PerFECT

Pertuzumab in First Line Treatment of HER2-positive metastatic breast cancer patients: A cohort study of patients treated either with docetaxel and Trastuzumab or docetaxel, trastuzumab and pertuzumab

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1 Summary

Indication

Metastatic or locally advanced, unresectable HER2-positive breast cancer (ABC), first line treatment.

Background

Between 18% and 20% of breast cancers show HER2 amplification and/or HER2 receptor overexpression. Such patients have a poor prognosis on conventional treatment [5]. The HER2 receptor is a protein belonging to the epidermal growth factor receptor (EGFR) family. The HER family consists of four structurally similar receptors – HER1/EGFR, HER2, HER3, HER4 – and regulates cell processes such as differentiation, invasion, proliferation, neo-angiogenesis, survival and metastatic potential [6-8]. In breast cancer HER2 positivity is associated with more aggressive tumors, higher relapse rates, lower and shorter treatment response and increased mortality [9-16].

Treatment of advanced HER2-positive breast cancer

Systemic treatment options in ABC include chemotherapy along with hormonal and targeted approaches. Tumor properties and patient-specific factors determine the choice of treatment [17, 18].

Trastuzumab (Herceptin®)

In patients with HER2-positive ABC, trastuzumab was the reference first-line treatment for many years [17-19]. Treatment-naive HER2–positive patients with ABC, who were treated with trastuzumab and taxane chemotherapy, showed significantly longer median time to progression (TTP), higher objective response rates (ORR) and longer median response and median survival than patients treated with chemotherapy alone [SmPC Herceptin®, April 2015]. Although trastuzumab has proved effective in combination with chemotherapy in the first-line treatment of patients with HER2-positive ABC, approximately 50% of patients experience disease progression within one year of starting treatment [20-23]. Mean survival in HER2-positive patients in the pivotal studies of trastuzumab in combination with a taxane was 24.8 and 31.2 months [21, 22].

Therefore there was high medical need for novel HER2-targeted therapies to improve survival outcomes in patients with HER2-positive ABC at the time where trastuzumab was the only approved drug in this therapy setting.
Pertuzumab (Perjeta®)
An essential step in activating downstream signaling pathways is homo- or heterodimerisation of the HER2 receptor with an other member of the HER family [24]. Inhibition of HER2 dimerisation inhibits the downstream signaling pathways that mediate cancer cell proliferation and survival [25-27]. Pertuzumab, a humanized monoclonal antibody, is the first HER2 dimerisation inhibitor (HDI). It binds specifically to the extracellular dimerisation domain of the HER2 receptor [28], which is responsible for dimerisation and thereby inhibiting ligand-dependent heterodimerisation of the receptor with other HER family members [29]. Pertuzumab actually inhibits ligand-activated intracellular signal transduction in two main signaling pathways – the mitogen-activated protein kinase (MAPK) pathway and the phosphoinositol-3-kinase (PI3K) pathway. Inhibition of these signaling pathways can arrest cell growth and cause apoptosis [25, 29, 30]. Pertuzumab also mediates antibody-dependent cell-mediated cytotoxicity (ADCC).

Pertuzumab and trastuzumab bind to different epitopes on the HER2 receptor [31]. Their mechanisms of action complement each other to ensure more comprehensive blockade of HER2-dependent signaling pathways.

CLEOPATRA trial
The phase III, multicenter, randomized, double-blind and placebo-controlled clinical CLEOPATRA trial compared pertuzumab plus trastuzumab plus docetaxel versus placebo plus trastuzumab plus docetaxel in 808 patients with HER2-positive metastatic, locally recurrent or inoperable breast cancer. Patients may have received one hormonal treatment for metastatic breast cancer before randomization. Patients may have received adjuvant or neoadjuvant chemotherapy with or without trastuzumab before randomization, with an interval of at least 12 months between completion of the adjuvant or neoadjuvant therapy and the diagnosis of metastatic breast cancer. Randomized patients were stratified by previous treatment status (with or without previous adjuvant/neoadjuvant therapy) and geographic location (Europe, North America, South America and Asia). Pertuzumab was given intravenously at a starting dose of 840 mg followed by a dose of 420 mg every 3 weeks. Trastuzumab was given intravenously at a starting dose of 8 mg/kg followed by a dose of 6 mg/kg every 3 weeks. Patients were treated with pertuzumab plus trastuzumab until disease progression, withdrawal of consent to participation or the development of uncontrollable toxicity. Docetaxel was given as an intravenous infusion at a starting dose of 75 mg/m² every 3 weeks for at least 6 cycles. If the starting dose was well-
tolerated, the dose of docetaxel could be increased up to 100 mg/m² at the investigator’s discretion.

