, %, n (cases)			
Polyneuropathy	2	0.9	2
Dizziness	2	0.9	2
Paraesthesia	1	0.5	1
Respiratory, thoracic and mediastinal disorders, n, %, n (cases)			
Dyspnea	2	0.9	2
Laryngeal pain	1	0.5	1
Musculoskeletal and connective tissue disorders, n, %, n (cases)			
Osteoarthritis	1	0.5	1
Arthralgia	1	0.5	1
Skin and subcutaneous tissue disorders, n, %, n (cases)			
Skin discoloration	1	0.5	1
Dermatitis	1	0.5	1
Palmar-plantar erythrodysaesthesia syndrome	1	0.5	1
Blood and lymphatic system disorders, n, %, n (cases)			
Leukopenia	1	0.5	1
Anemia	1	0.5	3
General disorders and administration site conditions, n, %, n (cases)			
Fatigue	1	0.5	1
Infections and infestations, n, %, n (cases)			
Oesophageal candidiasis	1	0.5	1
Psychiatric disorders, n, %, n (cases)			
Sleep disorder	1	0.5	1

[Source: Herceptin_Abschlussanalyse_Tables; Table 16.8].
AE = Adverse event; AP = Analysis population; CTCAE = Common Terminology Criteria for Adverse Events; N/n = Number
Multiple entries per patient possible.

8.6.3.2 Adverse Events Not Related to Herceptin Treatment (Onset of AEs Before 10 April 2014) – CTCAE Grade 2 (Preferred Terms)

In total, 27 (12.5%) patients were reported with AEs of CTCAE grade 2 assessed as not related to Herceptin (42 cases) and with onset of the AEs before 10 April 2014 (Table 8-96). The most frequently reported (≥2 patients) AEs were leukopenia (n=3; 1.4%),

polyneuropathy (n=3; 1.4%), anemia (n=2; 0.9%), diarrhea (n=2; 0.9%), dizziness (n=2; 0.9%) and nausea (n=2; 0.9%).

Table 8-96 CTCAE grade 2 adverse events (AEs) not related to Herceptin (onset of the AEs before 10 April 2014) – preferred terms (AP)

	N Patients	% Patients	N Cases
Total number of patients, N	*216*	*100*	
Patients with any AE (CTCAE grade 2), n, %, n (cases)	27	12.5	42
Nervous system disorders, n, %, n (cases)			
Polyneuropathy	3	1.4	3
Dizziness	2	0.9	2
Headache	1	0.5	1
Neuropathy peripheral	1	0.5	1
Blood and lymphatic system disorders, n, %, n (cases)			
Leukopenia	3	1.4	3
Anemia	2	0.9	3
Gastrointestinal disorders, n, %, n (cases)			
Nausea	2	0.9	3
Diarrhea	2	0.9	2
Ascites	1	0.5	1
General disorders and administration site conditions, n, %, n (cases)			
General physical health deterioration	1	0.5	1
Injection site pain	1	0.5	1
Fatigue	1	0.5	1
Infections and infestations, n, %, n (cases)			
Pneumonia	1	0.5	1
Gastroenteritis	1	0.5	1
Metabolism and nutrition disorders, n, %, n (cases)			
Decreased appetite	1	0.5	1
Hyperglycaemia	1	0.5	1
Musculoskeletal and connective tissue disorders, n, %, n (cases)			
Osteoporosis	1	0.5	1
Arthralgia	1	0.5	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps) n, %, n (cases)			
Metastases to bone	1	0.5	1
Cholangiocarcinoma	1	0.5	1
Psychiatric disorders, n, %, n (cases)			

	N Patients	% Patients	N Cases
Anxiety	1	0.5	1
Depression	1	0.5	1
Respiratory, thoracic and mediastinal disorders, n, %, n (cases)			
Dyspnea	1	0.5	1
Bronchial hemorrhage	1	0.5	1
Skin and subcutaneous tissue disorders, n, %, n (cases)			
Skin disorder	1	0.5	1
Erythema	1	0.5	1
Palmar-plantar erythrodysaesthesia syndrome	1	0.5	1
Injury, poisoning and procedural complications, n, %, n (cases)			
Femoral neck fracture	1	0.5	1
Investigations, n, %, n (cases)			
Weight decreased	1	0.5	1
Renal and urinary disorders, n, %, n (cases)			
Renal failure	1	0.5	1
Reproductive system and breast disorders, n, %, n (cases)			
Menorrhagia	1	0.5	1
Vascular disorders, n, %, n (cases)			
Thrombosis	1	0.5	1

[Source: Herceptin_Abschlussanalyse_Tables; Table 16.9].
AE = Adverse event; AP = Analysis population; CTCAE = Common Terminology Criteria for Adverse Events; N/n = Number
Multiple entries per patient possible.

8.6.3.3 Adverse Events Not Related to Herceptin Treatment (Onset of AEs Before 10 April 2014) – CTCAE Grade 3 (Preferred Terms)

Overall, 16 (7.4%) patients were reported with AEs of CTCAE grade 3 assessed as not related to Herceptin (33 cases) and with onset of the AEs before 10 April 2014 (Table 8-97). The most frequently documented (≥2 patients) AEs were leukopenia (n=3; 1.4%), nausea (n=3; 1.4%), dyspnea (n=2; 0.9%), gastrointestinal pain (n=2; 0.9%), urinary tract infection (n=2; 0.9%) and vomiting (n=2; 0.9%).

Table 8-97 CTCAE grade 3 adverse events (AEs) not related to Herceptin (onset of the AEs before 10 April 2014) – preferred terms (AP)

	N Patients	% Patients	N Cases
Total number of patients, N	*216*	*100*	

	N Patients	% Patients	N Cases
Patients with any AE (CTCAE grade 3), n, %, n (cases)	16	7.4	33
Gastrointestinal disorders, n, %, n (cases)			
Nausea	3	1.4	3
Gastrointestinal pain	2	0.9	2
Vomiting	2	0.9	2
Abdominal pain	1	0.5	1
Gastritis hemorrhagic	1	0.5	1
Colitis	1	0.5	1
Blood and lymphatic system disorders, n, %, n (cases)			
Leukopenia	3	1.4	8
Anemia	1	0.5	1
Neutropenia	1	0.5	1
General disorders and administration site conditions, n, %, n (cases)			
Ulcer hemorrhage	1	0.5	1
Breast complication associated with device	1	0.5	1
General physical health deterioration	1	0.5	1
Asthenia	1	0.5	1
Infections and infestations, n, %, n (cases)			
Urinary tract infection	2	0.9	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps), n, %, n (cases)			
Metastases to central nervous system	1	0.5	1
Malignant neoplasm progression	1	0.5	1
Metastasis	1	0.5	1
Respiratory, thoracic and mediastinal disorders, n, %, n (cases)			
Dyspnea	2	0.9	2
Musculoskeletal and connective tissue disorders, n, %, n (cases)			
Bone pain	1	0.5	1
Skin and subcutaneous tissue disorders, n, %, n (cases)			
Palmar-plantar erythrodysaesthesia syndrome	1	0.5	1

[Source: Herceptin_Abschlussanalyse_Tables; Table 16.10].
AE = Adverse event; AP = Analysis population; CTCAE = Common Terminology Criteria for Adverse Events; N/n = Number
Multiple entries per patient possible.

8.6.3.4 Adverse Events Not Related to Herceptin Treatment (Onset of AEs Before 10 April 2014) – CTCAE Grade 4 (Preferred Terms)

In total, 4 (1.9%) patients were documented with AEs of CTCAE grade 4 assessed as not related to Herceptin (5 cases) and with onset of the AEs before 10 April 2014 (Table 8-98).

The reported AEs were leukopenia (n=2; 0.9%), appendicitis perforated (n=1; 0.5%) and ileus (n=1; 0.5%).

Table 8-98 CTCAE grade 4 adverse events (AEs) not related to Herceptin (onset of the AEs before 10 April 2014) – preferred terms (AP)

	N Patients	% Patients	N Cases
Total number of patients, N	*216*	*100*	
Patients with any AE (CTCAE grade 4), n, %, n (cases)	4	1.9	5
Blood and lymphatic system disorders, n, %, n (cases)			
Leukopenia	2	0.9	3
Gastrointestinal disorders, n, %, n (cases)			
Ileus	1	0.5	1
Infections and infestations, n, %, n (cases)			
Appendicitis perforated	1	0.5	1

[Source: Herceptin_Abschlussanalyse_Tables; Table 16.11].
AE = Adverse event; AP = Analysis population; CTCAE = Common Terminology Criteria for Adverse Events; N/n = Number
Multiple entries per patient possible.

8.6.3.5 Adverse Events Not Related to Herceptin Treatment (Onset of AEs Before 10 April 2014) – CTCAE Grade 3/4 (Preferred Terms)

Overall, 19 (8.8%) patients were reported with AEs of CTCAE grade 3/4 assessed as not related to Herceptin (38 cases) and with onset of the AEs before 10 April 2014 (Table 8-99). The most commonly reported (≥2 patients) AEs were leukopenia (n=4; 1.9%), nausea (n=3; 1.4%), dyspnea (n=2; 0.9%), gastrointestinal pain (n=2; 0.9%), urinary tract infection (n=2; 0.9%) and vomiting (n=2; 0.9%).

Table 8-99 CTCAE grade 3/4 adverse events (AEs) not related to Herceptin (onset of the AEs before 10 April 2014) – preferred terms (AP)

	N Patients	% Patients	N Cases
Total number of patients, N	*216*	*100*	
Patients with any AE (CTCAE grade 3/4), n, %, n (cases)	19	8.8	38
Gastrointestinal disorders, n, %, n (cases)			
Nausea	3	1.4	3
Gastrointestinal pain	2	0.9	2
Vomiting	2	0.9	2

	N Patients	% Patients	N Cases
Abdominal pain	1	0.5	1
Gastritis hemorrhagic	1	0.5	1
Colitis	1	0.5	1
Ileus	1	0.5	1
Blood and lymphatic system disorders, n, %, n (cases)			
Leukopenia	4	1.9	11
Anemia	1	0.5	1
Neutropenia	1	0.5	1
General disorders and administration site conditions, n, %, n (cases)			
Ulcer hemorrhage	1	0.5	1
Breast complication associated with device	1	0.5	1
General physical health deterioration	1	0.5	1
Asthenia	1	0.5	1
Infections and infestations, n, %, n (cases)			
Urinary tract infection	2	0.9	2
Appendicitis perforated	1	0.5	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps), n, %, n (cases)			
Metastases to central nervous system	1	0.5	1
Malignant neoplasm progression	1	0.5	1
Metastasis	1	0.5	1
Respiratory, thoracic and mediastinal disorders, n, %, n (cases)			
Dyspnea	2	0.9	2
Musculoskeletal and connective tissue disorders, n, %, n (cases)			
Bone pain	1	0.5	1
Skin and subcutaneous tissue disorders, n, %, n (cases)			
Palmar-plantar erythrodysaesthesia syndrome	1	0.5	1

[Source: Herceptin_Abschlussanalyse_Tables; Table 16.13].
AE = Adverse event; AP = Analysis population; CTCAE = Common Terminology Criteria for Adverse Events; N/n = Number
Multiple entries per patient possible.

8.6.3.6 Adverse Events Not Related to Herceptin Treatment (Onset of AEs Before 10 April 2014) – CTCAE Grade 5 (Preferred Terms)

In total, 8 (3.7%) patients were reported with SAEs of CTCAE grade 5 (fatal outcome) assessed as not related to Herceptin (8 cases) and with onset of the SAEs before 10 April 2014 (Table 8-100). The documented fatal SAEs were general physical health deterioration (n=3; 1.4%), death (n=2; 0.9%), dyspnea (n=1; 0.5%), malignant neoplasm

progression (n=1; 0.5%), and toxic epidermal necrolysis (n=1; 0.5%). Please refer to section 8.1.6.1 for narratives of respective death cases.

Table 8-100 CTCAE grade 5 serious adverse events (SAEs) not related to Herceptin (onset of the AEs before 10 April 2014) – preferred terms (AP)

	N Patients	% Patients	N Cases
Total number of patients, N	*216*	*100*	
Patients with any fatal SAE (CTCAE grade 5)[1], n, %, n (cases)	8	3.7	8
General disorders and administration site conditions, n, %, n (cases)			
General physical health deterioration	3	1.4	3
Death	2	0.9	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps), n, %, n (cases)			
Malignant neoplasm progression	1	0.5	1
Respiratory, thoracic and mediastinal disorders, n, %, n (cases)			
Dyspnea	1	0.5	1
Skin and subcutaneous tissue disorders, n, %, n (cases)			
Toxic epidermal necrolysis	1	0.5	1

[Source: Herceptin_Abschlussanalyse_Tables; Table 16.12].
AP = Analysis population; CTCAE = Common Terminology Criteria for Adverse Events;
N/n = Number; SAE = Serious adverse event
Multiple entries per patient possible.
[1]The 8 fatal SAEs corresponded to the following patients: death (n=2; pat IDs 407001 and 859001); dyspnea (n=1; pat ID 223001); general physical health deterioration (n=3; pat IDs 659006, 701002 and 973004); malignant neoplasm progression (n=1; pat ID 888002); toxic epidermal necrolysis (n=1; pat ID 860001) [Patient Listing 23.2]. However, for pat IDs 223001, 659006, 701002, 860001 and 973004, the reported cause of death was neoplastic disease.

8.6.3.7 Adverse Events Not Related to Herceptin Treatment Leading to Discontinuation of Herceptin Re-Therapy (Onset of AEs Before 10 April 2014) – Preferred Terms

Overall, 9 (4.2%) patients were documented with AEs leading to discontinuation of Herceptin re-therapy (9 cases), which were assessed as not related to Herceptin and with onset of the AEs before 10 April 2014 (Table 8-101). The reported AEs were general physical health deterioration (n=3; 1.4%), dyspnea (n=2; 0.9%), death (n=1; 0.5%), dizziness (n=1; 0.5%), ileus (n=1; 0.5%) and malignant neoplasm progression (n=1; 0.5%).

Table 8-101 Adverse events (AEs) not related to Herceptin (onset of the AEs before 10 April 2014) leading to discontinuation of Herceptin re-therapy – preferred terms (AP)

	N Patients	% Patients	N Cases
Total number of patients, N	*216*	*100*	
Patients with any AE leading to discontinuation of Herceptin re-therapy, n, %, n (cases)	9	4.2	9
General disorders and administration site conditions, n, %, n (cases)			
General physical health deterioration	3	1.4	3
Death	1	0.5	1
Respiratory, thoracic and mediastinal disorders, n, %, n (cases)			
Dyspnea	2	0.9	2
Gastrointestinal disorders, n, %, n (cases)			
Ileus	1	0.5	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps), n, %, n (cases)			
Malignant neoplasm progression	1	0.5	1
Nervous system disorders, n, %, n (cases)			
Dizziness	1	0.5	1

[Source: Herceptin_Abschlussanalyse_Tables; Table 16.14].
AE = Adverse event; AP = Analysis population; CTCAE = Common Terminology Criteria for Adverse Events; N/n = Number
Multiple entries per patient possible.

8.6.4 Adverse Events Not Related to Herceptin Treatment (Onset of AEs on or After 10 April 2014) – Preferred Terms

In total, 3 (1.4%) patients were reported with AEs assessed as not related to Herceptin (5 cases) and with onset of AEs on or after 10 April 2014 (Table 8-102). The documented AEs were arthralgia, blood creatinine increased, bone pain, osteonecrosis and syncope (all CTCAE grade 2, n=1; 0.5%).

There were neither patients reported with non-related AEs of CTCAE grade 1/3/4/5 nor patients with non-related AEs leading to discontinuation of Herceptin re-therapy where the AE had started on or after 10 April 2014 (Table 8-93).

Table 8-102 Adverse events (AEs) not related to Herceptin (onset of the AEs on or after 10 April 2014) – preferred terms (AP)

	N Patients	% Patients	N Cases
Total number of patients, N	*216*	*100*	
Patients with any AE (all CTCAE grade 2), n, %, n (cases)	3	1.4	5
Musculoskeletal and connective tissue disorders, n, %, n (cases)			
Osteonecrosis	1	0.5	1
Bone pain	1	0.5	1
Arthralgia	1	0.5	1
Investigations, n, %, n (cases)			
Blood creatinine increased	1	0.5	1
Nervous system disorders, n, %, n (cases)			
Syncope	1	0.5	1

[Source: Herceptin_Abschlussanalyse_Tables; Table 16.3, Table 16.16].
AE = Adverse event; AP = Analysis population; CTCAE = Common Terminology Criteria for Adverse Events; N/n = Number
Multiple entries per patient possible.

8.6.5 Adverse Drug Reactions (Preferred Terms)

Adverse drug reactions were continuously monitored throughout the entire observational period of this NIS including the 90-day safety follow-up period, whereas the not-related events followed a different documentation requirement. In total, 52 (24.1%) patients were documented with ADRs of any CTCAE grade (186 cases; Table 8-103). The most frequently reported (>2% of patients) ADRs were headache (n=8; 3.7%), chills (n=7; 3.2%), diarrhea (n=7; 3.2%), nausea (n=7; 3.2%), bone pain (n=6; 2.8%), dyspnea (n=6; 2.8%), peripheral neuropathy (n=6; 2.8%), decreased ejection fraction (n=5; 2.3%) and dizziness (n=5; 2.3%).

Table 8-103 Adverse drug reactions (ADRs) – preferred terms (AP)

	N Patients	% Patients	N Cases
Total number of patients, N	*216*	*100*	
Patients with any ADR (any CTCAE grade), n, %, n (cases)	52	24.1	186
General disorders and administration site conditions, n, %, n (cases)			
Chills	7	3.2	7
Fatigue	4	1.9	4
Pain	3	1.4	3
Peripheral edema	2	0.9	2

	N Patients	% Patients	N Cases
Edema	2	0.9	3
Mucosal inflammation	1	0.5	1
Multiple organ dysfunction syndrome	1	0.5	1
Mucosal dryness	1	0.5	1
Chest pain	1	0.5	3
Pyrexia	1	0.5	1
General physical health deterioration	1	0.5	1
Nervous system disorders, n, %, n (cases)			
Headache	8	3.7	11
Peripheral neuropathy	6	2.8	6
Dizziness	5	2.3	6
Lethargy	2	0.9	6
Polyneuropathy	1	0.5	1
Paraesthesia	1	0.5	1
Attention deficit	1	0.5	1
Dysgeusia	1	0.5	1
Gastrointestinal disorders, n, %, n (cases)			
Nausea	7	3.2	8
Diarrhea	7	3.2	11
Vomiting	3	1.4	3
Stomatitis	3	1.4	3
Constipation	2	0.9	4
Upper abdominal pain	2	0.9	2
Lower abdominal pain	1	0.5	1
Gastritis	1	0.5	1
Melaena	1	0.5	1
Musculoskeletal and connective tissue disorders, n, %, n (cases)			
Bone pain	6	2.8	6
Musculoskeletal pain	3	1.4	3
Myalgia	2	0.9	2
Arthralgia	2	0.9	2
Back pain	2	0.9	3
Muscle spasms	2	0.9	2
Skin and subcutaneous tissue disorders, n, %, n (cases)			
Rash	4	1.9	5
Erythema	2	0.9	3
Nail disorder	2	0.9	2
Hyperhidrosis	1	0.5	1

	N Patients	% Patients	N Cases
Alopecia	1	0.5	1
Palmar-plantar erythrodysaesthesia syndrome	1	0.5	1
Pruritus	1	0.5	1
Cardiac disorders, n, %, n (cases)			
Left ventricular dysfunction	2	0.9	2
Congestive cardiac failure	2	0.9	2
Ventricular dysfunction	1	0.5	1
Left ventricular failure	1	0.5	1
Pericardial effusion	1	0.5	1
Mitral valve incompetence	1	0.5	1
Palpitations	1	0.5	1
Respiratory, thoracic and mediastinal disorders, n, %, n (cases)			
Dyspnea	6	2.8	8
Pleural effusion	2	0.9	2
Cough	2	0.9	2
Pulmonary embolism	1	0.5	1
Investigations, n, %, n (cases)			
Decreased ejection fraction	5	2.3	5
Weight loss	2	0.9	2
Weight gain	1	0.5	1
Infections and infestations, n, %, n (cases)			
Upper respiratory tract infection	2	0.9	2
Bronchitis	2	0.9	2
Laryngitis	1	0.5	1
Pharyngitis	1	0.5	1
Pneumonia	1	0.5	1
Vascular disorders, n, %, n (cases)			
Lymphoedema	2	0.9	2
Hypotension	1	0.5	1
Hypertension	1	0.5	1
Hot flush	1	0.5	1
Blood and lymphatic system disorders, n, %, n (cases)			
Anemia	3	1.4	3
Thrombocytopenia	1	0.5	1
Leukopenia	1	0.5	1
Febrile neutropenia	1	0.5	1
Psychiatric disorders, n, %, n (cases)			
Insomnia	2	0.9	2

	N Patients	% Patients	N Cases
Sleep disorder	1	0.5	1
Ear and labyrinth disorders, n, %, n (cases)			
Vestibular disorder	1	0.5	1
Eye disorders, n, %, n (cases)			
Blindness	1	0.5	1
Immune system disorders, n, %, n (cases)			
Anaphylactic reaction	1	0.5	1
Metabolism and nutrition disorders, n, %, n (cases)			
Hyperglycaemia	1	0.5	2
Benign, malignant and unspecified neoplasms (incl. cysts and polyps), n, %, n (cases)			
Skin metastases	1	0.5	1
Pregnancy, puerperium and perinatal conditions, n, %, n (cases)			
Oligohydramnios	1	0.5	1
Renal and urinary disorders, n, %, n (cases)			
Pollakisuria [sic]	1	0.5	1
Surgical and medical procedures, n, %, n (cases)			
Gastrointestinal ulcer prevention	1	0.5	1

[Source: Herceptin_Abschlussanalyse_Tables; Table 16.4].
ADR = Adverse drug reaction; AP = Analysis population; CTCAE = Common Terminology Criteria for Adverse Events; N/n = Number
Multiple entries per patient possible.