The primary study endpoint was progression-free survival (PFS), assessed by an independent review facility (IRF) and defined as the interval between randomization and disease progression or death (from any cause), where death occurred within 18 weeks of the last disease assessment. The secondary endpoints were overall survival (OS), (investigator-rated) PFS, objective response rate (ORR), duration of response and time to progression (TTP).

Demographic characteristics were evenly balanced (mean age was 54 years, most [59%] were Caucasian and all but two were female). In each treatment group approximately half the patients had hormone (estrogen or progesterone) receptor-positive disease and had received previous adjuvant or neoadjuvant therapy (184 patients [45.8%] in the pertuzumab group vs. 192 patients [47.3%] in the placebo group). Most (37.3% and 40.4%, respectively) had previously received anthracyclines and approximately 10% had previously received trastuzumab (11.7% and 10.1%). A total of 43% of patients from both groups had received prior radiotherapy. The mean baseline left ventricular ejection fraction (LVEF) was 64.8% in the pertuzumab group and 65.6% in the placebo group (median 65.0%, range 50%–88% in the two groups).

The CLEOPATRA study showed statistically significant improvement of IRF-rated PFS in the pertuzumab group vs. placebo (hazard ratio [HR]=0.62; 95% CI=0.51; 0.75, p<0.0001) and an increase in median PFS of 6.1 months. Median PFS was 18.5 months in the pertuzumab group vs. 12.4 months in the placebo group[32]. Moreover, CLEOPATRA showed statistically significant improvement of overall survival in the pertuzumab group vs placebo (hazard ratio [HR]=0.68; 95% CI=0.56; 0.84, p<0.0002) and an increase in median OS of 15.7 months. Median OS was 56.5 months in the pertuzumab group vs. 40.8 months in the placebo group [33].

Despite the clear benefit of a combination therapy of pertuzumab plus trastuzumab plus docetaxel when compared with a combination therapy of trastuzumab and docetaxel the study populations of the CLEOPATRA study might be slightly different from a patient population, in which pertuzumab, plus trastuzumab plus docetaxel or trastuzumab plus docetaxel are applied in routine clinical practice.
This non-interventional approach aims to assess the clinically relevant outcomes shown in the phase III CLEOPATRA study in patients with advanced HER2-positive breast cancer [32] in routine practice. Data on efficacy, safety, tolerability and quality of life will be documented for this purpose [34].

Objectives and Outcome Measures

Primary: The primary objective of this study is to assess the progression free survival rate at month 12 for both treatment cohorts in routine clinical practice treated with either pertuzumab plus trastuzumab plus chemotherapy or trastuzumab plus chemotherapy, defined as probability of progression free survival at month 12, calculated using Kaplan-Meier estimates.

Secondary:
- to assess efficacy between the two treatment cohorts as assessed by progression free survival (PFS). PFS is defined as time interval from start of therapy until progressive disease (PD) or death from any cause, whichever comes first.
- to assess efficacy between the two treatment cohorts as assessed by overall response rate (ORR) defined as rate of complete (CR) and partial responses (PR) in patients (CR, PR, SD, and PD are evaluated according to daily clinical practice)
- to assess quality of life based on the evaluation of the EORTC QLQ-C30 and EORTC QLQ-BR23 questionnaires within the first line treatment either with chemotherapy and trastuzumab or chemotherapy, trastuzumab and pertuzumab.
- to evaluate the safety and tolerability of the study treatments (all AE’s of all grades of severity, all serious adverse events). Incidence of adverse events, serious adverse events will be reported according to NCI Common Toxicity Criteria Version 4.03.

Study design The study will be conducted as a prospective non-interventional study. The assignment of the patient to a particular treatment falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the non-interventional study.

Enrollment of patients may only be initiated following approval of the IRB of the University Hospital of Erlangen.

Treatment Patients are treated either with pertuzumab plus trastuzumab plus chemotherapy or trastuzumab plus chemotherapy as first line therapy. Docetaxel is recommended as chemotherapy, however, any treatment choice or change in regimen is performed at the discretion of each treating physician.
Main In- and Exclusion Criteria

Inclusion criteria

• Adult breast cancer patients (age ≥18 years)
• Patients with metastatic or locally advanced, unresectable HER2-positive breast cancer proven by clinical measures (i.e. standard imaging) in first line treatment (Locally advanced disease must not be amenable to resection with curative intent)
• Patients are treated either with trastuzumab plus chemotherapy or pertuzumab plus trastuzumab plus chemotherapy as first line therapy according to each center’s medical practice. The first line anti-HER2 treatment must not have started more than 28 days before study entry
• No prior chemotherapy or HER2-directed therapy for metastatic or locally advanced disease, prior therapy for early breast cancer is allowed
• Written and signed informed consent prior to onset of documentation

Exclusion criteria

• Patients who are not eligible for observation due to severe comorbidities or unavailability according to the treating physician

Statistical Methods

This NIS will be considered as a registry: a registry is a complete collection of patients for a given time period (between 01 Feb 2016 and approx. 30 Jan 2020 and for centers willing to participate). No formal statistical hypothesis and no formal sample size calculation will be performed.

All efficacy and safety variables documented in this study will be analyzed by means of descriptive analysis.

Continuous data will be summarized using mean, standard deviation, median, minimum and maximum. Categorical variables will be expressed as absolute and relative number. Progression-free survival rates will be calculated using the Kaplan-Meier method. Patients will be documented until progression of disease.

Collateral Research

The PerFECT study will be conducted in cooperation with the PRAEGNANT study network. PerFECT will be a designated feeder study of the PRAEGNANT study. This will not have an influence on the conduction of this non-interventional study.
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Planned number of sites

Duration of Study

- IRB Submission: December 2015 (planned)
- FPI: May 2016
- LPI: January 2018 (planned)
- LPO: January 2020 (planned)
- Interim analysis: April 2018 (planned)/Data cut off January 2018 (planned)
- Final clinical study report: July 2020 (planned)

Publication Plan

Planned Journal Name: e.g. European Journal of Cancer, target Journal Date: planned for Oct 2020. A publication may be submitted after planned interim analysis. Trial in progress abstracts/posters to be submitted at international and local conferences e.g. (SABCS, ESMO, DGS, DGHO)
2 Background and Rationale

2.1 Breast Cancer Epidemiology and Treatment

Breast cancer is the most common cancer in women worldwide with an estimated 1.4 million new diagnoses in 2008 and 1.6 million cases estimated for 2015. In 2008 breast cancer was responsible for approximately 23% of all new cancer diagnoses in women. It is also the commonest cause of cancer deaths in women worldwide: in 2008 some 458,500 women died from breast cancer, with a further 538,500 projected for 2015 [1].

In developed countries most breast cancers (in 94%–95% of patients in the EU and USA) are diagnosed while the tumor is confined to the breast – with or without locoregional lymph node involvement [2, 3]. At this early breast cancer (EBC) stage the disease is normally operable and can be treated curatively. Metastatic breast cancer (MBC) is less common and occurs in 5%–6% of newly diagnosed cases [2, 3].

Despite advances in the treatment of EBC approximately 30% of women develop local recurrence or metastases [4]. In the USA and Europe patients with MBC survive for a mean 24 months and have a 5-year survival rate of 18%–23% [2, 3].

Between 18% and 20% of breast cancers show human epidermal growth factor receptor 2 (HER2) gene amplification and/or HER2 overexpression. Such patients have a poor prognosis on conventional treatment [5]. HER2 is a protein belonging to the epidermal growth factor receptor (EGFR) family. The HER family consists of four structurally similar receptors – HER1/EGFR, HER2, HER3, HER4 – and regulates cell processes such as differentiation, invasion, proliferation, neoangiogenesis, survival and metastatic potential [6, 35, 36]. In breast cancer HER2 positivity is associated with more aggressive tumors, higher relapse rates, lower and shorter treatment response and increased mortality [7, 9-14, 16, 37].