ADRs of CTCAE grade 1/2/3/5 are detailed in the following sections. There were no patients reported with ADRs of CTCAE grade 4 (Table 8-93).

8.6.5.1 Adverse Drug Reactions – CTCAE Grade 1 (Preferred Terms)

Overall, 24 (11.1%) patients were documented with ADRs of CTCAE grade 1 (66 cases; Table 8-104). The most common ADRs (≥2 patients) were headache (n=5; 2.3%), diarrhea (n=4; 1.9%), fatigue (n=3; 1.4%), nausea (n=3; 1.4%), peripheral neuropathy (n=3; 1.4%), rash (n=3; 1.4%), vomiting (n=3; 1.4%), dyspnea (n=2; 0.9%), erythema (n=2; 0.9%) and stomatitis (n=2; 0.9%).

Table 8-104 CTCAE grade 1 adverse drug reactions (ADRs) – preferred terms (AP)

	N Patients	% Patients	N Cases
Total number of patients, N	*216*	*100*	
Patients with any ADR (CTCAE grade 1), n, %, n (cases)	24	11.1	66
Gastrointestinal disorders, n, %, n (cases)			

	N Patients	% Patients	N Cases
Diarrhea	4	1.9	8
Nausea	3	1.4	3
Vomiting	3	1.4	3
Stomatitis	2	0.9	2
Constipation	1	0.5	1
Gastritis	1	0.5	1
Nervous system disorders, n, %, n (cases)			
Headache	5	2.3	6
Peripheral neuropathy	3	1.4	3
Polyneuropathy	1	0.5	1
Dizziness	1	0.5	1
Lethargy	1	0.5	3
Dysgeusia	1	0.5	1
General disorders and administration site conditions, n, %, n (cases)			
Fatigue	3	1.4	3
Pain	1	0.5	1
Mucosal inflammation	1	0.5	1
Chills	1	0.5	1
Peripheral edema	1	0.5	1
Pyrexia	1	0.5	1
Skin and subcutaneous tissue disorders, n, %, n (cases)			
Rash	3	1.4	4
Erythema	2	0.9	3
Nail disorder	1	0.5	1
Alopecia	1	0.5	1
Musculoskeletal and connective tissue disorders, n, %, n (cases)			
Myalgia	1	0.5	1
Bone pain	1	0.5	1
Musculoskeletal pain	1	0.5	1
Blood and lymphatic system disorders, n, %, n (cases)			
Anemia	1	0.5	1
Thrombocytopenia	1	0.5	1
Cardiac disorders, n, %, n (cases)			
Congestive cardiac failure	1	0.5	1
Pericardial effusion	1	0.5	1
Investigations, n, %, n (cases)			
Weight loss	1	0.5	1
Weight gain	1	0.5	1

	N Patients	% Patients	N Cases
Respiratory, thoracic and mediastinal disorders, n, %, n (cases)			
Dyspnea	2	0.9	2
Eye disorders, n, %, n (cases)			
Blindness	1	0.5	1
Infections and infestations, n, %, n (cases)			
Upper respiratory tract infection	1	0.5	1
Metabolism and nutrition disorders, n, %, n (cases)			
Hyperglycaemia	1	0.5	1
Renal and urinary disorders, n, %, n (cases)			
Pollakisuria [sic]	1	0.5	1
Vascular disorders, n, %, n (cases)			
Hypertension	1	0.5	1

[Source: Herceptin_Abschlussanalyse_Tables; Table 16.22].
ADR = Adverse drug reaction; AP = Analysis population; CTCAE = Common Terminology Criteria for Adverse Events; N/n = Number
Multiple entries per patient possible.

8.6.5.2 Adverse Drug Reactions – CTCAE Grade 2 (Preferred Terms)

Overall, 35 (16.2%) patients were reported with ADRs of CTCAE grade 2 (89 cases; Table 8-105). The most frequent ADRs (≥2 patients) were bone pain (n=4; 1.9%), decreased ejection fraction (n=4; 1.9%), dizziness (n=4; 1.9%), nausea (n=4; 1.9%), chills (n=3; 1.4%), diarrhea (n=3; 1.4%), dyspnea (n=3; 1.4%), peripheral neuropathy (n=3; 1.4%), arthralgia (n=2; 0.9%), back pain (n=2; 0.9%), cough (n=2; 0.9%), edema (n=2; 0.9%), headache (n=2; 0.9%), insomnia (n=2; 0.9%), lymphoedema (n=2; 0.9%), muscle spasms (n=2; 0.9%), musculoskeletal pain (n=2; 0.9%), pain (n=2; 0.9%), upper abdominal pain (n=2; 0.9%).

Table 8-105 CTCAE grade 2 adverse drug reactions (ADRs) – preferred terms (AP)

	N Patients	% Patients	N Cases
Total number of patients, N	*216*	*100*	
Patients with any ADR (CTCAE grade 2), n, %, n (cases)	35	16.2	89
General disorders and administration site conditions, n, %, n (cases)			
Chills	3	1.4	3
Edema	2	0.9	3
Pain	2	0.9	2
Fatigue	1	0.5	1

	N Patients	% Patients	N Cases
Peripheral edema	1	0.5	1
Mucosal dryness	1	0.5	1
Chest pain	1	0.5	3
Musculoskeletal and connective tissue disorders, n, %, n (cases)			
Bone pain	4	1.9	4
Arthralgia	2	0.9	2
Back pain	2	0.9	3
Musculoskeletal pain	2	0.9	2
Muscle spasms	2	0.9	2
Myalgia	1	0.5	1
Nervous system disorders, n, %, n (cases)			
Dizziness	4	1.9	5
Peripheral neuropathy	3	1.4	3
Headache	2	0.9	3
Paraesthesia	1	0.5	1
Attention deficit	1	0.5	1
Lethargy	1	0.5	1
Gastrointestinal disorders, n, %, n (cases)			
Nausea	4	1.9	5
Diarrhea	3	1.4	3
Upper abdominal pain	2	0.9	2
Lower abdominal pain	1	0.5	1
Constipation	1	0.5	2
Melaena	1	0.5	1
Respiratory, thoracic and mediastinal disorders, n, %, n (cases)			
Dyspnea	3	1.4	5
Cough	2	0.9	2
Pleural effusion	1	0.5	1
Investigations, n, %, n (cases)			
Decreased ejection fraction	4	1.9	4
Skin and subcutaneous tissue disorders, n, %, n (cases)			
Hyperhidrosis	1	0.5	1
Rash	1	0.5	1
Palmar-plantar erythrodysaesthesia syndrome	1	0.5	1
Pruritus	1	0.5	1
Blood and lymphatic system disorders, n, %, n (cases)			
Anemia	1	0.5	1
Leukopenia	1	0.5	1

	N Patients	% Patients	N Cases
Febrile neutropenia	1	0.5	1
Cardiac disorders, n, %, n (cases)			
Congestive cardiac failure	1	0.5	1
Mitral valve incompetence	1	0.5	1
Palpitations	1	0.5	1
Infections and infestations, n, %, n (cases)			
Upper respiratory tract infection	1	0.5	1
Laryngitis	1	0.5	1
Bronchitis	1	0.5	1
Psychiatric disorders, n, %, n (cases)			
Insomnia	2	0.9	2
Sleep disorder	1	0.5	1
Vascular disorders, n, %, n (cases)			
Lymphoedema	2	0.9	2
Hypotension	1	0.5	1
Metabolism and nutrition disorders, n, %, n (cases)			
Hyperglycaemia	1	0.5	1
Surgical and medical procedures, n, %, n (cases)			
Gastrointestinal ulcer prevention	1	0.5	1

[Source: Herceptin_Abschlussanalyse_Tables; Table 16.23].
ADR = Adverse drug reaction; AP = Analysis population; CTCAE = Common Terminology Criteria for Adverse Events; N/n = Number
Multiple entries per patient possible.

8.6.5.3 Adverse Drug Reactions – CTCAE Grade 3 (Preferred Terms)

In total, 18 (8.3%) patients were reported with ADRs of CTCAE grade 3 (24 cases; Table 8-106). The most frequently reported ADRs (≥2 patients) were chills (n=3; 1.4%), headache (n=2; 0.9%) and left ventricular dysfunction (n=2; 0.9%).

Table 8-106 CTCAE grade 3 adverse drug reactions (ADR) – preferred terms (AP)

	N Patients	% Patients	N Cases
Total number of patients, N	*216*	*100*	
Patients with any ADR (CTCAE grade 3), n, %, n (cases)	18	8.3	24
Cardiac disorders, n, %, n (cases)			
Left ventricular dysfunction	2	0.9	2
Ventricular dysfunction	1	0.5	1
Left ventricular failure	1	0.5	1

	N Patients	% Patients	N Cases
General disorders and administration site conditions, n, %, n (cases)			
Chills	3	1.4	3
Nervous system disorders, n, %, n (cases)			
Headache	2	0.9	2
Lethargy	1	0.5	2
Gastrointestinal disorders, n, %, n (cases)			
Constipation	1	0.5	1
Stomatitis	1	0.5	1
Infections and infestations, n, %, n (cases)			
Bronchitis	1	0.5	1
Pharyngitis	1	0.5	1
Respiratory, thoracic and mediastinal disorders, n, %, n (cases)			
Dyspnea	1	0.5	1
Pulmonary embolism	1	0.5	1
Blood and lymphatic system disorders, n, %, n (cases)			
Anemia	1	0.5	1
Ear and labyrinth disorders, n, %, n (cases)			
Vestibular disorder	1	0.5	1
Immune system disorders, n, %, n (cases)			
Anaphylactic reaction	1	0.5	1
Musculoskeletal and connective tissue disorders, n, %, n (cases)			
Bone pain	1	0.5	1
Pregnancy, puerperium and perinatal conditions, n, %, n (cases)			
Oligohydramnios	1	0.5	1
Skin and subcutaneous tissue disorders, n, %, n (cases)			
Nail disorder	1	0.5	1
Vascular disorders, n, %, n (cases)			
Hot flush	1	0.5	1

[Source: Herceptin_Abschlussanalyse_Tables; Table 16.24].
ADR = Adverse drug reaction; AP = Analysis population; CTCAE = Common Terminology Criteria for Adverse Events; N/n = Number
Multiple entries per patient possible.

8.6.5.4 Adverse Drug Reactions – CTCAE Grade 5 (Preferred Terms)

In total, 2 (0.9%) patients were reported with SADRs of CTCAE grade 5 (fatal outcome; 4 cases) as displayed in Table 8-107. The documented fatal SADRs were general physical health deterioration, multiple organ dysfunction syndrome, pleural effusion and pneumonia.

Please refer to section 8.1.6.1 for narratives of respective death case.

Table 8-107 CTCAE grade 5 serious adverse drug reactions (SADRs) – preferred terms (AP)

	N Patients	% Patients	N Cases
Total number of patients, N	*216*	*100*	
Patients with any fatal SADR (CTCAE grade 5)[1], n, %, n (cases)	2	0.9	4
General disorders and administration site conditions, n, %, n (cases)			
Multiple organ dysfunction syndrome	1	0.5	1
General physical health deterioration	1	0.5	1
Infections and infestations, n, %, n (cases)			
Pneumonia	1	0.5	1
Respiratory, thoracic and mediastinal disorders, n, %, n (cases)			
Pleural effusion	1	0.5	1

[Source: Herceptin_Abschlussanalyse_Tables; Table 16.26].
AP = Analysis population; CTCAE = Common Terminology Criteria for Adverse Events;
N/n = Number; SADR = Serious adverse drug reaction
Multiple entries per patient possible
[1]The 4 fatal SADR cases corresponded to the following patients: general physical health deterioration, pleural effusion and pneumonia (all 3 related, fatal events were reported for pat ID 223001); multiple organ dysfunction syndrome (pat ID 507005) [Patient Listing 23.2]. Patient 223001 was also documented with a non-related fatal SAE (dyspnea) (Table 8-100). However, for pat IDs 223001 and 507005, the reported cause of death was neoplastic disease.

8.6.5.5 Adverse Drug Reactions Leading to Discontinuation of Herceptin Re-Therapy (Preferred Terms)

In total, 10 (4.6%) patients were documented with ADRs that led to discontinuation of Herceptin re-therapy (14 cases; Table 8-108). The most common ADRs were decreased ejection fraction and pleural effusion (2 patients each; 0.9%).

Table 8-108 Adverse drug reactions (ADRs) leading to discontinuation of Herceptin re-therapy – preferred terms (AP)

	N Patients	% Patients	N Cases
Total number of patients, N	*216*	*100*	
Patients with any ADR leading to discontinuation of Herceptin re-therapy, n, %, n (cases)	10	4.6	14
Respiratory, thoracic and mediastinal disorders, n, %, n (cases)			
Pleural effusion	2	0.9	2
Dyspnea	1	0.5	1
Cardiac disorders, n, %, n (cases)			
Left ventricular failure	1	0.5	1
Mitral valve incompetence	1	0.5	1

	N Patients	% Patients	N Cases
General disorders and administration site conditions, n, %, n (cases)			
Multiple organ dysfunction syndrome	1	0.5	1
General physical health deterioration	1	0.5	1
Investigations, n, %, n (cases)			
Decreased ejection fraction	2	0.9	2
Gastrointestinal disorders, n, %, n (cases)			
Melaena	1	0.5	1
Infections and infestations, n, %, n (cases)			
Pneumonia	1	0.5	1
Nervous system disorders, n, %, n (cases)			
Attention deficit	1	0.5	1
Pregnancy, puerperium and perinatal conditions, n, %, n (cases)			
Oligohydramnios	1	0.5	1
Vascular disorders, n, %, n (cases)			
Hypotension	1	0.5	1

[Source: Herceptin_Abschlussanalyse_Tables; Table 16.28].
ADR = Adverse drug reaction; AP = Analysis population; N/n = Number
Multiple entries per patient possible

8.6.6 Serious Adverse Events Not Related to Herceptin Treatment (Onset of SAEs Before 10 April 2014) – Preferred Terms

In total, 22 (10.2%) patients were reported with SAEs assessed as not related to Herceptin and with onset of SAEs before 10 April 2014 (37 cases;

Table 8-109). The most frequently reported SAEs (≥2 patients) were general physical health deterioration (n=5; 2.3%), dyspnea (n=4; 1.9%), malignant neoplasm progression (n=3; 1.4%), nausea (n=3; 1.4%), death (n=2; 0.9%) and vomiting (n=2; 0.9%).

Table 8-109 Serious adverse events (SAEs) not related to Herceptin (onset of SAEs before 10 April 2014) – preferred terms (AP)

	N Patients	% Patients	N Cases
Total number of patients, N	*216*	*100*	
Patients with any SAE, n, %, n (cases)	22	10.2	37
General disorders and administration site conditions, n, %, n (cases)			
General physical health deterioration	5	2.3	5
Death	2	0.9	2
Ulcer hemorrhage	1	0.5	1
Asthenia	1	0.5	1
Gastrointestinal disorders, n, %, n (cases)			
Nausea	3	1.4	3
Vomiting	2	0.9	2
Abdominal pain	1	0.5	1
Gastritis hemorrhagic	1	0.5	1
Colitis	1	0.5	1
Gastrointestinal pain	1	0.5	1
Ileus	1	0.5	1
Respiratory, thoracic and mediastinal disorders, n, %, n (cases)			
Dyspnea	4	1.9	4
Bronchial hemorrhage	1	0.5	1
Infections and infestations, n, %, n (cases)			
Urinary tract infection	1	0.5	1
Pneumonia	1	0.5	1
Appendicitis perforated	1	0.5	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps), n, %, n (cases)			
Malignant neoplasm progression	3	1.4	3
Metastases to central nervous system	1	0.5	1
Injury, poisoning and procedural complications, n, %, n (cases)			
Femoral neck fracture	1	0.5	1
Investigations, n, %, n (cases)			
C-reactive protein increased	1	0.5	1
Metabolism and nutrition disorders, n, %, n (cases)			
Hyperglycaemia	1	0.5	1
Renal and urinary disorders, n, %, n (cases)			
Renal failure	1	0.5	1
Skin and subcutaneous tissue disorders, n, %, n (cases)			
Toxic epidermal necrolysis	1	0.5	1
Vascular disorders, n, %, n (cases)			

	N Patients	% Patients	N Cases
Thrombosis	1	0.5	1

[Source: Herceptin_Abschlussanalyse_Tables; Table 16.5].
AP = Analysis population; N/n = Number; SAE = Serious adverse event
Multiple entries per patient possible

There were no patients reported with SAEs assessed as not related to Herceptin where the onset of SAEs was on or after 10 April 2014 (Table 8-93).

8.6.7 Serious Adverse Drug Reactions

In total, 17 (7.9%) patients were reported with SADRs (27 cases; Table 8-110). The most frequent SADRs (>1 patient) were decreased ejection fraction (n=4; 1.9%) and dyspnea (n=3; 1.4%).

Table 8-110 Serious adverse drug reactions (SADRs) – preferred terms (AP)

	N Patients	% Patients	N Cases
Total number of patients, N	*216*	*100*	
Patients with any SADR, n, %, n (cases)	17	7.9	27
Cardiac disorders, n, %, n (cases)			
Left ventricular dysfunction	1	0.5	1
Congestive cardiac failure	1	0.5	1
Ventricular dysfunction	1	0.5	1
Pericardial effusion	1	0.5	1
Mitral valve incompetence	1	0.5	1
Investigations, n, %, n (cases)			
Decreased ejection fraction	4	1.9	4
Respiratory, thoracic and mediastinal disorders, n, %, n (cases)			
Dyspnea	3	1.4	4
Pulmonary embolism	1	0.5	1
Pleural effusion	1	0.5	1
General disorders and administration site conditions, n, %, n (cases)			
Chills	1	0.5	1
Multiple organ dysfunction syndrome	1	0.5	1
General physical health deterioration	1	0.5	1
Gastrointestinal disorders, n, %, n (cases)			
Nausea	1	0.5	1
Stomatitis	1	0.5	1
Infections and infestations, n, %, n (cases)			

	N Patients	% Patients	N Cases
Bronchitis	1	0.5	1
Pneumonia	1	0.5	1
Blood and lymphatic system disorders, n, %, n (cases)			
Febrile neutropenia	1	0.5	1
Ear and labyrinth disorders, n, %, n (cases)			
Vestibular disorder	1	0.5	1
Immune system disorders, n, %, n (cases)			
Anaphylactic reaction	1	0.5	1
Nervous system disorders, n, %, n (cases)			
Attention deficit	1	0.5	1
Vascular disorders, n, %, n (cases)			
Hypotension	1	0.5	1

[Source: Herceptin_Abschlussanalyse_Tables; Table 16.7].
AP = Analysis population; N/n = Number; SADR = Serious adverse drug reaction.
Multiple entries per patient possible

9. DISCUSSION

9.1 KEY RESULTS

This NIS evaluated the effectiveness and safety of re-therapy with Herceptin in routine clinical practice in patients with HER2-positive BC having relapsed following completed (neo-) adjuvant anti-HER2-therapy with Herceptin for HER2-positive EBC. The report includes data from 216 patients (APand 49 patients (SmPC-population).

In the AP, the median age of patients at time of initiation of Herceptin re-therapy was 56.1 years. All patients had HER2-positive BC, whereas HR-positive tumors were reported in 54.6% of patients. Most patients were reported with invasive ductal carcinoma (88.0%) and tumors of grade G3 (59.3%). In total, 79 (36.6%) patients were documented with local recurrence. Distant metastases were documented in 173 (80.1%) patients with bone (35.6%), liver (31.0%) and lung (23.6%) being the most frequent metastatic sites. At least one comorbidity was documented in 50% of patients.

9.1.1 Observational Period

- Estimated median observational period (AP): 59.3 months (95% CI: 57.3 – 59.9).
- Events: n=82 (38.0%).

9.1.2 Disease-Free Survival (Effectiveness of Prior (Neo-) Adjuvant Anti-HER2 Therapy)

AP (N=216)	N	Median	Min	Max
Disease-free survival (months)				
Total	214	36.5	8.0	135.1
Anthracycline	45	39.7	8.0	96.7
Taxane	13	28.6	15.4	46.3
Anthracycline and taxane	145	36.3	8.1	135.1
Other chemotherapy	2	30.0	21.7	38.3
No (neo-) adjuvant chemotherapy	9	32.2	24.3	42.2

AP = Analysis population; Min = Minimum; Max = Maximum; N = Number
Anthracycline: Patients receiving an anthracycline-based regimen in combination with adjuvant Herceptin therapy (but no taxanes)
Taxane: Patients receiving a taxane-based regimen in combination with adjuvant Herceptin therapy (but no anthracyclines)
Anthracycline and Taxane: Patients receiving anthracycline and taxane-based regimen in combination with adjuvant Herceptin therapy

9.1.3 Herceptin Re-Therapy

	AP (N=216)
Deciding factors for choice of Herceptin re-therapy[1] (>30% of patients), n (%)	
HER2-status	202 (93.5)
Efficacy of (neo-) adjuvant anti-HER2 therapy	102 (47.2)
Tolerability of (neo-) adjuvant anti-HER2 therapy	100 (46.3)
Study results/publications	94 (43.5)
Patient's performance status	73 (33.8)
Median time span between end of adjuvant anti-HER2 treatment and onset of Herceptin re-therapy (months) [min – max]	21.1 months [0.6 – 98.3]
Initial dose of Herceptin re-therapy n (%)	
8 mg/kg	111 (51.4)
4 mg/kg	76 (35.2)
Other dose	29 (13.4)
Median duration of Herceptin re-therapy (months) [min – max]	9.0 months [0.0- 74.7]
Modification of Herceptin re-therapy, n (%)	
Patients with ≥1 therapy modification	82 (38.0)
Type of modification of Herceptin re-therapy[1], n (%)	
≥1 dose modification	57 (26.4)
≥1 therapy delay	25 (11.6)
≥1 therapy interruption	23 (10.6)
Reason for discontinuation of Herceptin re-therapy (>5% of patients), n (%)	

	AP (N=216)
Disease progression (recurrence/metastasis)	111 (51.4)
Patient death	22 (10.2)
Treating physician's decision	21 (9.7)
Patient's request	13 (6.0)

AP = Analysis population; HER2 = Human epidermal growth factor receptor 2; Min = Minimum; Max = Maximum; N/n = Number
[1]Multiple entries per patient possible.