2.2 Treatment of advanced Human Epidermal Growth Factor Receptor 2 (HER2)-positive breast cancer

Systemic treatment options in MBC include chemotherapy along with hormonal and targeted approaches. Tumor properties and patient-specific factors determine the choice of treatment [17, 18].

In HER2-positive MBC trastuzumab was for many years the reference in first-line treatment [17-19]. Treatment-naive HER2-positive patients with MBC treated with trastuzumab and taxane chemotherapy showed significantly longer median time to progression (TTP), higher objective response rates (ORR) and longer median response and median survival than patients treated with chemotherapy alone [SmPC Herceptin®, April 2015]. Although trastuzumab has proven effective in combination with chemotherapy in first-line treatment of patients with HER2-positive MBC, approximately 50% of patients experience disease progression within one year of treatment initiation [20-23]. Median survival in HER2-positive patients in the pivotal studies of trastuzumab in combination with a taxane was 24.8 and 31.2 months [21, 22].
Therefore there is high medical need for novel HER2-targeted therapies to improve survival outcomes in patients with HER2-positive MBC. An essential step in activating downstream signaling pathways is homodimerisation of HER2 with other members of the HER family [24]. Inhibition of HER2 dimerisation inhibits the downstream signaling pathways that mediate cancer cell proliferation and survival [25-27]. Pertuzumab, a humanized monoclonal antibody, is the first HER2 dimerisation inhibitor (HDI). Inhibition of downstream signaling pathways can arrest cell growth and cause apoptosis [25, 29, 30]. Pertuzumab also mediates antibody-dependent cell-mediated cytotoxicity (ADCC).

The mechanisms of action of the antibodies pertuzumab and trastuzumab complement each other to ensure a more comprehensive blockade of HER2-dependent signaling pathways [31].

The phase III, multicenter, randomised, double-blind and placebo-controlled clinical CLEOPATRA trial compared pertuzumab plus trastuzumab plus docetaxel vs. placebo plus trastuzumab plus docetaxel in 808 patients with HER2-positive metastatic, locally recurrent or inoperable breast cancer. Patients were allowed to have received one hormonal treatment for metastatic breast cancer before randomization. Patients may have received adjuvant or neoadjuvant chemotherapy with or without trastuzumab before randomization, with an interval of at least 12 months between completion of the adjuvant or neoadjuvant therapy and the diagnosis of metastatic breast cancer. Randomised patients were stratified by previous treatment status (with or without previous adjuvant/neoadjuvant therapy) and geographic location (Europe, North America, South America and Asia). Pertuzumab was given intravenously at a starting dose of 840 mg followed by a dose of 420 mg every 3 weeks. Trastuzumab was given intravenously at a starting dose of 8 mg/kg followed by a dose of 6 mg/kg every 3 weeks. Patients were treated with pertuzumab plus trastuzumab until disease progression, withdrawal of consent or development of uncontrollable toxicity. Docetaxel was given as an intravenous infusion at a starting dose of 75 mg/m² every 3 weeks for at least 6 cycles. If the starting dose was well-tolerated, the dose of docetaxel could be increased up to 100 mg/m² at the Physician’s discretion.

The primary study endpoint was progression-free survival (PFS), assessed by an independent review facility (IRF) and defined as the interval between randomisation and disease progression or death (from any cause), where death occurred within 18 weeks of the last disease assessment. The secondary endpoints were overall survival (OS), (physician-assessed) PFS, objective response rate (ORR), duration of response and time to progression (TTP).

Demographic characteristics were evenly balanced (mean age was 54 years, most patients [59%] were Caucasian and all but two were female). In each treatment group approximately half the patients had hormone (estrogen or progesterone) receptor-positive disease and had received previous adjuvant or neoadjuvant therapy (184 patients [45.8%] in the pertuzumab group vs 192 patients [47.3%] in the placebo group). Most patients (37.3% and 40.4%, respectively) had previously received anthracyclines and approximately 10% had previously received trastuzumab (11.7% and 10.1%). A total 43% of patients from both groups had received prior

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radiotherapy. The mean baseline left ventricular ejection fraction (LVEF) was 64.8% in the pertuzumab group and 65.6% in the placebo group (median 65.0%, range 50%–88% in the two groups).