9.1.4 Concomitant Treatments With Herceptin Re-Therapy

	AP (N=216)
Concomitant chemotherapy (N=145)	
Deciding factors for choice of concomitant chemotherapy[1] (>30% of patients), n (%)	
Guidelines	105 (48.6)
Patient's performance status	84 (38.9)
Study results/Publications	78 (36.1)
Patient age	71 (32.9)
Drugs used in the first line of concomitant chemotherapy with Herceptin re-therapy[1] (>10% of patients), n (%)	
Paclitaxel	53 (24.5)
Vinorelbine	40 (18.5)
Capecitabine	31 (14.4)
Docetaxel	23 (10.6)
Concomitant endocrine therapy (N=69)	
Drugs used in concomitant endocrine therapy with Herceptin re-therapy[1] (>5% of patients), n (%)	
Exemestane	19 (8.8)
Fulvestrant	18 (8.3)
Tamoxifen	18 (8.3)
Anastrozole	16 (7.4)
Letrozole	16 (7.4)

AP = Analysis population; N/n = Number
[1]Multiple entries per patient possible.

9.1.5 LVEF <50% During Study

	AP (N=216)
Number of patients with ≥1 documented post-baseline LVEF measurement, N (%)	129 (100)[1]
Lowest post-baseline LVEF <50%[2], n (%)	14 (10.9)
Lowest post-baseline LVEF ≥50%, n (%)	115 (89.1)

AP = Analysis population; LVEF = Left ventricular ejection fraction; N/n = Number
[1]This corresponds to 60% of the patients in the total AP, who were reported with post-baseline LVEF measurement following start of re-therapy with Herceptin.

[2]To be reported as an AE if the LVEF was <45% or in cases where the LVEF had dropped by >10% compared to baseline measurement. However, in cases where LVEF <45% or LVEF drop >10%, a corresponding AE had not been reported in all affected patients.

9.1.6 LVEF Decrease >10% Compared to Baseline

	AP (N=216)
Number of patients with a documented baseline LVEF measurement and ≥1 post-baseline LVEF measurement, N (%)	84 (100)[1]
LVEF nadir at least 10% lower than the baseline value, n (%)	30 (35.7)
Difference in LVEF nadir of less than 10% versus baseline (or nadir greater than baseline value), n (%)	54 (64.3)

AP = Analysis population; LVEF = Left ventricular ejection fraction; N/n = Number
[1]The analysis included data from patients with a documented baseline LVEF (4 weeks before or after initiation of re-therapy with Herceptin) and at least one post-baseline LVEF measurement over the course of the study.
The nadir was defined as the lowest post-baseline LVEF documented over the course of the study (including follow-up documentation and the period after discontinuation of Herceptin re-therapy). However, in cases where LVEF <45% or LVEF drop >10%, a corresponding AE had not been reported in all affected patients..

9.1.7 Effectiveness

9.1.7.1 Progression-Free Survival

	Total population (AP)	SmPC-population[1]
Total number of patients	*216*	*49*
Events, n (%)	166 (76.9)	45 (91.8)
Median PFS (months) [95% CI]	12.7 (10.5 - 14.8)	9.8 (7.9 - 12.7)
PFS rates (%) [95% CI]		
6-month	82.0% (76.1% - 86.5%)	77.6% (63.1% - 86.9%)
12-month	52.8% (45.7% - 59.4%)	38.3% (24.8% - 51.7%)

AP = Analysis population; CI = Confidence interval; n = Number; PFS = Progression-free survival; SmPC = Summary of Product Characteristics
[1]The SmPC-population was defined *post-hoc*.

9.1.7.1.1 Progression-Free Survival – Subgroup[1] "Metastases / Local Recurrence only"

	No metastases (local recurrence only)	Non-visceral	Visceral
Analysis population (AP): Total N=216			
Total number of patients (subgroups)[2], N	*43*	*61*	*110*
Events, n (%)	24 (55.8)	44 (72.1)	97 (88.2)
Median PFS (months) [95% CI]	26.1 (12.7 - NA)	16.3 (9.6 - 21.5)	10.2 (8.0 - 11.4)
SmPC-population[3]: Total N=49			
Total number of patients (subgroups), N	*6*	*8*	*35*
Events, n (%)	4 (66.7)	6 (75.0)	35 (100)
Median PFS (months) [95% CI]	36.9 (10.2 - NA)	17.5 (3.3 - 18.6)	7.9 (6.6 - 9.8)

AP = Analysis population; CI = Confidence interval; N/n = Number; NA = Not reached; PFS = Progression-free survival; SmPC = Summary of Product Characteristics

[1]Subgroups of patients with no metastases (local recurrence only), patients with non-visceral metastases (± local recurrence, no visceral metastases) and patients with visceral metastases (± non-visceral metastases ± local recurrence).
[2]The metastatic status of 2 patients could not be classified as only the free-text entries "secondary contralateral carcinoma" and "increased tumor marker" were recorded in the eCRF, respectively.
[3]The SmPC-population was defined *post-hoc*.

9.1.7.1.2 Progression-Free Survival – Subgroup[1] "Combination Therapy"

	Herceptin mono re-therapy	Taxanes	Endocrine therapy	Other CTx	CTx and endocrine therapy
Analysis population (AP): Total N=216 Total number of patients (subgroups)	*36*	*51*	*35*	*74*	*20*
Events, n (%)	22 (61.1)	49 (96.1)	26 (74.3)	56 (75.7)	13 (65.0)
Median PFS (months) [95% CI]	18.2 (10.4 - 35.0)	8.9[2] (7.2 - 10.3)	12.2 (8.3 - 27.3)	13.4 (10.2 - 16.6)	19.9 (12.7 - 54.6)

AP = Analysis population; CI = Confidence interval; CTx = Chemotherapy; N/n = Number; NA = Not reached; PFS = Progression-free survival;
[1]Subgroups of patients having received combination therapy with Herceptin re-therapy.
[2]70% patients with visceral metastases in this subgroup (taxanes) versus 60% in the "other CTx" subgroup.

9.1.7.1.3 Progression-Free Survival – Subgroup[1] "Chemotherapy"

	Taxane	Vinorelbine	Capecitabine
Analysis population (AP): Total N=216 *Total number of patients (subgroups), N*	*51*	*27*	*23*
Events, n (%)	49 (96.1)	18 (66.7)	16 (69.6)
Median PFS (months) [95% CI]	8.9 (7.2 - 10.3)[2]	12.1 (9.3 - 31.3)	12.5 (6.4 - 17.1)

AP = Analysis population; CI = Confidence interval; N/n = Number; PFS = Progression-free survival
[1]Subgroups of patients having received mono-chemotherapy (no endocrine therapy) in combination with Herceptin re-therapy.
[2]70% patients with visceral metastases in this subgroup (taxanes) versus 60% in the "other CTx" subgroup.

9.1.7.2 Overall Survival (OS)

	Total population (AP)	SmPC-population[1]
Total number of patients, N	*216*	*49*
Events, n (%)	134 (62.0)	37 (75.5)
Median OS (months) [95% CI]	77.3 (66.2 - 88.8)	76.4 (57.6 - 88.8)
OS rates (%) [95% CI]		
12-month	100.0% (100.0% - 100.0%)	100.0% (100.0% - 100.0%)
24-month	99.5% (96.7% - 99.9%)	100.0% (100.0% - 100.0%)
36-month	92.9% (88.5% - 95.7%)	91.7% (79.3% - 96.8%)
48-month	80.3% (74.3% - 85.1%)	81.2% (67.1% - 89.8%)

AP = Analysis population; CI = Confidence interval; N/n = Number; OS = Overall survival; SmPC = Summary of Product Characteristics
[1]The SmPC-population was defined *post-hoc*.

9.1.7.3 Overall Survival (OS-2)

	Total population (AP)	SmPC-population[1]
Total number of patients, N	*216*	*49*
Events, n (%)	134 (62.0)	37 (75.5)
Median OS-2 (months) [95% CI]	31.6 (28.8 - 38.4)	21.8 (15.0 - 36.1)
OS-2 rates (%) [95% CI]		
12-month	82.9% (77.1% - 87.4%)	73.4% (58.6% - 83.6%)
24-month	62.9% (55.9% - 69.2%)	48.9% (34.0% - 62.3%)
36-month	45.3% (38.2% - 52.0%)	37.8% (24.0% - 51.5%)
48-month	37.1% (30.4% - 43.9%)	26.7% (14.9% - 39.9%)

AP = Analysis population; CI = Confidence interval; N/n = Number; OS = Overall survival; SmPC = Summary of Product Characteristics
[1]The SmPC-population was defined *post-hoc*.

9.1.7.3.1 Overall Survival (OS-2) – Subgroup[1] "Metastases / Local Recurrence Only"

	No metastases (local recurrence only)	Non-visceral	Visceral
Analysis population (AP): Total N=216 *Total number of patients (subgroups)[2], N*	*43*	*61*	*110*
Events, n (%)	18 (41.9)	32 (52.5)	84 (76.4)
Median OS-2 (months) [95% CI]	NA	49.2 (33.1 - NA)	20.8 (17.3 - 28.8)
SmPC-population[3]: Total N=49 *Total number of patients (subgroups), N*	*6*	*8*	*35*
Events, n (%)	3 (50.0)	5 (62.5)	29 (82.9)
Median OS-2 (months) [95% CI]	NA	67.4 (15.6 - 98.6)	16.3 (9.0 - 27.6)

AP = Analysis population; CI = Confidence interval; N/n = Number; NA = Not reached; OS = Overall survival; SmPC = Summary of Product Characteristics
[1]Subgroups of patients with no metastases (local recurrence only), patients with non-visceral metastases (± local recurrence, no visceral metastases) and patients with visceral metastases (± non-visceral metastases ± local recurrence).
[2]The metastatic status of 2 patients could not be classified as only the free-text entries "secondary contralateral carcinoma" and "increased tumor marker" were recorded in the eCRF, respectively.
[3]The SmPC-population was defined *post-hoc*.

9.1.7.3.2 Overall Survival (OS-2) – Subgroup[1] "Combination Therapy"

	Herceptin mono re-therapy	Taxanes	Endocrine therapy	Other CTx	CTx and endocrine therapy
Analysis population (AP): Total N=216 *Total number of patients (subgroups)*	*36*	*51*	*35*	*74*	*20*
Events, n (%)	16 (44.4)	43 (84.3)	20 (57.1)	44 (59.5)	11 (55.0)
Median OS-2 (months) [95% CI]	58.7 (33.1 - NA)	18.5[2] (15.0 - 27.6)	36.1 (27.0 - NA)	29.6 (25.4 - 47.1)	57.6 (21.6 - NA)

AP = Analysis population; CI = Confidence interval; CTx = Chemotherapy; N/n = Number; NA = Not reached; OS = Overall survival;
[1]Subgroups of patients having received combination therapy with Herceptin re-therapy.

[2]70% patients with visceral metastases in this subgroup (taxanes) versus 60% in the "other CTx" subgroup.

9.1.7.3.3 Overall Survival (OS-2) – Subgroup[1] "Chemotherapy"

	Taxane	Vinorelbine	Capecitabine
Analysis population (AP): Total N=216 *Total number of patients (subgroups), N*	*51*	*27*	*23*
Events, n (%)	43 (84.3)	18 (66.7)	12 (52.2)

Median OS-2 (months) [95% CI]	18.5 (15.0 - 27.6)[2]	29.6 (17.3 - 49.2)	25.4 (11.1 - NA)

AP = Analysis population; CI = Confidence interval; N/n = Number; NA = Not reached; OS = Overall survival
[1]Subgroups of patients having received mono-chemotherapy (no endocrine therapy) in combination with Herceptin re-therapy.[2]70% patients with visceral metastases in this subgroup (taxanes) versus 60% in the "other CTx" subgroup.

9.1.7.4 Overall Response (ORR)

	Total population (AP)	SmPC-population[1]
Total number of patients, N	*216*	*49*
Best tumor response[2] (ORR), n (%)		
CR	20 (9.3)	6 (12.2)
PR	56 (25.9)	18 (36.7)
ORR	76 (35.2)	24 (49.0)

AP = Analysis population; CR = Complete remission; N/n = Number; ORR = Overall response rate; PR = Partial remission; SmPC = Summary of Product Characteristics
[1]The SmPC-population was defined *post-hoc*.
[2]As assessed by the respective treating physician. There were 41 (19.0%) patients with unknown tumor response (AP).

9.1.8 Safety

9.1.8.1 Discrepancy Between the Safety Database and Clinical Database (Annex 2)

- Altogether, 63 events were discrepant between SDB and CDB (64 differences in total).

- A causal relationship with Herceptin was reported for or assigned by sponsor in 26 of these 63 events.

- One death was reported in the CDB. The fatal SAE was assigned to pulmonary embolism (pat ID1004001. The cause of death was tumor progression). The sponsor assessed the event of pulmonary embolism as related to Herceptin. Pulmonary embolism is not a known side effect of Herceptin.

9.1.8.2 Number of Patients With (S)AEs

	Patients N (%)	Cases N
Total number of patients (AP), N	*216 (100)*	
Onset of the (S)AE before 10 April 2014 (not related to Herceptin treatment) n (%), n (cases)		
Patients reported with AEs of any CTCAE grade	48 (22.2%)	125
Patients reported with a SAE	22 (10.2%)	37
Patients reported with AEs of CTCAE grade 3/4	19 (8.8%)	38
Onset of the (S)AE on or after 10 April 2014 (not related to Herceptin treatment) n (%), n (cases)		
Patients reported with an AE (all AEs of CTCAE grade 2)	3 (1.4%)	5
Patients with a SAE	0	0

AE = Adverse event; AP = Analysis population; CTCAE = Common Terminology Criteria for Adverse Events; N/n = Number; SAE = Serious adverse event

9.1.8.3 Most Frequent (S)AEs

- Onset of the (S)AEs before 10 April 2014 (not related to Herceptin; retrospective documentation)

    - Most frequently reported AEs (>2% of patients): nausea (n=7; 3.2%), leukopenia (n=6; 2.8%), dyspnea (n=5; 2.3%), general physical health deterioration (n=5; 2.3%), and polyneuropathy (n=5; 2.3%).

    - Most commonly reported AEs of CTCAE grade 3/4 (≥2 patients): leukopenia (n=4; 1.9%), nausea (n=3; 1.4%), dyspnea (n=2; 0.9%),

gastrointestinal pain (n=2; 0.9%), urinary tract infection (n=2; 0.9%) and vomiting (n=2; 0.9%).

- Most frequently reported SAEs (≥2 patients): general physical health deterioration (n=5; 2.3%), dyspnea (n=4; 1.9%), malignant neoplasm progression (n=3; 1.4%), nausea (n=3; 1.4%), death (n=2; 0.9%) and vomiting (n=2; 0.9%).

- Onset of AEs on or after 10 April 2014 (not related to Herceptin)
  - The documented AEs were arthralgia, blood creatinine increased, bone pain, osteonecrosis and syncope (all CTCAE grade 2, n=1; 0.5%).

9.1.8.4 Number of Patients With (S)ADRs

	Patients N (%)	Cases N
Total number of patients (AP), N	*216 (100)*	
Patients reported with a (S)ADR, n (%), n (cases)		
Patients reported with an ADR	52 (24.1)	186
Patients reported with a SADR	17 (7.9)	27
Patients with ADRs of CTCAE grade 3	18 (8.3)	24
Patients with ADRs of CTCAE grade 4	0	0

ADR = Adverse drug reaction; AP = Analysis population; CTCAE = Common Terminology Criteria for Adverse Events; N/n = Number; SADR = Serious adverse drug reaction

9.1.8.5 Most Frequent (S)ADRs (continuously monitored)

- Most frequently reported ADRs (>2% of patients): headache (n=8; 3.7%), chills (n=7; 3.2%), diarrhea (n=7; 3.2%), nausea (n=7; 3.2%), bone pain (n=6; 2.8%), dyspnea (n=6; 2.8%), peripheral neuropathy (n=6; 2.8%), decreased ejection fraction (n=5; 2.3%) and dizziness (n=5; 2.3%).

- Most frequently reported ADRs of CTCAE grade 3 (≥2 patients): chills (n=3; 1.4%), headache (n=2; 0.9%) and left ventricular dysfunction (n=2; 0.9%).

- Most frequent SADRs (>1 patient): decreased ejection fraction (n=4; 1.9%) and dyspnea (n=3; 1.4%).

9.1.8.6 Pregnancy Cases

- In total, 2 patients were documented with a pregnancy during the entire study period.

- 1 of these patients was reported with oligohydramnios assessed as related to Herceptin treatment (ADR).

9.1.8.7 Death Cases and Fatal Serious Adverse Events

- 135 (62.5%) patients died in total during the whole study period

- 9 (4.2%) patients were reported with fatal SAEs and/or fatal SADR (patient 223001 was documented with both non-related and related fatal events)

    - 8 (3.7%) patients with fatal SAEs not related to Herceptin (8 cases): general physical health deterioration (n=3), death (n=2), dyspnea (n=1), malignant neoplasm progression (n=1), and toxic epidermal necrolysis (n=1).

    - 2 (0.9%) patients with fatal SADRs (4 cases): general physical health deterioration, pleural effusion, and pneumonia (all 3 related, fatal events were reported for the same patient) and multiple organ dysfunction syndrome.

9.1.9 Second-Line Therapy

- In total, 98 (45.4%) patients were documented with second-line therapy following end of Herceptin re-therapy.

- In second-line therapy, combination therapy with capecitabine and lapatinib (n=21; 9.7%) or monotherapy with trastuzumab (n=14; 6.5%) were the most common treatments reported.

9.2 LIMITATIONS

- As data were collected in routine clinical practice within the current version of the SmPC of Herceptin (23), bias in reporting may have occurred (e.g., underreporting of adverse events).

- Retrospective documentation of AEs (Amendment 3): An underestimation of AEs without causal relationship to Herceptin in the period before Amendment 3 became effective is to be expected.

- Unlike procedures in controlled clinical trials there was no formal requirement to report corresponding AEs in case of e.g. a LVEF drop by more than 10% compared to baseline or an absolute LVEF value below 50%. Nevertheless, abnormal laboratory findings were supposed to be reported if they were accompanied by clinical symptoms, led to changes in treatment, required medical intervention, have been assessed as clinically relevant by the investigator or indicated cardiac toxicity, infusion related reaction and/or pulmonary event. This remains the medical opinion of the treating physician whether they assess a certain finding as an adverse event or an adverse drug reaction. Therefore, no numerical correlation between recorded LVEF-drops or LVEF values below 50% and corresponding AE-reporting could be established.

- The NIS setting of this study *per se* limits comparability to clinical trial data.

- Patients excluded from the AP (due to violation of eligibility criteria), reducing the size of the final analysis sample by nearly 10% (n=23; 9.6%).

- Collection of re-biopsies of recurrent, local tumor or metastasis is not standard in routine clinical practice. Such samples may provide important information on receptor discordance or concordance. However, in this study such biopsies were very low in numbers and further data are not available.

- No standardization of tumor assessment according to RECIST, which may be a bias to PFS and ORR.

- A moderate to high number of censored (25% – 38%) cases may limit the interpretability of OS and OS-2.

- OS is partially retrospective (time from initial tumor resection to death), which may further limit the interpretation of the OS data.

- Heterogeneous distribution of patient and disease characteristics, in particular regarding the distribution of visceral metastases between subgroups (higher proportion of patients with visceral metastases within the SmPC-population [71.4% in the SmPC-population versus 47.6% in the PP versus 51% in the AP], and for

patients treated with taxanes as compared to other chemotherapies within the AP (70.6% versus 59.9%).

- Certain subgroups were rather small, e.g., “CTx and endocrine therapy” (N=20, AP;), “no metastases” (; N=6, SmPC-population) and “non-visceral” (N=8, SmPC-population), which may limit the interpretability of the data.

- This report includes missing data records due to incomplete data entries in the eCRF despite follow-up queries, e.g., LVEF at initiation of Herceptin re-therapy (Missing: n=44; 20.4%).

- There were 41 (19.0%) patients with unknown tumor response. This may limit the interpretation of best tumor response (ORR).

- The logistic regression analysis (overall tumor response) was limited to 74 (34.9%) responders.

9.3 INTERPRETATION

The estimated median observational period (59.3 months) of the patients included in the AP is well in line with the planned, protocol-defined observational period (60 months in total per patient).

Comparison of the data obtained in this NIS with data in the pivotal trials is limited as the NIS setting of this study *per se* limits the comparability to clinical trial data.

9.3.1 Effectiveness

The median PFS observed in this NIS (AP: 12.7 months;; SmPC-population: 9.8 months) was longer than the median PFS (8.0 months) reported in the pivotal RHEA trial (21), bearing in mind the retrospective inclusion and data collection (AP only) and the limited comparability of the data in this NIS to clinical trial data such as differences in patient populations. Nevertheless, it is important to (cautiously) put the data obtained in this NIS in context with the data reported in the pivotal study. The estimated median OS-2 (AP: 31.6 months;) was longer than the reported median OS (25.0 month) in the RHEA trial (21), whereas the median OS-2 in the SmPC-population was shorter (21.8 months), bearing in mind the differences in disease characteristics such as the distribution of

patients with visceral metastases and the number of censored cases (25% – 38%) in this NIS, which may limit the interpretability of the OS-2 further. Clearly, more patients in the SmPC-population were reported with visceral metastases (71%) as compared to the AP (51%) Important to highlight in this context is the fact that the SmPC-population comprised only patients having received Herceptin re-therapy in combination with taxanes +/- endocrine treatment, hence in-label therapy as per current SmPC of Herceptin (23). Interestingly, when comparing the effectiveness between subgroups of patients within the AP receiving Herceptin re-therapy combined with a taxane versus chemotherapy other than taxanes (Capecitabine, Vinorelbine), again, the effectiveness outcome in terms of PFS and OS in patients having received Herceptin re-therapy in combination with a taxane was less favorable (median PFS: 8.9 months; median OS-2: 18.5 months; AP). Several reasons might explain the differences between subgroups regarding PFS and OS-2 observed in this NIS, including differences in patient characteristics, tumor characteristics and prior treatments. When looking at the most common drug combinations used in (neo-) adjuvant chemotherapy no major difference was observed between subgroups as the drug combinations “cyclophosphamide, docetaxel, and epirubicin” (neoadjuvant) and “cyclophosphamide, epirubicin, and fluorouracil” (adjuvant) had been commonly used across all the subgroups of patients with concomitant treatment with Herceptin re-therapy. Patients having received taxanes as (neo-) adjuvant anti-HER2 therapy had the shortest median DFS (28.6 months) as compared to patients having received anthracyclines (39.7 months) or anthracyclines and taxanes (36.3 months), though, this doesn’t allow any further interpretation concerning the DFS in the different subgroups with concomitant therapy with Herceptin re-therapy. When looking at patient characteristics (AP), the median age was similar between the subgroup of patients having received a taxane (58.0 years) and the subgroup of patients with non-taxane-based chemotherapy (57.4 years) or any chemo-/immunotherapy and endocrine therapy (55.1 years) in combination with Herceptin re-therapy, whereas it was markedly higher compared to the subgroup of patients with endocrine therapy in combination with Herceptin re-therapy (49.0 years). A comparison with the two latter subgroups is however limited by the fact that patients in these subgroups have a superior prognosis and present with completely different tumor biology. However, differences in patient characteristics between subgroups were observed for certain other important factors known to negatively influence treatment and outcome in BC. The highest proportion of patients with comorbidities (≥1 comorbidity) was

observed in the taxanes subgroup (60.8%) as compared to the other subgroups (41.7% – 50.0%). Pre-existing comorbidities have been reported to negatively impact overall prognosis of BC and to potentially affect treatment and outcomes (31). Furthermore, the proportion of patients with visceral metastases was highest in the subgroup of patients receiving taxanes in combination with Herceptin re-therapy (70.6%) as compared to the other subgroups (14.3% – 60.0%). The presence of visceral metastases may possibly have a stronger impact on overall prognosis in terms of PFS and OS, while the clinical response to treatment (CR, PR or even SD) may not be affected that much as observed in this NIS for patients with visceral metastases where the ORR was rather similar across the AP and the SmPC-population (actually the most favorable ORR was seen in the latter population), whereas PFS and OS-2 were clearly different. This is supported by the multivariable Cox regression analysis (AP), in which it was observed that patients with visceral metastases had an inferior outcome (median PFS: 10.2 months) as compared to patients with no metastases (median PFS: 26.1 months; HR = 2.89; $p<0.001$). Indeed, the shortest median PFS (AP) was observed in the subgroup of patients having received a taxane in combination with Herceptin re-therapy (8.9 months) versus patients having received chemotherapy other than taxanes together with Herceptin re-therapy (13.4 months). The longest median PFS was seen in the subgroup of patients having received any chemo-/immunotherapy and endocrine therapy in combination with Herceptin re-therapy (19.9 months), though, as aforementioned, a comparison with the latter subgroup is limited due to differences in tumor biology (HR status). The proportion of patients with visceral metastases in the subgroup of patients having received non-taxane-based chemotherapy in combination with Herceptin re-therapy was somewhat lower (59.5%), though the data are reflective of the AP. However, this analysis was not pre-defined in the SAP and therefore not included in the final analysis. Nevertheless, it is well-known that MBC patients with visceral metastases are associated with short-term survival (32–34).

Interestingly, despite clear differences in median PFS and OS-2, the median OS was similar across the AP and SmPC-population. This may be due to retrospective data collection for OS (initial resection might have taken place several years before enrollment).

Regarding the response rates in this NIS, the highest ORR was actually found in the SmPC-population (49.0%), though lower compared to the ORR (61%) reported in the RHEA trial (21), keeping in mind the limited interpretability of the data in this NIS (19.0%

of patients with unknown tumor response) and the limited comparability of data between a NIS and clinical trials regarding tumor assessment criteria. In the multivariable logistic regression analysis in this NIS, no factor (baseline demographics and clinical characteristics) could be identified having an impact on the overall response (all individual *p*-values >0.1; global likelihood ratio test *p*=0.2977), which might be due to the low number of responders (34.9%).

It must be stressed that 36 (16.7%) patients in this study were reported having received Herceptin re-therapy as monotherapy. However, according to AGO-guidelines (Gynecological Oncology Working Group) and grades of recommendation, this treatment approach has not received general recommendation as first-line therapeutic intervention in HER2-positive MBC (35). Efficacy of sequential therapy of trastuzumab monotherapy followed by trastuzumab plus docetaxel compared to trastuzumab plus docetaxel as first-line therapy in patients with HER2-positive MBC was evaluated in a randomized phase III trial (36). In this trial it was observed that Herceptin monotherapy followed by Herceptin plus docetaxel was significantly associated with an inferior median PFS (HR = 4.24) and OS (HR = 2.72) as compared to Herceptin plus docetaxel as first-line therapy. Though of pure speculative nature, the difference in outcomes between the two treatment arms may be partly associated with differences in patient and disease characteristics as the proportion of patients with more than one metastatic site (74% versus 66%) and bone metastases (39% versus 28%) was higher among patients having received first-line Herceptin monotherapy as compared to the patients with Herceptin plus docetaxel as first-line therapy (36). However, the proportion of patients with visceral metastases was similar between both treatment arms (72% versus 70%) as was the median age (57.5 years versus 54.3 years) and the proportion of patients with prior treatment with paclitaxel (13% versus 11%) or anthracyclines (31% versus 32%). As per current SmPC of Herceptin, Herceptin is indicated as monotherapy for the treatment of patients who have received at least two chemotherapy regimens for their metastatic disease (23). This contrasts with treatment reality based on the data obtained in this NIS as apparently patients are subjected to Herceptin re-therapy as monotherapy in the first-line setting for treatment of MBC in routine clinical practice. Although it would have been interesting to know, the reason for this treatment decision was not captured in this study.

9.3.2 Herceptin Re-Therapy and Further-Line Therapy

The most frequently reported deciding factors for choosing Herceptin re-therapy reflect HER2 as a well-established predictive biomarker of benefit from HER2-directed therapies coupled with the favorable safety profile of Herceptin. Most patients were reported with an initial dose of Herceptin at 8 mg/kg (51.4%) or 4 mg/kg (35.2%) on a three-weekly schedule (69.9%) or weekly schedule (25.9%). This is in line with the current SmPC of Herceptin, which recommends an initial loading dose at 8 mg/kg body weight for a three-weekly schedule or 4 mg/kg body weight for a weekly schedule (23). The main documented reason for discontinuation of Herceptin re-therapy was disease progression (51.4%), followed by patient death (10.2%). Herceptin re-therapy was discontinued due to cardiac side effects in 3.7% of the patients. Patients treated with Herceptin are at increased risk for developing cardiac dysfunction (23). Therefore, LVEF assessment is critical during Herceptin therapy. If LVEF percentage drops <50%, treatment with Herceptin should be suspended and if LVEF does not improve and/or symptomatic congestive heart failure (CHF) has developed treatment with Herceptin should be discontinued (23). In this NIS, 14 (10.9%) patients were reported with LVEF <50% and 3 (1.4%) patients were documented with CHF reported as an ADR (n=2; CTCAE grade 1/2) and SADR (n=1). The incidence of CHF in this NIS may have been expected to be higher as 58% of the patients were reported having been subjected to an anthracycline-based regimen or an anthracycline and taxane-based regimen in combination with adjuvant Herceptin therapy. The reason for the low rates of CHF in this study may be due to underreporting, the long-time span between end of adjuvant anti-HER2 treatment and initiation of Herceptin re-therapy (median 21.1 months) or the exclusion of patients with LVEF ≤50% at baseline and patients with symptomatic heart failure or coronary artery disease. In the RHEA trial, no patients were reported with CHF although 93% of patients had previously been treated with an anthracycline (21). Optimal therapy management is paramount to achieve best possible outcomes for patients. This may include temporary therapy interruptions, therapy delay and dose modifications to address AEs or ADRs. In this NIS, 82 (38.0%) patients were reported with ≥1 therapy modification while on Herceptin re-therapy; 23 (10.6%) patients were documented with ≥1 therapy interruption (due to toxicity in 3 patients). The results from this study therefore provide important data suggesting that Herceptin may be temporary interrupted for a time period long enough to allow management of ADRs or AEs with subsequent resumption of Herceptin therapy. However, the results should be interpreted with caution as there are no data available on

the length of interruption or outcome of patients with resumption of Herceptin therapy as these variables were not defined in the study protocol and therefore not set up in the eCRF and hence not captured in the EDC.

The most common drugs used in concomitant chemotherapy with Herceptin re-therapy included those having market approval (paclitaxel and docetaxel) for treatment of MBC in combination with Herceptin in the first-line therapy setting (23). The drugs most frequently used in concomitant endocrine therapy with Herceptin re-therapy comprised the most common aromatase inhibitors (exemestane, anastrozole and letrozole) and ER antagonists / modulators (fulvestrant / tamoxifen) currently in clinical use in treatment of advanced BC or MBC with positive HR-status.

Second-line therapy (following end of Herceptin re-therapy) was reported in 45.4% of patients in this study with capecitabine and lapatinib combination therapy (9.7%) or monotherapy with trastuzumab (6.5%) being the most common treatments reported. Capecitabine and lapatinib combination therapy in patients with HER2-positive MBC who previously have received trastuzumab and chemotherapy has FDA approval in this therapy setting. The FDA approval was based on a pivotal phase III trial comparing lapatinib and capecitabine combination therapy versus capecitabine alone in patients with HER2-positive MBC with prior exposure to trastuzumab and chemotherapy. The addition of lapatinib was associated with an improved PFS, although with no significant effect on OS, compared with capecitabine alone (37).

9.3.3 Safety

9.3.3.1 Discrepancy Between Clinical Database and Safety Database

Altogether, 63 events were identified to be discrepant between SDB and CDB during the final safety reconciliation. A causal relationship with Herceptin was reported for or assigned by sponsor in 26 of these 63 events. Two of these 26 events were related to another compound of the sponsor (Capecitabine). The remaining events were predominantly known side effects of Herceptin. Of note, one death was reported in the CDB. In the narrative provided for the report of this fatal SAE the event was assigned to pulmonary embolism (however, the cause of death was tumor progression). The sponsor assessed the event of pulmonary embolism as related to Herceptin. Pulmonary embolism is not a known side effect of Herceptin.

The 26 related AEs represent about 7% of all reported AEs within this NIS. Safety results including the differences between the clinical and the company´s SDB have been subject of thorough evaluation and scientific discussion. This included an assessment of (S)AE rates in the CDB versus the SDB, a judgement of the differences in the types of (S)AEs in both databases and the impact of discrepancies for the safety profile of the NIS and/or the risk-benefit profile of the product. No noticeable safety aspects could be identified between the two safety databases.

9.3.3.2 Adverse Drug Reactions and Fatalities

This NIS collected safety information the respective treating physician considered as related, i.e. (S)ADRs. In addition, fatal SAEs (regardless of causality) were reported.

The most frequently (>2% of patients) reported ADRs (PT) were headache, chills, diarrhea, nausea, bone pain, dyspnea, peripheral neuropathy, decreased ejection fraction and dizziness.

Of note, 2 patients (pat ID 632002 and pat ID 1014006) were documented with pregnancy during the study period. One of these patients (pat ID 632002) was reported with oligohydramnios assessed by the treating physician as related to Herceptin treatment. This ADR was of CTCAE grade 3 but not flagged as serious and lasted for about 3 months (start date: 19 May 2011; end date: 27 August 2011) with onset of the ADR about 10 months following initiation of Herceptin re-therapy (15 July 2010). The ADR was resolved following permanent discontinuation of Herceptin treatment (2 May 2011); interestingly, Herceptin re-therapy was discontinued prior to onset of the ADR and yet assessed as attributable to the ADR [Listing 23.1 and Listing 23.8]. In this context, it is of utmost importance to follow up on the outcome of the pregnancy (fetus). As per documented information from the Roche Safety Department (designated pregnancy reporting form), both patients gave birth to healthy babies of normal size and weight and with APGAR scores of 9 (pat ID 1014006) and 8-10 (pat ID 632002), respectively. No AE concerning the babies has been reported following birth or ever after.

The most frequently (>1 patient) reported SADRs were decreased ejection fraction and dyspnea.

In total, 135 patients died during the study with 9 patients reported with fatal SAEs (one patient was reported with both related and non-related fatal events). Of these, 8 patients (8 cases) experienced fatal SAEs assessed by the treating physician as not related to Herceptin treatment. Notably, one of these patients (pat ID 860001) aged 42.3 years at inclusion into the study was reported with the fatal SAE “toxic epidermal necrolysis” (TEN), which emerged about 3.5 months following initiation of Herceptin re-therapy (31 March 2010). The event lasted for 16 days with onset of TEN on 13 July 2010 and was still ongoing at time of death, which occurred on 28 July 2010 [Listing 23.2]. The cause of this SAE was however not captured in the eCRF. TEN is most commonly a severe drug-induced (mucocutaneous) skin reaction (38, 39). As per documented information from the Roche Safety Department (designated SAE reporting form), this patient had received Herceptin re-therapy together with docetaxel and carboplatin. Treatment was permanently discontinued following the onset of TEN, which was likely to be attributable to docetaxel as assessed by the treating physician. The reported cause of death was neoplastic disease.

Two patients (4 cases) were reported with fatal SADRs (general physical health deterioration, pleural effusion, pneumonia (all reported for the same patient) and multiple organ dysfunction syndrome).

Conclusion on the overall safety assessments from this NIS corroborate the known safety profile of the product Herceptin (23).

9.4 GENERALIZABILITY

Generalizability of data collected within a NIS is subject to limitations as outlined above.

However, the patients included in this study consisted of an unselected population recruited in 122 study sites across Germany (routine clinical practice), reflecting the “real-world” setting of the study.

The number of enrolled patients (239) and the maximum of a 5-year observational period per patient sufficed to meet the objectives of the study.

The EDC system (*iostudy office edc*) used in this study is a password-protected, validated and secure system, operating as per guidelines of FDA 21 CFR Part 11; hence, providing a reliable source of data. In addition, remote and on-site monitoring were performed for source data verification as well as reconciliation of safety data.

This NIS was designed to evaluate the effectiveness and safety of re-therapy with Herceptin in routine clinical practice in patients with HER2-positive BC having relapsed following completed (neo-) adjuvant anti-HER2-therapy with Herceptin for HER2-positive EBC. The data obtained in this study provides an estimate of how clinical efficacy translates into effectiveness in routine clinical practice in Germany.

10. OTHER INFORMATION

Not applicable.

11. CONCLUSION

The data obtained in this study provides a valuable and important estimate of how clinical efficacy documented in controlled, randomized clinical studies translates into effectiveness in routine clinical practice in Germany.

Herceptin re-therapy is effective in routine clinical practice, while a direct comparison with the results obtained in the pivotal study is subject to limitations due to differences in patient characteristics and study settings including clear cut inclusion and exclusion criteria, assessment schemes and assessment specifications.

The safety information reported in this study is consistent with the known safety profile of Herceptin.

12. REFERENCES

1. Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science. 1987 Jan 9;235(4785):177–82.

2. Paik S, Hazan R, Fisher ER, Sass RE, Fisher B, Redmond C, et al. Pathologic findings from the National Surgical Adjuvant Breast and Bowel Project: prognostic

significance of erbB-2 protein overexpression in primary breast cancer. J Clin Oncol Off J Am Soc Clin Oncol. 1990 Jan;8(1):103–12.

3. Ross JS, Fletcher JA, Linette GP, Stec J, Clark E, Ayers M, et al. The Her-2/neu gene and protein in breast cancer 2003: biomarker and target of therapy. The Oncologist. 2003;8(4):307–25.

4. Ross JS, Slodkowska EA, Symmans WF, Pusztai L, Ravdin PM, Hortobagyi GN. The HER-2 receptor and breast cancer: ten years of targeted anti-HER-2 therapy and personalized medicine. The oncologist. 2009 Apr;14(4):320–68.

5. Cobleigh MA, Vogel CL, Tripathy D, Robert NJ, Scholl S, Fehrenbacher L, et al. Multinational study of the efficacy and safety of humanized anti-HER2 monoclonal antibody in women who have HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease. J Clin Oncol Off J Am Soc Clin Oncol. 1999 Sep;17(9):2639–48.

6. Ravdin PM, Chamness GC. The c-erbB-2 proto-oncogene as a prognostic and predictive marker in breast cancer: a paradigm for the development of other macromolecular markers--a review. Gene. 1995 Jun 14;159(1):19–27.

7. Bartsch R, Wenzel C, Steger GG. Trastuzumab in the management of early and advanced stage breast cancer. Biol Targets Ther. 2007 Mar;1(1):19–31.

8. Pietras RJ, Pegram MD, Finn RS, Maneval DA, Slamon DJ. Remission of human breast cancer xenografts on therapy with humanized monoclonal antibody to HER-2 receptor and DNA-reactive drugs. Oncogene. 1998 Oct 29;17(17):2235–49.

9. Huston JS, George AJ. Engineered antibodies take center stage. Hum Antibodies. 2001;10(3–4):127–42.

10. Marty M. Randomized Phase II Trial of the Efficacy and Safety of Trastuzumab Combined With Docetaxel in Patients With Human Epidermal Growth Factor Receptor 2-Positive Metastatic Breast Cancer Administered As First-Line Treatment: The M77001 Study Group. J Clin Oncol. 2005 Jul 1;23(19):4265–74.

11. Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med. 2001 Mar 15;344(11):783–92.

12. Cameron D, Piccart-Gebhart MJ, Gelber RD, Procter M, Goldhirsch A, de Azambuja E, et al. 11 years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant (HERA) trial. Lancet Lond Engl. 2017 25;389(10075):1195–205.

13. Gianni L, Dafni U, Gelber RD, Azambuja E, Muehlbauer S, Goldhirsch A, et al. Treatment with trastuzumab for 1 year after adjuvant chemotherapy in patients with HER2-positive early breast cancer: a 4-year follow-up of a randomised controlled trial. Lancet Oncol. 2011 Mar;12(3):236–44.

14. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, Goldhirsch A, Untch M, Smith I, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med. 2005 Oct 20;353(16):1659–72.

15. Tan-Chiu E, Piccart M. Moving forward: Herceptin in the adjuvant setting. Oncology. 2002;63 Suppl 1:57–63.

16. Wolff AC, Hammond MEH, Schwartz JN, Hagerty KL, Allred DC, Cote RJ, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. Arch Pathol Lab Med. 2007;131(1):18–43.

17. Perez EA, Romond EH, Suman VJ, Jeong J-H, Sledge G, Geyer CE, et al. Trastuzumab Plus Adjuvant Chemotherapy for Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer: Planned Joint Analysis of Overall Survival From NSABP B-31 and NCCTG N9831. J Clin Oncol. 2014 Nov 20;32(33):3744–52.

18. Perez EA, Romond EH, Suman VJ, Jeong J-H, Davidson NE, Geyer CE, et al. Four-year follow-up of trastuzumab plus adjuvant chemotherapy for operable human epidermal growth factor receptor 2-positive breast cancer: joint analysis of data from NCCTG N9831 and NSABP B-31. J Clin Oncol Off J Am Soc Clin Oncol. 2011 Sep 1;29(25):3366–73.

19. Slamon D, Eiermann W, Robert N, Pienkowski T, Martin M, Press M, et al. Adjuvant Trastuzumab in HER2-Positive Breast Cancer. N Engl J Med. 2011 Oct 6;365(14):1273–83.

20. Martin M, López-Tarruella S. Emerging Therapeutic Options for HER2-Positive Breast Cancer. Am Soc Clin Oncol Educ Book Am Soc Clin Oncol Meet. 2016;35:e64-70.

21. Láng I, Bell R, Feng FY, Lopez RI, Jassem J, Semiglazov V, et al. Trastuzumab retreatment after relapse on adjuvant trastuzumab therapy for human epidermal growth factor receptor 2-positive breast cancer: final results of the retreatment after herceptin adjuvant trial. Clin Oncol R Coll Radiol G B. 2014 Feb;26(2):81–9.

22. WHO | WHO Model Lists of Essential Medicines [Internet]. WHO. [cited 2018 Jul 30]. Available from: http://www.who.int/medicines/publications/essentialmedicines/en/

23. Herceptin 150mg Powder for concentrate for solution for infusion - Summary of Product Characteristics (SmPC) - (eMC) [Internet]. [cited 2019 Apr 2]. Available from: https://www.medicines.org.uk/emc/product/3856/smpc

24. Kaplan EL, Meier P. Nonparametric Estimation from Incomplete Observations. J Am Stat Assoc. 1958;53(282):457–81.

25. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373–83.

26. Hanker L, Hitschold T, Grafe A, Förster F, Schröder J, Janssen J, et al. Efficacy of trastuzumab re-therapy in the clinical routine of HER2-positive breast cancer patients who relapsed after completed anti-HER2 (neo)adjuvant therapy – 5th interim analysis of the national non-interventional study (NIS) ML21589. Cancer Res [Internet]. 2016 Feb 15 [cited 2017 Jun 9];76 (4 Suppl)(P4-14–08). Available from: http://cancerres.aacrjournals.org/content/76/4_Supplement/P4-14-08

27. Hanker L, Hitschold T, Grafe A, Förster F, Schröder J, Janssen J, et al. Efficacy of anti-HER2 ReTherapy with Herceptin® at first relapse and/or first occurrence of metastases of HER2-positive breast cancer in clinical routine – 4th interim analysis of the non-interventional study (NIS) ML21589. Ann Oncol. 2014;25(suppl4):iv131 (400P).

28. Hanker L, Hitschold T, Grafe A, Förster F, Schröder J, Janssen J, et al. Wirksamkeit erneuter Anti-HER2-Therapie mit Herceptin® in der klinischen Routine bei erstem Rezidiv und/oder erster Metastasierung des HER2-positiven Mammakarzinoms – 4. Interimanalyse der nichtinterventionellen Studie (NIS) ML21589. Senol - Z Für Mammadiagnostik -Ther. 2014;11(02):A50(P027).

29. Hanker L, Hitschold T, Hesse T, Grafe A, Förster F, Schröder J, et al. Efficacy of trastuzumab re-therapy in routine treatment of HER2-positive breast cancer patients who relapsed after completed (neo-)adjuvant anti-HER2 therapy. J Clin Oncol. 2013;31(suppl; abstr 602).

30. Hanker L, Prange-Krex G, Janssen J, Reichert D, Schröder J, Förster F, et al. Erneute Anti-HER2-Therapie mit Herceptin® beim ersten Rezidiv des HER2-positiven Mammakarzinoms-1. Interimsanalyse der nichtinterventionellen Studie (NIS) ML21589. Senol - Z Für Mammadiagnostik -Ther [Internet]. 2012 Jun 5 [cited 2012 Sep 19];9(02). Available from: https://www.thieme-connect.com/ejournals/abstract/10.1055/s-0032-1313426

31. Hong C-C, Ambrosone CB, Goodwin PJ. Comorbidities and Their Management: Potential Impact on Breast Cancer Outcomes. Adv Exp Med Biol. 2015;862:155–75.

32. Foukakis T, Fornander T, Lekberg T, Hellborg H, Adolfsson J, Bergh J. Age-specific trends of survival in metastatic breast cancer: 26 years longitudinal data from a population-based cancer registry in Stockholm, Sweden. Breast Cancer Res Treat. 2011 Nov;130(2):553–60.

33. Klar N, Rosenzweig M, Diergaarde B, Brufsky A. Features Associated With Long-Term Survival in Patients With Metastatic Breast Cancer. Clin Breast Cancer. 2019 Feb 6;

34. Li S, Zhao J, Zhu L, Su F, Chen K. Development and validation of a nomogram predicting the overall survival of stage IV breast cancer patients. Cancer Med. 2017 Nov;6(11):2586–94.

35. Thill M, Liedtke C, Müller V, Janni W, Schmidt M, AGO Breast Committee. AGO Recommendations for the Diagnosis and Treatment of Patients with Advanced and Metastatic Breast Cancer: Update 2018. Breast Care Basel Switz. 2018;13(3):209–15.

36. Inoue K, Nakagami K, Mizutani M, Hozumi Y, Fujiwara Y, Masuda N, et al. Randomized phase III trial of trastuzumab monotherapy followed by trastuzumab plus docetaxel versus trastuzumab plus docetaxel as first-line therapy in patients with HER2-positive metastatic breast cancer: the JO17360 Trial Group. Breast Cancer Res Treat. 2010 Jan;119(1):127–36.

37. Geyer CE, Forster J, Lindquist D, Chan S, Romieu CG, Pienkowski T, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med. 2006 Dec 28;355(26):2733–43.

38. Lerch M, Mainetti C, Terziroli Beretta-Piccoli B, Harr T. Current Perspectives on Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis. Clin Rev Allergy Immunol. 2018 Feb;54(1):147–76.

39. Miliszewski MA, Kirchhof MG, Sikora S, Papp A, Dutz JP. Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: An Analysis of Triggers and Implications for Improving Prevention. Am J Med. 2016 Nov;129(11):1221–5.

APPENDICES

TREATING PHYSICIAN'S DECISION, PATIENT'S REQUEST, AND OTHER REASONS FOR DISCONTINUATION OF HERCEPTIN RE-THERAPY

Table 1 Specification of treating physician's decision, patient's request, and other reasons for discontinuation of Herceptin re-therapy (AP)

	N	%
Total number of patients, N	*216*	*100*
Specification of treating physician's decision, patient's request, and other reasons for discontinuation of Herceptin re-therapy[1], n, %		
Treating physician's decision: Only monotherapy with an aromatase inhibitor currently planned	1	0.5
Treating physician's decision: Number of necessary cycles reached	1	0.5
Treating physician's decision: Discontinuation after 1 year of treatment; patient's request	1	0.5
Treating physician's decision: Treatment as in adjuvant therapy due to similar risk because of local recurrence with R0 resection and no data to justify longer treatment time.	1	0.5
Treating physician's decision: No signs of progression on diagnostic imaging, however, increasing CA15-3 levels suggest some level of resistance to Herceptin	1	0.5
Treating physician's decision: Breast Cancer Board's decision	1	0.5
Treating physician's decision: End of planned treatment period	1	0.5
Treating physician's decision: Discontinuation after 12 months	1	0.5
Treating physician's decision: Planned Herceptin treatment duration of one year	1	0.5
Treating physician's decision: Favorable progress	1	0.5
Treating physician's decision: No evidence of recurrence	1	0.5
Treating physician's decision: No reliable evidence of liver metastases from breast cancer. (Secondary cancer: Cholangiocellular carcinoma)	1	0.5
Treating physician's decision: Palliative treatment with Herceptin was planned to last 1 year	1	0.5
Treating physician's decision: Pat. with significantly impaired AZ -> Pat. monitored by the SAPV (spezialisierte ambulante palliativmedizinische Versorgung [specialised outpatient palliative care team])	1	0.5
Treating physician's decision: Patient didn't attend next scheduled visit	1	0.5
Treating physician's decision: Other	1	0.5
Treating physician's decision: Stable disease	1	0.5
Treating physician's decision: Stable disease	1	0.5
Treating physician's decision: Treatment was planned to last 1 year	1	0.5
Treating physician's decision: Treatment discontinued as planned	1	0.5
Treating physician's decision: Moved in with caregiver	1	0.5
Other: Dizziness, unsteady gait => ID brain metastases on August 2010; progression of liver metastases (ID 03/2010)	1	0.5
Other: Treatment not discontinued???!!!!	1	0.5
Other: Treatment discontinued after 18 cycles	1	0.5
Other: Treatment discontinued after 4 years of follow up	1	0.5
Other: Anti-HER2 re-therapy continued, basic documentation at 12 months - has	1	0.5

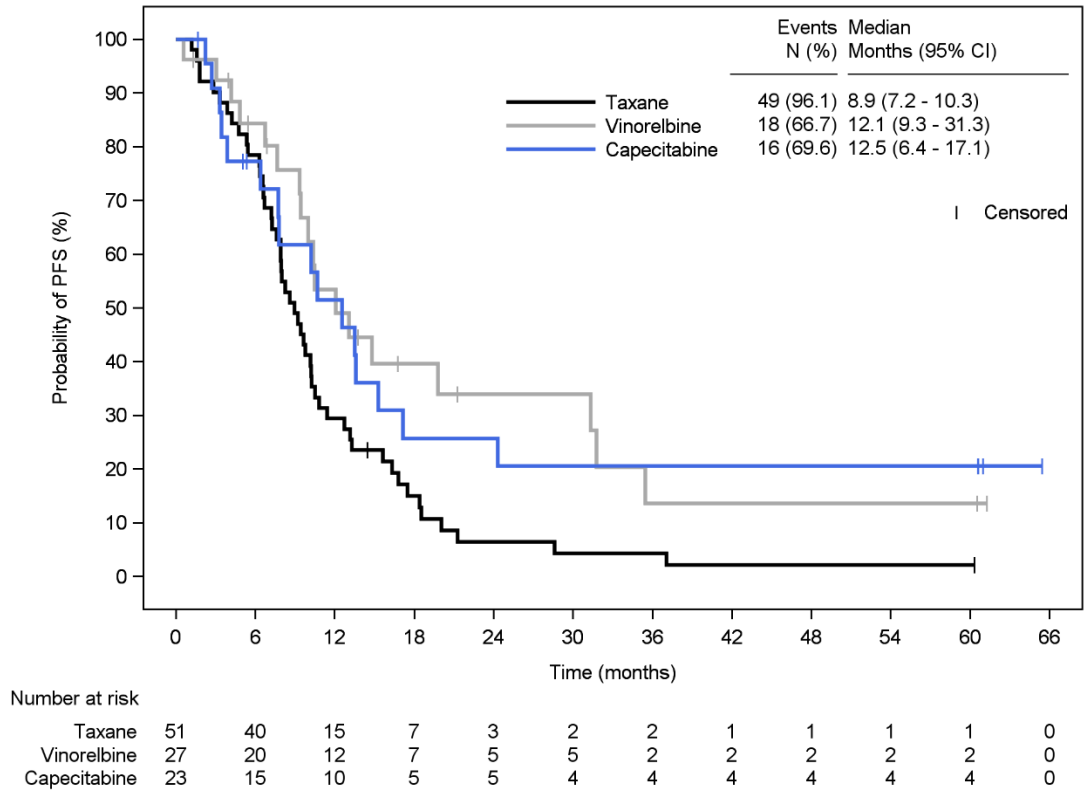
	N	%
discontinued		
Other: Deterioration of AZ (allgemein Zustand [general condition])	1	0.5
Other: Basic documentation stopped after 12 months of Herceptin re-therapy, Herceptin continued until disease progression	1	0.5
Other: Basic documentation stopped, Herceptin therapy continued beyond 18 cycles	1	0.5
Other: Incipient increase in tumour marker CA15-3 [sic]	1	0.5
Other: One year of re-therapy	1	0.5
Other: End of basic documentation	1	0.5
Other: End of documentation for NIS	1	0.5
Other: Decision to discontinue palliative chemotherapy and Herceptin therapy in agreement with the patient due to significant disease progression	1	0.5
Other: Dilated DHC (Ductus hepatocholedochus [common bile duct]) and gastrointestinal bleeding	1	0.5
Other: Continuation	1	0.5
Other: Herceptin not yet discontinued	1	0.5
Other: Herceptin re-therapy not discontinued	1	0.5
Other: Herceptin continued beyond progression	1	0.5
Other: Herceptin only discontinued 12 months later	1	0.5
Other: Recent re-staging due to deterioration of AZ: Revealed suspected encapsulated effusion with progression of liver metastases. Patient in moderately impaired AZ.	1	0.5
Other: Connection to outpatient palliative care team (SAPV) in July 2012	1	0.5
Other: Lost to follow up	1	0.5
Other: Patient continued treatment in another facility	1	0.5
Other: Patient moved and will continue treatment near her new place of residence.	1	0.5
Other: Progression, Herceptin therapy continued	1	0.5
Other: Progression and change of HER2/neu status to HER2/neu negative	1	0.5
Other: Pregnancy	1	0.5
Other: Patient became pregnant during Herceptin therapy; discontinuation of therapy due to oligohydramnios.	1	0.5
Other: Treatment is ongoing	1	0.5
Other: Treatment ongoing, basic documentation stopped after 12 months	1	0.5
Other: Treatment continued ex domo.	1	0.5
Other: Treatment fatigue, remission	1	0.5
Other: Change of practice	1	0.5
Other: Change of hospital	1	0.5
Patient's request:	1	0.5
Patient's request: 19 December 2011 abdominal CT: Recurrence of large metastases in the left lobe of the liver, pulmonary metastases no longer detectable on either side.	1	0.5
Patient's request: Patient expressed the wish to discontinue treatment on 24 February 2011.	1	0.5
Patient's request: Patient renounced treatment on 14 August 2012 because she wanted to wait for her liver ultrasound. The ultrasound revealed progression.	1	0.5
Patient's request: Patient generally rejected further anticancer treatment	1	0.5
Patient's request: Patient currently refusing further treatment	1	0.5
Patient's request: Patient moved to other hospital	1	0.5
Patient's request: Patient refusing treatment for the time being	1	0.5
Patient's request: Patient continuing treatment in her home town	1	0.5

	N	%
Patient's request: Patient wants to resort to alternative medicine	1	0.5
Patient's request: Patient moved to Spain and receives further treatment there.	1	0.5
Patient's request: Currently refusing further treatment	1	0.5
Patient's request: Interim documentation incl. cycle 70 of 26 January 2017	1	0.5

[Source: Herceptin_Abschlussanalyse_Tables; Table 13.11].
AP = Analysis population; AZ = allgemein Zustand (general condition); CA15-3 = Cancer antigen 15-3 (tumor marker); CT = Computer tomography; DHC = Ductus hepatocholedochus (common bile duct); EDC = Electronic data capture; HER2 = Human epidermal growth factor receptor 2; N/n = Number; NIS = Non-interventional study; SAPV = spezialisierte ambulante palliativmedizinische Versorgung (specialised outpatient palliative care team)
[1]Free-text entries extracted from the EDC and translated into English.

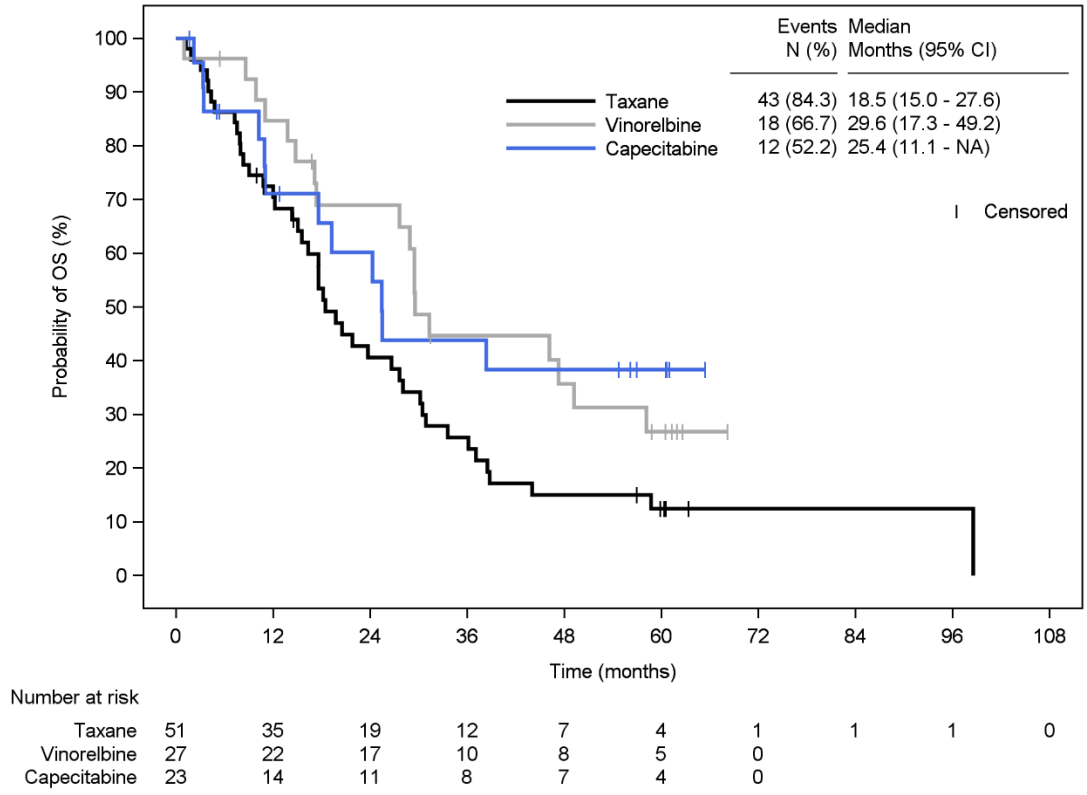
KAPLAN-MEIER PLOTS (PFS / OS-2) – ACCORDING TO CHEMOTHERAPY (AP)

Figure 1 Progression-free survival – subgroup "chemotherapy" (AP)



[Source: Herceptin_Abschlussanalyse_Figures; Figure 22.1-d].
AP = Analysis population; CI = Confidence interval; N = Number; PFS = Progression-free survival
Taxane: Patients receiving a taxane in combination with their Herceptin re-therapy (no other chemotherapy and no endocrine therapy)
Vinorelbine: Patients receiving vinorelbine in combination with their Herceptin re-therapy (no other chemotherapy and no endocrine therapy)
Capecitabine: Patients receiving capecitabine in combination with their Herceptin re-therapy (no other chemotherapy and no endocrine therapy)
Progression-free survival was estimated by using the Kaplan-Meier method.
Progression-free survival was defined as the time from diagnosis of local recurrent tumor / distant metastasis, which led to the initiation of anti-HER2 re-therapy with Herceptin® to progression or death due to any cause.
Due to the small number of patients included, the subgroups "Carboplatin" (n=2) and "Other CTx" (n=1) are not depicted. The PFS of the carboplatin-treated patients was 0.26 months and 6.28 months, respectively; the PFS of the patient treated with other CTx (doxorubicin) was 23.33 months.

Figure 2 Overall survival (OS-2) from recurrence / distant metastases – subgroup "chemotherapy" (AP)



[Source: Herceptin_Abschlussanalyse_Figures; Figure 22.3-d].
AP = Analysis population; CI = Confidence interval; N = Number; NA = Not reached; OS = Overall survival
Taxane: Patients receiving a taxane in combination with their Herceptin re-therapy (no other chemotherapy and no endocrine therapy)
Vinorelbine: Patients receiving vinorelbine in combination with their Herceptin re-therapy (no other chemotherapy and no endocrine therapy)
Capecitabine: Patients receiving capecitabine in combination with their Herceptin re-therapy (no other chemotherapy and no endocrine therapy)
Overall survival (OS-2) was estimated by using the Kaplan-Meier method.
OS-2 was defined as the time from diagnosis of local recurrent tumor / distant metastasis, which led to the initiation of anti-HER2 re-therapy with Herceptin® to death due to any cause.
The subgroups "Carboplatin" (n=2) and "Other Chemotherapy" (n=1) are not displayed due to small sample size. For the two patients treated with carboplatin, the median OS-2 was 2.43 months and. 31.71 months; for the patient treated with other chemotherapy (doxorubicin) the median OS-2 was 31.25 months.

PER-PROTOCOL POPULATION (PP)

Definition of the PP

The PP comprised patients of the AP with a higher compliance to study protocol. Inclusion criteria were as follows: an initial Herceptin dose of 4 or 8 mg/kg, prospective enrolment, LVEF >50%, absence of coronary heart disease or symptomatic cardiac insufficiency, "in-

label" combination chemotherapy (i.e. taxanes) concomitant to Herceptin re-therapy or no combination chemotherapy, and no pregnancy during study participation. While in the AP retrospective documentation (9 weeks) was permitted, this was not allowed in the PP.

Total Number and Number of Patients in Different Subgroups of the PP

Table 2 Patient disposition – subgroups[1] (PP)

	PP
Total number of patients, N	*107*
Number of patients in respective subgroup, N	
Metastases	
No metastases	23
Non-visceral	33
Visceral	51
Anthracycline / Taxane [(neo-) adjuvant CTx][2]	
Anthracycline	27
Taxane	6
Anthracycline + Taxane	67
Other	2
No (neo)adjuvant CTx	5
Combination therapy[3]	
Herceptin Monotherapy	29
Taxanes	40
Endocrine therapy	29
Other CTx	0
CTx[4] and endocrine therapy	9
Mono-chemotherapy[5]	
Taxane	40
Vinorelbine	0
Capecitabine	0

[Source: Herceptin_Abschlussanalyse_Tables; Table 9.4-b, Table 21.1-f, Table 21.1-g].
CTx = Chemotherapy; N = Number; NC = Not calculated; PP = Per-protocol population
[1]Definition of the subgroups is provided in Table 7-5 (section 7.7.4.7 Subgroup Analyses). [2]Type of chemotherapeutic regimen in combination with adjuvant Herceptin therapy. [3]Comination therapy with Herceptin re-therapy. [4]Only taxanes. [5]Patients with mono-chemotherapy in combination with Herceptin re-therapy (no endocrine therapy).

Reasons for Exclusion of Patients from the PP

The main reason for exclusion of patients (n=132; 55.2%) from the PP (N=107) was patients having received combination chemotherapy other than taxanes together with Herceptin re-therapy (n=58; 24.3%; Table 3).

Table 3 Reasons for exclusion from the per-protocol population (total population)

	N	%
Total number of patients enrolled, N	*239*	*100*
Excluded from the per-protocol population, n, %	132	55.2
Reasons, n, %		
Combination chemotherapy other than taxanes	58	24.3
Initial Herceptin dose not 4 or 8 mg/kg; combination chemotherapy other than taxanes	15	6.3
Initial Herceptin dose not 4 or 8 mg/kg	12	5.0
Combination chemotherapy other than taxanes; retrospective inclusion	9	3.8
Retrospective inclusion	9	3.8
Chemotherapy or immunotherapy for recurrent/metastatic disease before initiation of Herceptin re-therapy	8	3.3
Chemotherapy or immunotherapy for recurrent/metastatic disease before initiation of Herceptin re-therapy; combination chemotherapy other than taxanes	3	1.3
Documented pregnancy	2	0.8
LVEF ≤ 50% at baseline (= start of Herceptin re-therapy)	2	0.8
Adjuvant treatment with Herceptin <1 year; initial Herceptin dose not 4 or 8 mg/kg	1	0.4
Initial Herceptin dose not 4 or 8 mg/kg; retrospective inclusion	1	0.4
Initial Herceptin dose not 4 or 8 mg/kg; symptomatic heart failure or coronary heart disease	1	0.4
No Herceptin given in the context of the study	1	0.4
No systemic adjuvant, or neoadjuvant and adjuvant anti-HER2 therapy for early breast cancer; combination chemotherapy other than taxanes	1	0.4
No systemic adjuvant, or neoadjuvant and adjuvant anti-HER2 therapy for early breast cancer; no Herceptin given in the context of the study	1	0.4
Adjuvant treatment with lapatinib instead of Herceptin; combination chemotherapy other than taxanes	1	0.4
Initial Herceptin dose not 4 or 8 mg/kg; combination chemotherapy other than taxanes	1	0.4
No recurrence/no (distant) metastasis after completion of adjuvant anti-HER2 therapy; no further documentation; no Herceptin given in the context of the study	1	0.4
Retrospective inclusion; combination chemotherapy other than taxanes	1	0.4

	N	%
Recurrence/(distant) metastases during (neo)adjuvant anti-HER2 therapy	1	0.4
Recurrence/(distant) metastases during (neo)adjuvant anti-HER2 therapy; adjuvant treatment with lapatinib instead of Herceptin; initial Herceptin dose not 4 or 8 mg/kg; retrospective inclusion	1	0.4
Study medication presumably used as adjuvant therapy against contralateral breast cancer (secondary cancer); initial Herceptin dose not 4 or 8 mg/kg; combination chemotherapy other than taxanes	1	0.4
Study medication presumably administered as (second-line) adjuvant therapy; combination chemotherapy other than taxanes	1	0.4

[Source: Herceptin_Abschlussanalyse_Tables; Table 1.3-b].
HER2 = Human epidermal growth factor receptor 2; LVEF = Left ventricular ejection fraction; N/n = Number

EFFECTIVENESS RESULTS (PP)

Progression-Free Survival

In the PP, 86 patients (80.4%) had experienced an event. The median PFS in the PP was 11.4 months (8.9 – 16.3 months) with an estimated 6-month and 12-month PFS rate at 77.1% and 48.7%, respectively (Table 4; Figure 3).

Table 4 Progression-free survival (PP)

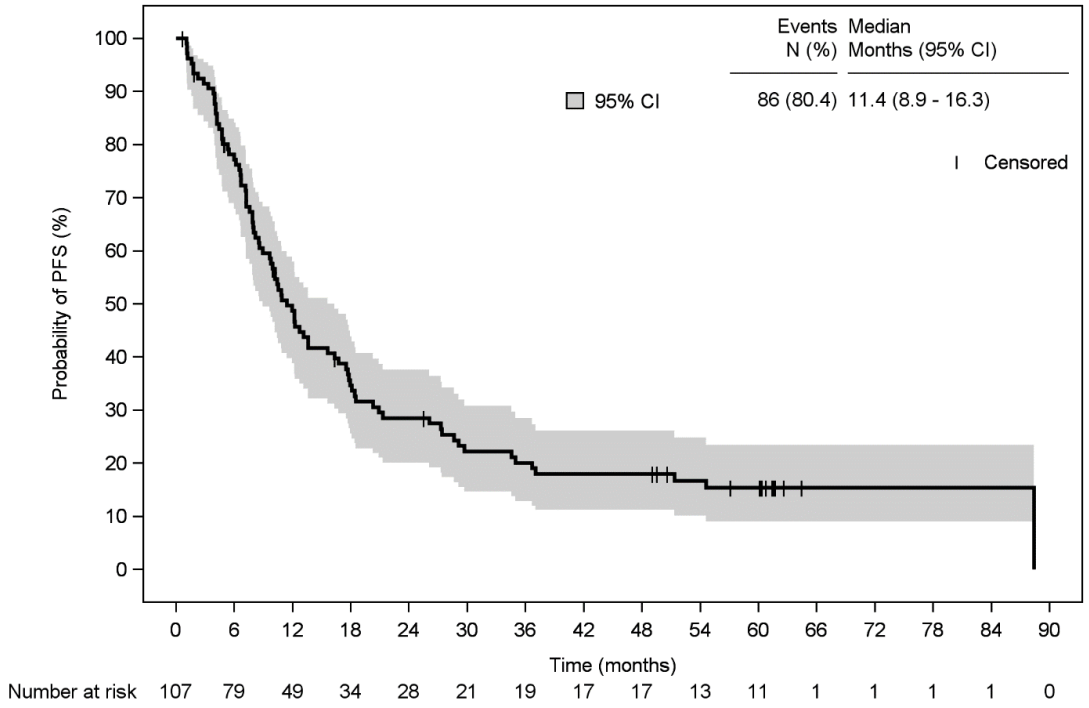
	Per-protocol population
Total number of patients, N	*107*
Events, n (%)	86 (80.4)
Quartiles (months)	
25% quantile [95% CI]	6.6 (4.5 - 7.9)
50% quantile [95% CI] (Median)	11.4 (8.9 - 16.3)
75% quantile [95% CI]	28.6 (18.1 - 51.3)
PFS rates (%) [95% CI]	
6-month	77.1% (67.8% - 84.0%)
12-month	48.7% (38.7% - 57.9%)

[Source: Herceptin_Abschlussanalyse_Tables; Table 21.1-e.
CI = Confidence interval; N/n = Number; PFS = Progression-free survival
Progression-free survival was estimated by using the Kaplan-Meier method.
Progression-free survival was defined as the time from diagnosis of local recurrent tumor / distant metastasis, which led to the initiation of anti-HER2 re-therapy with Herceptin® to progression or death due to any cause. Patients without an event (progression or death) before change of therapy or at end of study participation were censored using the earliest date of one of the following:

- Date of change of therapy (start of second-line therapy)
- Date of last patient contact

If none of the above dates was available, the date of last documented dose of Herceptin was used for the censored case.

Figure 3 Progression-free survival (PP)



[Source: Herceptin_Abschlussanalyse_Figures; Figure 22.1-e].
CI = Confidence interval; N = Number; PFS = Progression-free survival; PP = Per-protocol population
Progression-free survival was estimated by using the Kaplan-Meier method.
Progression-free survival was defined as the time from diagnosis of local recurrent tumor / distant metastasis, which led to the initiation of anti-HER2 re-therapy with Herceptin to progression or death due to any cause.

Progression-Free Survival – Subgroup "Metastases / Local Recurrence Only"

In the PP, the median PFS was shortest in the subgroup of patients with visceral metastases (7.9 months (6.5 – 10.5 months)), whereas the longest median PFS was observed in the subgroup of patients with no metastases (local recurrence only) (51.3 months (11.9 months – not reached)) as further detailed in Table 5 and Figure 4. The lowest 6-month (65.9%) and 12-month (30.9%) PFS rates were seen in the subgroup of patients with visceral metastases.

Table 5 Progression-free survival – subgroup "metastases / local recurrence only" (PP)

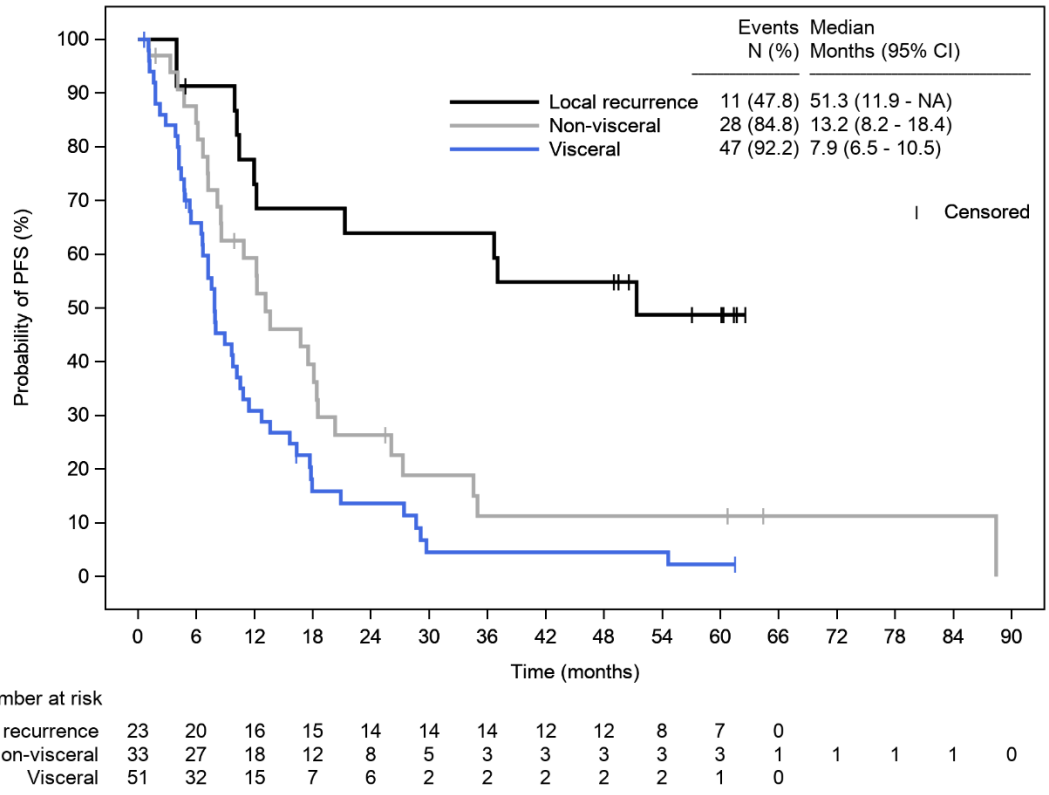
	No metastases (local recurrence only)	Non-visceral	Visceral
Per-protocol population (PP): Total N=107			
Total number of patients (subgroups), N	*23*	*33*	*51*
Events, n (%)	11 (47.8)	28 (84.8)	47 (92.2)
Quartiles (months)			
25% quantile [95% CI]	11.9 (3.9 - 37.1)	7.2 (4.1 - 10.9)	4.5 (2.3 - 6.6)
50% quantile [95% CI] (Median)	51.3 (11.9 - NA)	13.2 (8.2 - 18.4)	7.9 (6.5 - 10.5)
75% quantile [95% CI]	NA	26.1 (17.5 - 88.4)	15.6 (10.2 - 20.9)
PFS rates (%) [95% CI]			
6-month	91.3% (69.5% - 97.8%)	84.5% (66.6% - 93.2%)	65.9% (51.0% - 77.2%)
12-month	73.0% (49.5% - 86.9%)	59.3% (40.4% - 74.0%)	30.9% (18.7% - 43.9%)

[Source: Herceptin_Abschlussanalyse_Tables; Table 21.1-f].
CI = Confidence interval; N/n = Number; NA = Not reached; PFS = Progression-free survival; PP = Per-protocol population
No metastases: Patients without metastases at start of Herceptin re-therapy (local recurrence only)
Non-visceral: Patients with non-visceral metastases only, i.e. bone, skin, lymph node and soft tissue metastases (± local recurrence, no visceral metastases)
Visceral: Patients with visceral metastases, i.e. lung, liver, CNS, pleural effusion, ascites, and other metastases (free-text entries) coded as visceral by medical experts (± non-visceral metastases ± local recurrence). This group comprises all patients with visceral metastases including those having additional non-visceral metastases.
Progression-free survival was estimated by using the Kaplan-Meier method.
Progression-free survival was defined as the time from diagnosis of local recurrent tumor / distant metastasis, which led to the initiation of anti-HER2 re-therapy with Herceptin to progression or death due to any cause. Patients without an event (progression or death) before change of therapy or at end of study participation were censored using the earliest date of one of the following:

- Date of change of therapy (start of second-line therapy)
- Date of last patient contact

If none of the above dates was available, the date of last documented dose of Herceptin was used for the censored case.

Figure 4 **Progression-free survival – subgroup "metastases / local recurrence only" (PP)**



[Source: Herceptin_Abschlussanalyse_Figures; Figure 22.1-f].
CI = Confidence interval; N = Number; NA = Not reached; PFS = Progression-free survival; PP = Per-protocol population
Local recurrence: Patients without metastases at start of Herceptin re-therapy (local recurrence only)
Non-visceral: Patients with non-visceral metastases only, i.e. bone, skin, lymph node and soft tissue metastases (± local recurrence, no visceral metastases)
Visceral: Patients with visceral metastases, i.e. lung, liver, CNS, pleural effusion, ascites, and other metastases (free-text entries) coded as visceral by medical experts (± non-visceral metastases ± local recurrence). This group comprises all patients with visceral metastases including those having additional non-visceral metastases.
Progression-free survival was estimated by using the Kaplan-Meier method.
Progression-free survival was defined as the time from diagnosis of local recurrent tumor / distant metastasis, which led to the initiation of anti-HER2 re-therapy with Herceptin to progression or death due to any cause.

Progression-Free Survival – Subgroup "Combination Therapy"

In the PP, the shortest median PFS was observed in the subgroup of patients having received a taxane in combination with Herceptin re-therapy (8.0 months (6.7 – 10.2 months)), whereas the longest median PFS was seen in the subgroup of patients having received a taxane and endocrine therapy in combination with Herceptin re-therapy (36.7 months (9.6 months – not reached)) as further detailed in Table 6. The lowest 6-month

(72.5%) and 12-month (27.5%) PFS rates were seen in the subgroup of patients having received a taxane in combination with Herceptin re-therapy.

Table 6 Progression-free survival – subgroup "combination therapy" (PP)

	Herceptin mono re-therapy	Taxanes	Endocrine therapy	Taxanes and endocrine therapy
Per-protocol population (PP): Total N=107				
Total number of patients (subgroups), N	*29*	*40*	*29*	*9*
Events, n (%)	17 (58.6)	39 (97.5)	24 (82.8)	6 (66.7)
Quartiles (months)				
25% quantile [95% CI]	7.2 (1.1 - 13.6)	5.4 (2.8 - 7.2)	6.2 (4.1 - 8.6)	17.9 (9.6 - 36.7)
50% quantile [95% CI] (Median)	20.9 (10.4 - NA)	8.0 (6.7 - 10.2)	12.2 (6.7 - 20.3)	36.7 (9.6 - NA)
75% quantile [95% CI]	NA	12.9 (9.8 - 18.4)	27.4 (12.2 - 88.4)	NA
PFS rates (%) [95% CI]				
6-month	78.0% (57.4% - 89.5%)	72.5% (55.9% - 83.7%)	75.9% (55.9% - 87.7%)	100.0% (100.0% - 100.0%)
12-month	65.7% (44.2% - 80.5%)	27.5% (14.9% - 41.7%)	51.7% (32.5% - 67.9%)	88.9% (43.3% - 98.4%)

[Source: Herceptin_Abschlussanalyse_Tables; Table 21.1-g].
CI = Confidence interval; CTx = Chemotherapy; N/n = Number; NA = Not reached; PFS = Progression-free survival; PP = Per-protocol population
Herceptin mono re-therapy: Patients who did not receive any combination therapy (neither chemo-/immunotherapy nor endocrine therapy) with their Herceptin re-therapy.
Taxanes: Patients receiving a taxane in combination with their Herceptin re-therapy (but no endocrine therapy).
Endocrine therapy: Patients receiving endocrine therapy in combination with their Herceptin re-therapy (but no chemo-/immunotherapy).
Taxanes and endocrine therapy: Patients receiving taxanes and endocrine therapy in combination with their Herceptin re-therapy.
Progression-free survival was estimated by using the Kaplan-Meier method.
Progression-free survival was defined as the time from diagnosis of local recurrent tumor / distant metastasis, which led to the initiation of anti-HER2 re-therapy with Herceptin to progression or death due to any cause. Patients without an event (progression or death) before change of therapy or at end of study participation were censored using the earliest date of one of the following:

- Date of change of therapy (start of second-line therapy)
- Date of last patient contact

If none of the above dates was available, the date of last documented dose of Herceptin was used for the censored case.

Overall Survival From Initial Tumor Resection (OS)

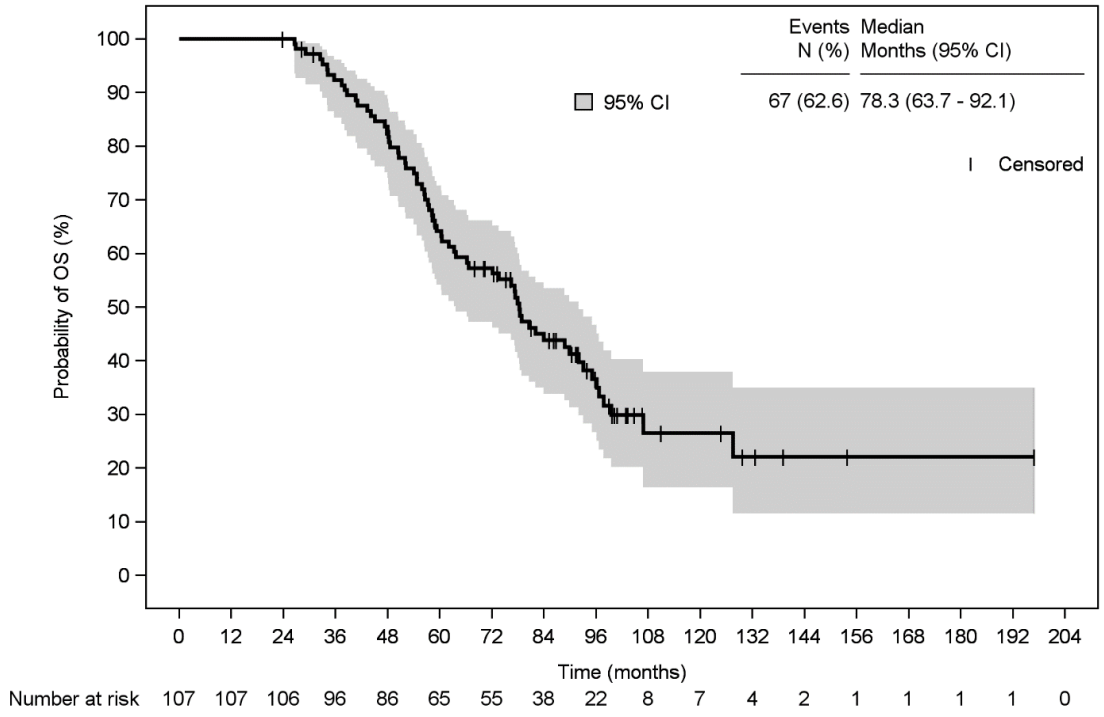
The median OS in the PP (events: n=67; 62.6%) was 78.3 months (63.7 – 92.1 months; Table 7; Figure 5). The 12-month and 24-month OS rates were both 100%, whereas the 36-month and 48-month OS rates were 92.4% and 83.7%, respectively.

Table 7 Overall survival from initial tumor resection (PP)

	Per-protocol population
Total number of patients, N	*107*
Events, n (%)	67 (62.6)
Quartiles (months)	
25% quantile [95% CI]	54.1 (48.1 - 58.4)
50% quantile [95% CI] (Median)	78.3 (63.7 - 92.1)
75% quantile [95% CI]	127.5 (96.2 - NA)
OS rates (%) [95% CI]	
12-month	100.0% (100.0% - 100.0%)
24-month	100.0% (100.0% - 100.0%)
36-month	92.4% (85.3% - 96.1%)
48-month	83.7% (75.1% - 89.5%)

[Source: Herceptin_Abschlussanalyse_Tables; Table 21.3-b].
CI = Confidence interval; N/n = Number; NA = Not reached; OS = Overall survival; PP = Per-protocol population
Overall survival was estimated by using the Kaplan-Meier method.
Overall survival was defined as the time from initial tumor resection to death due to any cause. Patients without documented date of death at the end of study were censored at the last date known to be alive. If this date was not available, the date of the last documented dose of Herceptin was used for the censored case. A total of 68 patients in the PP died during the study. For one patient, the date of death was not available. The overall survival of this patient was therefore included in the analysis as a censored case (date of last contact).

Figure 5 Overall survival from initial tumor resection (PP)



[Source: Herceptin_Abschlussanalyse_Figures; Figure 22.2-b].
CI = Confidence interval; N = Number; PP = Per-protocol population; OS = Overall survival
Overall survival was estimated by using the Kaplan-Meier method.
Overall survival was defined as the time from initial tumor resection to death due to any cause. In total, 68 patients in the PP died during the study. For one patient, date of death was not available. Therefore, the OS of this patient was censored at date of last contact.

Overall Survival from Recurrence / Distant Metastases (OS-2)

The median OS-2 in the PP (events: n=67; 62.6%) was 34.5 months (27.0 – 40.9 months) with estimated OS-2 rates at 79.1% (12 months), 60.3% (24 months), 47.2% (36 months) and 38.0% (48 months) as detailed in Table 8 and Figure 6.

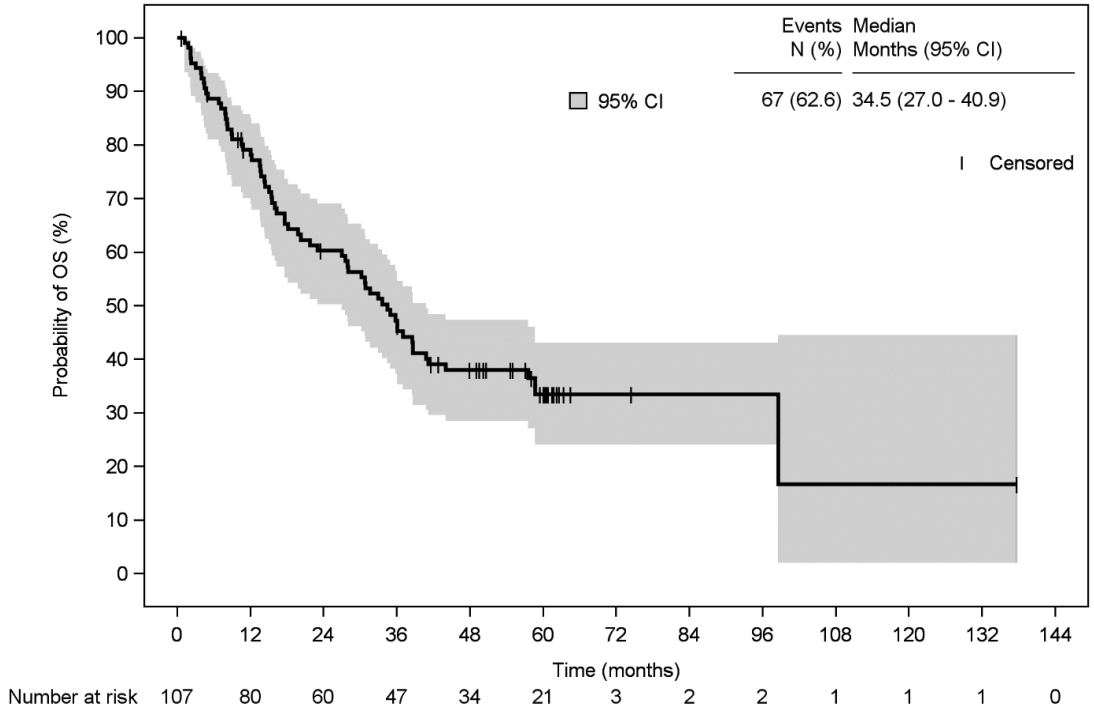
Table 8 Overall survival (OS-2) from recurrence / distant metastases (PP)

	Per-protocol population
Total number of patients, N	*107*
Events, n (%)	67 (62.6)
Quartiles (months)	
25% quantile [95% CI]	13.8 (8.3 – 17.6)
50% quantile [95% CI] (Median)	34.5 (27.0 - 40.9)
75% quantile [95% CI]	98.6 (58.8 - NA)

	Per-protocol population
OS-2 rates (%) [95% CI]	
12-month	79.1% (70.0% - 85.7%)
24-month	60.3% (50.2% - 69.0%)
36-month	47.2% (37.3% - 56.6%)
48-month	38.0% (28.5% - 47.3%)

[Source: Herceptin_Abschlussanalyse_Tables; Table 21.4-e].
CI = Confidence interval; N/n = Number; NA = Not reached; OS = Overall survival; PP = Per-protocol population
Overall survival (OS-2) was estimated by using the Kaplan-Meier method.
OS-2 was defined as the time from diagnosis of local recurrent tumor / distant metastasis, which led to the initiation of anti-HER2 re-therapy with Herceptin® to death due to any cause. Patients without documented date of death at the end of study were censored at the last date known to be alive. If this date was not available, the date of the last documented dose of Herceptin® was used for the censored case. A total of 68 patients in the PP died during the study. For one patient, the date of death was not available. The overall survival of this patient was therefore included in the analysis as a censored case (date of last contact).

Figure 6 Overall survival (OS-2) from recurrence / distant metastases (PP)



[Source: Herceptin_Abschlussanalyse_Figures; Figure 22.3-e].
CI = Confidence interval; N = Number; PP = Per-protocol population; OS = Overall survival
Overall survival (OS-2) was estimated by using the Kaplan-Meier method.
OS-2 was defined as the time from diagnosis of local recurrent tumor / distant metastasis, which led to the initiation of anti-HER2 re-therapy with Herceptin to death due to any cause. A total of 68 patients in the PP died during the study. For one patient, the date of death was not available. The overall survival of this patient was therefore included in the analysis as a censored case (date of last contact).

Overall Survival (OS-2) – Subgroup “Metastases / Local Recurrence Only”

In the PP, the median OS-2 was shortest in the subgroup of patients with visceral metastases (17.6 months (10.5 – 27.6 months)) versus the median OS-2 in the subgroups of patients with no metastases (local recurrence only) (not reached) and patients with non-visceral metastases (41.2 months (27.9 months – not reached)) as detailed in Table 9 and Figure 7.

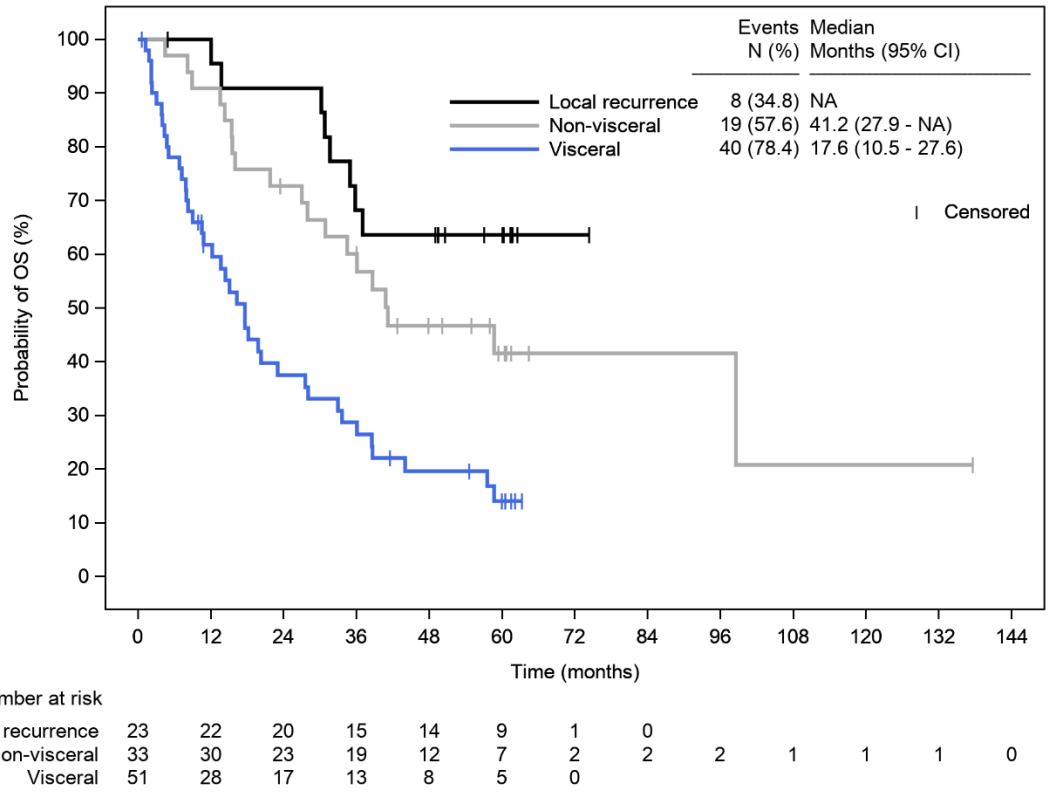
The lowest OS-2 rates were observed in the subgroup of patients with visceral metastases with a 12-month rate at 61.7%, 24-month rate at 37.5%, 36-month rate at 28.7% and 48-month rate at 19.6%.

Table 9 Overall survival (OS-2) from recurrence / distant metastases – subgroup "metastases / local recurrence only" (PP)

	No metastases (local recurrence only)	Non-visceral	Visceral
Per-protocol population (PP): Total N=107			
Total number of patients (subgroups), N	*23*	*33*	*51*
Events, n (%)	8 (34.8)	19 (57.6)	40 (78.4)
Quartiles (months)			
25% quantile [95% CI]	35.0 (12.0 - NA)	21.8 (8.9 - 34.5)	7.2 (3.9 - 10.8)
50% quantile [95% CI] (Median)	NA	41.2 (27.9 - NA)	17.6 (10.5 - 27.6)
75% quantile [95% CI]	NA	98.6 (58.7 - NA)	38.5 (23.0 - NA)
OS-2 rates (%) [95% CI]			
12-month	100.0% (100.0% - 100.0%)	90.9% (74.4% - 97.0%)	61.7% (46.8% - 73.6%)
24-month	90.9% (68.3% - 97.6%)	72.7% (54.1% - 84.8%)	37.5% (23.9% - 51.0%)
36-month	68.2% (44.6% - 83.4%)	60.1% (41.3% - 74.6%)	28.7% (16.6% - 42.0%)
48-month	63.6% (40.3% - 79.9%)	46.7% (28.8% - 62.8%)	19.6% (9.6% - 32.2%)

[Source: Herceptin_Abschlussanalyse_Tables; Table 21.4-f].
CI = Confidence interval; N/n = Number; NA = Not reached; OS = Overall survival; PP = Per-protocol population
No metastases: Patients without metastases at start of Herceptin re-therapy (local recurrence only)
Non-visceral: Patients with non-visceral metastases only, i.e. bone, skin, lymph node and soft tissue metastases (± local recurrence, no visceral metastases)
Visceral: Patients with visceral metastases, i.e. lung, liver, CNS, pleural effusion, ascites, and other metastases (free-text entries) coded as visceral by medical experts (± non-visceral metastases ± local recurrence). This group comprises all patients with visceral metastases including those having additional non-visceral metastases.
Overall survival (OS-2) was estimated by using the Kaplan-Meier method.
OS-2 was defined as the time from diagnosis of local recurrent tumor / distant metastasis, which led to the initiation of anti-HER2 re-therapy with Herceptin to death due to any cause. Patients without documented date of death at the end of study were censored at the last date known to be alive. If this date was not available, the date of the last documented dose of Herceptin was used for the censored case.
A total of 20 patients (PP) with exclusively non-visceral metastases died during the study. For one patient, the date of death was not available. The overall survival of this patient was therefore included in the analysis as a censored case (date of last contact).

Figure 7 Overall survival (OS-2) from recurrence / distant metastases – subgroup "metastases / local recurrence only" (PP)



[Source: Herceptin_Abschlussanalyse_Figures; Figure 22.3-f].
CI = Confidence interval; N = Number; NA = Not reached; PP = Per-protocol population; OS = Overall survival
Local recurrence: Patients without metastases at start of Herceptin re-therapy (local recurrence only)
Non-visceral: Patients with non-visceral metastases only, i.e. bone, skin, lymph node and soft tissue metastases (± local recurrence, no visceral metastases)
Visceral: Patients with visceral metastases, i.e. lung, liver, CNS, pleural effusion, ascites, and other metastases (free-text entries) coded as visceral by medical experts (± non-visceral metastases ± local recurrence). This group comprises all patients with visceral metastases including those having additional non-visceral metastases.
Overall survival (OS-2) was estimated by using the Kaplan-Meier method.
OS-2 was defined as the time from diagnosis of local recurrent tumor / distant metastasis, which led to the initiation of anti-HER2 re-therapy with Herceptin to death due to any cause.
In total, 20 patients (PP) with non-visceral metastases only deceased during the study. For one patient, date of death was not available. Therefore, OS of this patient was censored at date of last contact.

Overall Survival (OS-2) – Subgroup "Combination Therapy"

In the PP, the shortest median OS-2 was observed in the subgroup of patients having received a taxane in combination with Herceptin re-therapy (17.6 months (12.0 – 28.0 months)), whereas the longest median OS-2 was seen in the subgroup of patients having

received Herceptin mono re-therapy (not reached) or Herceptin re-therapy in combination with taxanes and endocrine therapy (not reached) as displayed in Table 10. The lowest OS-2 rates were seen in the subgroup of patients having received a taxane in combination with Herceptin re-therapy with a 12-month rate at 67.4%, 24-month rate at 37.7%, 36-month rate at 24.3% and 48-month rate at 13.5%.

Table 10 Overall survival (OS-2) from recurrence / distant metastases – subgroup "combination therapy (PP)

	Herceptin mono re-therapy	Taxanes	Endocrine therapy	Taxanes and endocrine therapy
Per-protocol population (PP): Total N=107				
Total number of patients (subgroups), N	*29*	*40*	*29*	*9*
Events, n (%)	12 (41.4)	35 (87.5)	18 (62.1)	2 (22.2)
Quartiles (months)				
25% quantile [95% CI]	13.8 (2.2 - 40.9)	8.1 (4.0 - 14.4)	16.0 (8.2 - 27.9)	NA
50% quantile [95% CI] (Median)	NA	17.6 (12.0 - 28.0)	35.0 (20.3 - NA)	NA
75% quantile [95% CI]	NA	33.6 (19.8 - 58.8)	NA	NA
OS-2 rates (%) [95% CI]				
12-month	81.7% (61.5% - 92.0%)	67.4% (50.6% - 79.6%)	86.2% (67.3% - 94.6%)	100.0% (100.0% - 100.0%)
24-month	74.3% (53.5% - 86.8%)	37.7% (22.7% - 52.7%)	65.5% (45.4% - 79.7%)	100.0% (100.0% - 100.0%)
36-month	63.1% (42.3% - 78.2%)	24.3% (12.1% - 38.7%)	47.3% (28.4% - 64.1%)	100.0% (100.0% - 100.0%)
48-month	59.2% (38.5% - 75.0%)	13.5% (4.9% - 26.3%)	36.4% (19.4% - 53.7%)	87.5% (38.7% - 98.1%)

[Source: Herceptin_Abschlussanalyse_Tables; Table 21.4-g].
CI = Confidence interval; N/n = Number; NA = Not reached; OS = Overall survival; PP = Per-protocol population
Herceptin mono re-therapy: Patients who did not receive any combination therapy (neither chemo-/immunotherapy nor endocrine therapy) with their Herceptin re-therapy.
Taxanes: Patients receiving a taxane in combination with their Herceptin re-therapy (but no endocrine therapy).
Endocrine therapy: Patients receiving endocrine therapy in combination with their Herceptin re-therapy (but no chemo-/immunotherapy).
Taxnes and endocrine therapy: Patients receiving taxanes and endocrine therapy in combination with their Herceptin re-therapy.
Overall survival (OS-2) was estimated by using the Kaplan-Meier method.
OS-2 was defined as the time from diagnosis of local recurrent tumor / distant metastasis, which led to the initiation of anti-HER2 re-therapy with Herceptin to death due to any cause. Patients without documented date of death at the end of study were censored at the last date known to be alive. If this date was not available, the date of the last documented dose of Herceptin® was used for the censored case.
A total of 19 patients (PP) with exclusively endocrine concomitant therapy died during the study. For one patient, the date of death was not available. The overall survival of this patient was therefore included in the analysis as a censored case (date of last contact).

Best Response (ORR)

In the PP, the ORR was 35.5% including 12 (11.2%) patients documented with a CR and 26 (24.3%) patients with a PR (Table 11).

Table 11 Best tumor response – (PP)

	N	%
Total number of patients, N	*107*	*100*
Best tumor response[1] (ORR), n, %		
CR	12	11.2
PR	26	24.3
ORR	38	35.5
NC (SD)	22	20.6
PD	29	27.1
Unknown	18	16.8

[Source: Herceptin_Abschlussanalyse_Tables; Table 21.5-b].
CR = Complete remission; N/n = Number; NC = No change; ORR = Overall response rate; PD = Progressive disease; PP = Per-protocol population; PR = Partial remission; SD = Stable disease
[1]As assessed by the respective treating physician.

KEY RESULTS (PP)

Progression-Free Survival

	Per-protocol population
Total number of patients	*107*
Events, n (%)	86 (80.4)
Median PFS (months) [95% CI]	11.4 (8.9 - 16.3)
PFS rates (%) [95% CI]	
6-month	77.1% (67.8% - 84.0%)
12-month	48.7% (38.7% - 57.9%)

CI = Confidence interval; n = Number; PFS = Progression-free survival

Progression-Free Survival – Subgroup[1] "Metastases / Local Recurrence Only"

	No metastases (local recurrence only)	Non-visceral	Visceral
Per-protocol population (PP): Total N=107			
Total number of patients (subgroups), N	*23*	*33*	*51*
Events, n (%)	11 (47.8)	28 (84.8)	47 (92.2)

	No metastases (local recurrence only)	Non-visceral	Visceral
Median PFS (months) [95% CI]	51.3 (11.9 - NA)	13.2 (8.2 - 18.4)	7.9 (6.5 - 10.5)

CI = Confidence interval; N/n = Number; NA = Not reached; PFS = Progression-free survival; PP = Per-protocol population
[1]Subgroups of patients with no metastases (local recurrence only), patients with non-visceral metastases (± local recurrence, no visceral metastases) and patients with visceral metastases (± non-visceral metastases ± local recurrence).

Progression-Free Survival – Subgroup[1] "Combination Therapy"

	Herceptin mono re-therapy	Taxanes	Endocrine therapy	Taxanes and endocrine therapy[3]
Per-protocol population (PP): Total N=107 *Total number of patients (subgroups)*	*29*	*40*	*29*	*9*
Events, n (%)	17 (58.6)	39 (97.5)	24 (82.8)	6 (66.7)
Median PFS (months) [95% CI]	20.9 (10.4 - NA)	8.0 (6.7 - 10.2)	12.2 (6.7 - 20.3)	36.7 (9.6 - NA)

CI = Confidence interval; N/n = Number; NA = Not reached; PFS = Progression-free survival; PP = Per-protocol population
[1]Subgroups of patients having received combination therapy with Herceptin re-therapy.

Overall Survival (OS)

	Per-protocol population
Total number of patients, N	*107*
Events, n (%)	67 (62.6)
Median OS (months) [95% CI]	78.3 (63.7 - 92.1)
OS rates (%) [95% CI]	
12-month	100.0% (100.0% - 100.0%)
24-month	100.0% (100.0% - 100.0%)
36-month	92.4% (85.3% - 96.1%)
48-month	83.7% (75.1% - 89.5%)

CI = Confidence interval; N/n = Number; OS = Overall survival

Overall Survival (OS-2)

	Per-protocol population
Total number of patients, N	*107*
Events, n (%)	67 (62.6)
Median OS-2 (months) [95% CI]	34.5 (27.0 - 40.9)
OS-2 rates (%) [95% CI]	
12-month	79.1% (70.0% - 85.7%)
24-month	60.3%

	Per-protocol population
	(50.2% - 69.0%)
36-month	47.2% (37.3% - 56.6%)
48-month	38.0% (28.5% - 47.3%)

CI = Confidence interval; N/n = Number; OS = Overall survival

Overall Survival (OS-2) – Subgroup[1] "Metastases / Local Recurrence Only"

	No metastases (local recurrence only)	Non-visceral	Visceral
Per-protocol population (PP): Total N=107 *Total number of patients (subgroups), N*	*23*	*33*	*51*
Events, n (%)	8 (34.8)	19 (57.6)	40 (78.4)
Median OS-2 (months) [95% CI]	NA	41.2 (27.9 - NA)	17.6 (10.5 - 27.6)

CI = Confidence interval; N/n = Number; NA = Not reached; OS = Overall survival
[1]Subgroups of patients with no metastases (local recurrence only), patients with non-visceral metastases (± local recurrence, no visceral metastases) and patients with visceral metastases (± non-visceral metastases ± local recurrence).

Overall Survival (OS-2) – Subgroup[1] "Combination Therapy"

	Herceptin mono re-therapy	Taxanes	Endocrine therapy	Taxanes and endocrine therapy[3]
Per-protocol population (PP): Total N=107 *Total number of patients (subgroups)*	*29*	*40*	*29*	*9*
Events, n (%)	12 (41.4)	35 (87.5)	18 (62.1)	2 (22.2)
Median OS-2 (months) [95% CI]	NA	17.6 (12.0 - 28.0)	35.0 (20.3 - NA)	NA

CI = Confidence interval; N/n = Number; NA = Not reached; OS = Overall survival; PP = Per-protocol population
[1]Subgroups of patients having received combination therapy with Herceptin re-therapy.

Overall Response (ORR)

	Per-protocol population
Total number of patients, N	*107*
Best tumor response[1] (ORR), n (%)	
CR	12 (11.2)
PR	26 (24.3)
ORR	38 (35.5)

CR = Complete remission; N/n = Number; ORR = Overall response rate; PP = Per-protocol population; PR = Partial remission
[1]As assessed by the respective treating physician.

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Table 1 List of stand-alone documents

Number	Document Reference Number[1]	Date[2]	Title
1	6.1	28 May 2008	Herceptin_ML21589_Beobachtungsplan_ Version 1.4_final_23072008
2	6.2	15 April 2011	ML21589_Amendment 1 Beobachtungsplan ML21589_gcp_for00348_v2_mit Unterschrift
3	6.2	7 July 2011	ML21589 Beobachtungsplan _V3.1_07.07.2011_mit Unterschrift
4	6.2	23 December 2013	Beobachtungsplan Version 4.0 final_23.12.2013 mit Originalunterschriftenseite
5	8.1	28 May 2008	ML21589_Herceptin_Patienteninformation_V1.1_20080528
6	7.1.1	24 March 2017	Herceptin_CRF_Screenshots_FINAL_V18_20170324
7	19.2	22 February 2019	20190222_Herceptin_Zentrenliste für CSR
8	19.1.1	29 January 2014	NIS Herceptin ReTherapie (ML21589)_SAP_Interimsanalysen_Version 1.0_final_20140129_signed_all
9	19.1.2	19 September 2010[3]	20101025_1. Interimsanalyse_Qualität_ML21589
10	19.1.2	18 March 2012[3]	2. Interimsanalyse_ML21589 NIS Herceptin ReTherapie_Datenstand_18032012
11	19.1.2	30 November 2012[3]	3. Interimsanalyse NIS Herceptin ReTherapie (ML21589)_ Datenstand_30112012
12	19.1.2	31 January 2014[3]	NIS ReTherapie (ML21589)_4. Interimsanalyse
13	19.1.2	27 September 2015[3]	Herceptin_Interimsanalyse_5
14	19.1.1	22 August 2018	ML21589 NIS ReTherapie_SAP Final Analysis_Vers.2.2_Final_20180822
15	19.1.1	09 May 2019	HERCEPTIN_NtF_SAPv2.2_PostHocAnalyses_20190509
16	19.1.3	25 April 2019	Herceptin_Abschlussanalyse_Listings_v1.2
17	19.1.3	25 April 2019	Herceptin_Abschlussanalyse_Figures_v1.2
18	19.1.3	25 April 2019	Herceptin_Abschlussanalyse_Tables_v1.2
19	19.2	See electronic date stamp on title page	Signature page of Scientific Responsible (title page)

Number	Document Reference Number[1]	Date[2]	Title

[1]The references correspond to the numbers of the Roche TMF table of contents .
[2]Effective date.
[3]The date of respective interim report reflects the time point for database cut.

ANNEX 2. DIFFERENCE BETWEEN THE CLINICAL DATABASE AND THE SAFETY DATABASE

Discrepancies With Respect to SOC: Blood and Lymphatic System Disorders

Three AEs were identified which have not been included in CDB (Table 1). Two of these events were related according to the company's assessment. Both events are known side effects of Herceptin.

Table 1 Blood and lymphatic system disorders

Patient	SAE Preferred Term	SAE Verbatim Term	Outcome	Discrepancy code
223001	Thrombocytopenia	THROMBOCYTOPENIA (Late In IRT: No, Comp: **Related**, Comp Serious: Serious, Rep Serious: Serious)	not recovered/ resolved	A, B
223001	Anemia of malignant disease	TUMOUR ANEMIA (Late In IRT: No, Comp: **Not Related**, Comp Serious: Serious, Rep Serious: Serious)		F
534003	Anemia	ANAEMIA (Late In IRT: No, Comp: **Related**, Comp Serious: Serious, Rep Serious: Serious)		A, C

A = Event missing in CDB; B = Seriousness upgraded by Roche; C = Not related (reporter) or no relationship provided:
F = Discrepancy between CDB and SDB remains, no event confirmed by reporter

Discrepancies With Respect to SOC: Cardiac Disorders

Altogether, four AEs were identified to be discrepant between SDB and CDB (Table 2). All but one event was reported to be related to Herceptin, the event for patient 859004 was related to bevacizumab. Seriousness upgrade by the sponsor occurred in the event from patient 266001. All related events reported are known side effects of Herceptin.

Table 2 Cardiac disorders

Patient	SAE Preferred Term	SAE Verbatim Term	Outcome	Discrepancy code
266001	Cardiac failure congestive	CONGESTIVE HEART FAILURE (Late In IRT: No, Comp: **Related**, Comp Serious: Serious, Rep Serious: Not Serious)	unknown	B, C
482001	Left ventricular dysfunction	LEFT VENTRICULAR SYSTOLIC DYSFUNCTION (Late In IRT: No, Comp: **Related**, Comp Serious: Serious, Rep Serious: Serious)	not recovered/ resolved	D
715001	Congestive cardiomyopathy	DILATED CARDIOMYOPATHY (Late In IRT: No, Comp: **Related**, Comp Serious: Serious, Rep Serious: Not Serious)	recovered/ resolved	D
859004	Left ventricular dysfunction	REDUCED LEFT VENTRICULAR FUNCTION (Late In IRT: No, Comp: **Related**, Comp Serious: Serious, Rep Serious: Serious)	not recovered/ resolved	X

B = Seriousness upgraded by Roche; C = Not related (reporter) or no relationship provided; D = Different PT coding (however, SOC identical); X = Adverse event is related to another Roche product

Discrepancies With Respect to SOC: Gastrointestinal Disorders

Nine AEs were identified to be discrepant between CDB and SDB (Table 3). Two events were related to Capecitabine. Three of the remaining seven events were not related to Herceptin. Main reason for discrepancies were changes in preferred terms, however derived from the same SOC. All related events reported are known side effects of Herceptin.

Table 3 Gastrointestinal disorders

Patient	SAE Preferred Term	SAE Verbatim Term	Outcome	Discrepancy code
223001	Faeces discoloured	BLACK STOOL (Late In IRT: No, Comp: **Not Related**, Comp Serious: Serious, Rep Serious: Not Serious)	unknown	D
223001	Ulcerative gastritis	ULCERATIVE ANTRAL GASTRITIS (Late In IRT: No, Comp: **Not Related**, Comp Serious: Serious, Rep Serious: Serious)	unknown	D
388002	Abdominal pain upper	STOMACH PAIN (Late In IRT: No, Comp: **Related**, Comp Serious: Not Serious, Rep Serious: Not Serious)	recovered/ resolved	D
445004	Nausea	NAUSEA (Late In IRT: No, Comp: **Related**, Comp Serious: Not Serious, Rep Serious: Not Serious)	recovered /resolved	C
445004	Vomiting	VOMITTING (Late In IRT: No, Comp: **Related**, Comp Serious: Not Serious, Rep Serious: Not Serious)	recovered/ resolved	C
534002	Gastrointestinal disorder	ABDOMINAL DISORDER (Late In IRT: No, Comp: **Not Related**, Comp Serious: Serious, Rep Serious: Serious)	unknown	D
534003	Diarrhoea	DIARRHOEA (Late In IRT: No, Comp: **Related**, Comp Serious: Serious, Rep Serious: Serious)		A, C
574001	Colitis	COLITIS (Late In IRT: No, Comp: **Related**, Comp Serious: Serious, Rep Serious: Serious)	recovered/ resolved	X
574001	Gastritis haemorrhagic	HEMORRHAGIC ANTRAL GASTRITIS (Late In IRT: No, Comp: **Not Related,** Comp Serious: Serious, Rep Serious: Serious)	recovered/ resolved	X

A = Event missing in CDB; C = Not related (reporter) or no relationship provided; D = Different PT coding (however, SOC identical); X = Adverse event is related to another Roche product

Discrepancies With Respect to SOC: General Disorders and Administration Site Conditions

Altogether, 13 discrepancies were identified within this SOC (Table 4). Out of these 13 events 9 were reported to be not related. The discrepant events mainly result from missing cases in CDB due to free text entries or doctors' letters. Of note, one death has been reported – however with unknown cause and consequently unknown relationship to Herceptin. All four related events are known side effects of Herceptin.

Table 4 General disorders and administration site conditions

Patient	SAE Preferred Term	SAE Verbatim Term	Outcome	Discrepancy code
423001	Multiple organ dysfunction syndrome	MULTI ORGAN FAILURE (Late In IRT: No, Comp: **Not Related**, Comp Serious: Serious, Rep Serious: Serious)		A
534003	Mucosal inflammation	MUCOSITIS (Late In IRT: No, Comp: **Related**, Comp Serious: Serious, Rep Serious: Serious)		A, C
534003	Pyrexia	FEVER (Late In IRT: No, Comp: **Related**, Comp Serious: Serious, Rep Serious: Serious)		A, C
573001	General physical health deterioration	BAD GENERAL CONDITION (Late In IRT: No, Comp: **Not Related**, Comp Serious: Not Serious, Rep Serious:)		A
614004	Death	DEATH CAUSE UNKNOWN (Late In IRT: No, Comp: **Not Related**, Comp Serious: Serious, Rep Serious: Serious)		A
717001	Nasal inflammation	MUCOSITIS OF NASAL MUCOUS MEMBRANES (Late In IRT: No, Comp: **Related**, Comp Serious: Not Serious, Rep Serious: Not Serious)	not recovered/ resolved	E

Patient	SAE Preferred Term	SAE Verbatim Term	Outcome	Discrepancy code
745001	Chills	CHILLS (Late In IRT: No, Comp: **Related,** Comp Serious: Not Serious, Rep Serious: Not Serious)		A
948001	Ill-defined disorder	THORACIC WALL RELAPSE (UNK DIAGNOSIS) (Late In IRT: No, Comp: **Not Related**, Comp Serious: Serious, Rep Serious: Serious)	recovered/ resolved	D
970001	General physical health deterioration	WORSENING OF GENERAL CONDITION (Late In IRT: No, Comp: **Not Relate**d, Comp Serious: Not Serious, Rep Serious:)		A
1335001	Pain	PAIN (Late In IRT: No, Comp: **Not Related**, Comp Serious: Serious, Rep Serious: Serious)		A
1494002	General physical health deterioration	BAD GENERAL CONDITION (Late In IRT: No, Comp: **Not Related**, Comp Serious: Not Serious, Rep Serious:)		A
1559003	Drug intolerance	POOR CHEMOTHERAPY TOLERANCE (DRUG INTOLERANCE) (Late In IRT: No, Comp: **Not Related**, Comp Serious: Not Serious, Rep Serious:)		A
1586001	Multiple organ dysfunction syndrome	MULTIORGAN FAILURE (Late In IRT: No, Comp: **Not Related**, Comp Serious: Serious, Rep Serious: Serious)		A

A = Event missing in CDB; C = Not related (reporter) or no relationship provided; D = Different PT coding (however, SOC identical); E = Different PT coding resulting in different SOC

Discrepancies With Respect to SOC: Infections and Infestations

Three events were identified to be discrepant under this SOC, two of these events were not related (Table 5). The remaining related AE is a known side effect of Herceptin. The (not related) event from patient 223001 was assigned to a different SOC on CDB.

Table 5 Infections and infestations

Patient	SAE Preferred Term	SAE Verbatim Term	Outcome	Discrepancy code
223001	Oesophagitis	ESOPHAGITIS (Late In IRT: No, Comp: **Not Related**, Comp Serious: Serious, Rep Serious: Serious)	unknown	E
1494001	Infection	INFECTION NOS (Late In IRT: No, Comp: **Related**, Comp Serious: Serious, Rep Serious:)		A
1040002	Appendicitis perforated	PERFORATED APPENDICITIS (Late In IRT: No, Comp: **Not Related**, Comp Serious: Serious, Rep Serious:)	recovered/ resolved	G

A = Event missing in CDB; E = Different PT coding resulting in different SOC; G = Discrepancy in seriousness between CDB and SDB (seriousness in CDB > SDB),

Discrepancies With Respect to SOC: Investigations

All six events were missing on CDB as events were found in narratives (Table 6). None of the events is related. The orientation of weight abnormality was not specified.

Table 6 Investigations

Patient	SAE Preferred Term	SAE Verbatim Term	Outcome	Discrepancy code
237001	Weight abnormal	WEIGHT CHANGE (UNKNOWN DIAGNOSIS) (Late In IRT: No, Comp: **Not Related**, Comp Serious: Not Serious, Rep Serious:)		A
463003	Weight abnormal	WEIGHT CHANGE (UNK DIAGNOSIS) (Late In IRT: No, Comp: **Not Related**, Comp Serious: Not Serious, Rep Serious:)		A
497003	Weight abnormal	WEIGHT CHANGE (UNK DIAGNOSIS) (Late In IRT: No, Comp: **Not Related**, Comp Serious: Not Serious, Rep Serious:)		A
585002	Weight abnormal	WEIGHT CHANGE (UNKNOWN DIAGNOSIS) (Late In IRT: No, Comp: **Not Related**, Comp Serious: Not Serious, Rep Serious:)		A

Patient	SAE Preferred Term	SAE Verbatim Term	Outcome	Discrepancy code
687002	Weight increased	WEIGHT INCREASED (Late In IRT: No, Comp: **Not Related**, Comp Serious: Not Serious, Rep Serious:)		A
1309002	Weight fluctuation	WEIGHT CHANGED (UNK DIAGNOSIS) (Late In IRT: No, Comp: Not Related, Comp Serious: Not Serious, Rep Serious:)		A

A = Event missing in CDB

Discrepancies With Respect to SOC: Neoplasms Benign, Malignant and Unspecified

Altogether, nine AEs were identified to be either missing on CDB or SDB (Table 7). None of these was reported to be related. Eight events are progressions of the underlying breast cancer, which was an endpoint of the NIS and therefore not reportable as an AE.

Table 7 Neoplasms benign, malignant and unspecified

Patient	SAE Preferred Term	SAE Verbatim Term	Outcome	Discrepancy code
343001	Malignant neoplasm progression	DISEASE PROGRESSION OF PRE-EXISTING CANCER (Late In IRT: No, Comp: **Not Related**, Comp Serious: Serious, Rep Serious: Serious)		A, H
487001	Malignant neoplasm progression	DISEASE PROGRESSION OF PRE-EXISTING CANCER (Late In IRT: No, Comp: **Not Related**, Comp Serious: Serious, Rep Serious: Serious)		A, H
535001	Breast cancer	DISEASE PROGRESSION OF BREAST CANCER (Late In IRT: No, Comp: **Not Related**, Comp Serious: Serious, Rep Serious: Serious)		A, H
726006	Progress	Progress; serious (Onset: 10.08.2012)	not recovered/ resolved	I, H
726006	Progress	Progress; serious (Onset: 01.11.2015)	Exitus / fatal	I, H

Patient	SAE Preferred Term	SAE Verbatim Term	Outcome	Discrepancy code
859002	Metastases to central nervous system	CEREBRAL METASTASES (Late In IRT: No, Comp: **Not Related**, Comp Serious: Serious, Rep Serious:)		A
1559003	Malignant neoplasm progression	DISEASE PROGRESSION OF PRE-EXISTING CANCER (Late In IRT: No, Comp: **Not Related**, Comp Serious: Serious, Rep Serious: Serious)		A, H
1560002	Breast cancer recurrent	LOCAL BREAST CANCER RELAPSE (Late In IRT: No, Comp: **Not Related**, Comp Serious: Serious, Rep Serious:)		A, H
1040002	Malignant neoplasm progression	DISEASE PROGRESSION OF PRE-EXISTING CANCER (Late In IRT: No, Comp: **Not Related**, Comp Serious: Serious, Rep Serious:)	unknown	H, C

A = Event missing in CDB; C = Not related (reporter) or no relationship provided; H = Progression of disease (PoD) with no need to report as AE on CDB; I = PoD not present in SDB

Discrepancies With Respect to SOC: Nervous System Disorders

In total, five AEs were identified for discrepant preferred term allocation to SOC (Table 8). All events were reported to be related to Herceptin. All but one event is known to be resolved. Vertigo is a known side effect of Herceptin.

Table 8 Nervous system disorders

Patient	SAE Preferred Term	SAE Verbatim Term	Outcome	Discrepancy code
388001	Vertigo	VERTIGO (Late In IRT: No, Comp: **Related**, Comp Serious: Not Serious, Rep Serious: Not Serious)	recovered/ resolved	E
445004	Vertigo	VERTIGO (Late In IRT: No, Comp: **Related**, Comp Serious: Not Serious, Rep Serious: Not Serious)	recovered/ resolved	E
548003	Vertigo	VERTIGO (Late In IRT: No, Comp: **Related**, Comp Serious: Not Serious, Rep Serious: Not Serious)	recovered/ resolved	E

Patient	SAE Preferred Term	SAE Verbatim Term	Outcome	Discrepancy code
574001	Vertigo	VERTIGO (Late In IRT: No, Comp: **Related,** Comp Serious: Not Serious, Rep Serious: Not Serious)	recovered/ resolved	E
743001	Vertigo	VERTIGO (Late In IRT: No, Comp: **Related,** Comp Serious: Not Serious, Rep Serious: Not Serious)	unknown	E

E = Different PT coding resulting in different SOC

Discrepancies With Respect to SOC: Respiratory, Thoracic and Mediastinal Disorders

Three events were identified to be discrepant between SDB and CDB (Table 9). Two of these three events were not related to Herceptin. One event of pulmonary embolism, which resulted in death of the patient (death of the patient is reported in CDB) was reported to be related. The event of pulmonary embolism is not expected for Herceptin.

Table 9 Respiratory, thoracic and mediastinal disorders

Patient	SAE Preferred Term	SAE Verbatim Term	Outcome	Discrepancy code
407001	Pulmonary embolism	SUSPECTED PULMONARY EMBOLISM (Late In IRT: No, Comp: **Related**, Comp Serious: Serious, Rep Serious:)		A
970001	Effusion	SUSPECTED LOCULATED EFFUSION (EFFUSION) (Late In IRT: No, Comp: **Not Related**, Comp Serious: Not Serious, Rep Serious: Not Serious)	unknown	E
1040002	Bronchial heamorrhage	ACUTE BLEEDING LEFT MAIN BRONCHUS (Late In IRT: No, Comp: **Not Related**, Comp Serious: Serious, Rep Serious:)	recovered/ resolved	C

A = Event missing in CDB; C = Not related (reporter) or no relationship provided; E = Different PT coding resulting in different SOC

Discrepancies With Respect to SOC: Vascular Disorders

In total, three AEs were discrepant between the databases (Table 10). Two of these events were reported not to be related to Herceptin. The related event hypertension is a known side effect of Herceptin. Discrepancy resulted from different relationship assessment. As

reporter described the event as not related to Herceptin, event is missing on CDB. The sponsor, however, judged the event to be related to Herceptin.

Table 10 Vascular disorders

Patient	SAE Preferred Term	SAE Verbatim Term	Outcome	Discrepancy code
534003	Hypertension	HYPERTENSION ARTERIAL (Late In IRT: No, Comp: **Related,** Comp Serious: Serious, Rep Serious: Serious)		A, C
1040002	pelvic venous thrombosis	PELVIC VEIN THROMBOSIS (Late In IRT: No, Comp: **Not Related**, Comp Serious: Serious, Rep Serious:)	recovered/ resolved	C
1040002	vena cava thrombosis	THROMBOSIS OF INFERIOR VENA CAVA (Late In IRT: No, Comp: **Not Related**, Comp Serious: Serious, Rep Serious:)	recovered/ resolved	C

A = Event missing in CDB; C = Not related (reporter) or no relationship provided,

Discrepancies with respect to SOC: Surgical and medical procedures

Three AEs were identified to be discrepant between the SDB and CDB (Table 11). Two events were identified in narratives, both were not related to Herceptin. The remaining event that is assessed as being related to Herceptin by the sponsor had been subject to a different PT-coding on SDB, however derived from the same SOC. The event “prophylaxis” is correlated to gastrointestinal symptoms, which are known side effects of the treatment with Herceptin. Therefore, stomach prophylaxis is a common medical procedure during treatment.

Table 11 Surgical and medical procedures

Patient	SAE Preferred Term	SAE Verbatim Term	Outcome	Discrepancy code
614002	Cancer surgery	METASTASECTOMY (Late In IRT: No, Comp: **Not Related**, Comp Serious: Serious, Rep Serious:)		A
859002	Prophylaxis	STOMACH PROPHYLAXIS (UNK DIAGNOSIS) (Late In IRT: No, Comp: **Related**, Comp Serious: Not Serious, Rep Serious: Not Serious)	recovered/ resolved	D

Patient	SAE Preferred Term	SAE Verbatim Term	Outcome	Discrepancy code
1328001	Mastectomy	ABLATIO MAMMAE (Late In IRT: No, Comp: **Not Related**, Comp Serious: Serious, Rep Serious:)		A

A = Event missing in CDB; D = Different PT coding (however, SOC identical),

Discrepancies From Other SOCs

Altogether, three discrepancies in other SOCs resulted from: “ear and labyrinth disorders” (Table 12), “musculoskeletal and connective tissue disorders” (Table 13) and “skin and subcutaneous tissue disorders” (Table 14). One of them was not related. The remaining two events were VIIIth nerve injury and pain in extremity. The injury of the vestibular nerve was coded differently on CDB, the event from patient 548005 was coded with a different PT, within the same SOC. Both events are reported on CDB as well as on SDB. Both events are not known to be side effects of Herceptin. However, it can be anticipated that vertigo (see SOC “nervous system disorders” for this patient) is a co-manifestation from VIIIth nerve injury. Vertigo is a known side effect of Herceptin.

Table 12 Ear and labyrinth disorders

Patient	SAE Preferred Term	SAE Verbatim Term	Outcome	Discrepancy code
743001	VIIIth nerve injury	VESTIBULAR NEUROPATHY RIGHT (VESTIBULAR NERVE DAMAGE) (Late In IRT: No, Comp: **Related**, Comp Serious: Serious, Rep Serious: Serious)	recovered/ resolved	E

E = Different PT coding resulting in different SOC

Table 13 Musculoskeletal and connective tissue disorders

Patient	SAE Preferred Term	SAE Verbatim Term	Outcome	Discrepancy code
548005	Pain in extremity	PAIN IN LIMBS (Late In IRT: No, Comp: **Related,** Comp Serious: Not Serious, Rep Serious: Not Serious)	recovered/ resolved	D

D = Different PT coding (however, SOC identical)

Table 14 Skin and subcutaneous tissue disorders

Patient	SAE Preferred Term	SAE Verbatim Term	Outcome	Discrepancy code
948001	Skin disorder	SUBCUTANEOUS RELAPSE (UNK DIAGNOSIS) (Late In IRT: No, Comp: **Not Related**, Comp Serious: Not Serious, Rep Serious:)		A

A = Event missing in CDB

ANNEX 3. ADDITIONAL INFORMATION

Table 1 Responsible parties and study administrative structure

Sponsor

Study Program Manager

Roche Pharma AG
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Data Manager

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CRO = Contract research organization