The CLEOPATRA study showed statistically significant improvement of PFS in the pertuzumab group vs. placebo (hazard ratio [HR]=0.62; 95% CI=0.51; 0.75; p<0.0001) and an increase in median PFS of 6.1 months. Median PFS was 18.5 months in the pertuzumab group vs 12.4 months in the placebo group [32]. Moreover, CLEOPATRA showed statistically significant improvement of overall survival in the pertuzumab group vs placebo (hazard ratio [HR]=0.68; 95% CI=0.56; 0.84; p<0.0002) and an increase in median OS by 15.7 months. Despite cross-over, median OS was 56.5 months in the pertuzumab group vs 40.8 months in the placebo group [33].

2.2.1 Pertuzumab (Perjeta®)

Pertuzumab is approved for the combined treatment with trastuzumab and docetaxel in adult patients with HER2-positive, metastatic or locally recurring inoperable breast cancer, who did not receive previous chemotherapy or anti HER2 therapy for the treatment of metastatic disease. Furthermore, pertuzumab is approved for the neoadjuvant treatment in combination with chemotherapy and trastuzumab in adult patients with HER2-positive, locally advanced inflammatory breast cancer or early breast cancer with high risk of relapse (SmPC Perjeta®, Roche Pharma AG, version July 2015).

Pertuzumab is a recombinant humanised monoclonal antibody. It binds specifically to the extracellular dimerisation (subdomain II) domain of HER2 [28], thereby inhibiting ligand-dependent heterodimerisation of the receptor with other HER family members (i.a. epidermal growth factor receptor EGFR, HER3, HER4) [29]. Sterical inhibition of heterodimerisation leads to a blockade of ligand-activated intracellular signal transduction in two main signaling pathways – the mitogen-activated protein kinase (MAPK) pathway and the phosphatidylinositol-3-kinase (PI3K) pathway. Inhibition of these signal pathways can arrest cell growth and cause apoptosis [25, 29, 30]. Pertuzumab also mediates antibody-dependent cell-mediated cytotoxicity (ADCC).

2.2.2 Trastuzumab (Herceptin®)

Trastuzumab is approved for the treatment of metastatic cancer of the stomach as well as for the therapy of early and metastatic breast cancer (SmPC Herceptin® i.v., SmPC Herceptin® SC, Roche Pharma AG, version July 2015).

In breast cancer patients trastuzumab may be only given if HER2 overexpression or amplification of the gene coding for HER2 in the tumor has been proven by validated assessment.

In early breast cancer (EBC) trastuzumab is indicated after surgery, chemotherapy and radiotherapy, after adjuvant chemotherapy with doxorubicin and cyclophosphamide plus paclitaxel or docetaxel, as a combined treatment with adjuvant chemotherapy with docetaxel or carboplatin as well as a combined treatment with neoadjuvant chemotherapy followed by trastuzumab adjuvant treatment.
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treatment in locally advanced, including inflammatory, breast cancer or tumors >2cm in diameter.
In MBC trastuzumab may be given as a monotherapy in patients who previously received at least two chemotherapeutic regimens for metastatic disease. Previous chemotherapy must have contained at least one anthracycline and one taxane in patients who are eligible for those regimens. Hormone treatment must have failed in hormone receptor positive patients, unless this treatment was not suitable for the patient. Furthermore, trastuzumab may be given together with paclitaxel in patients who did not receive previous chemotherapy for metastatic disease and who are not eligible for anthracycline treatment or together with docetaxel in patients who did not receive previous chemotherapy for metastatic disease. In postmenopausal patients with hormone receptor positive MBC trastuzumab may be given together with an aromatase inhibitor in patients not pretreated with trastuzumab.

Trastuzumab is a recombinant humanised monoclonal IgG1 antibody binding to HER2 subdomain IV, a juxtamembrane region in the extracellular domain of the receptor. Binding of trastuzumab interferes with the ligand-independent HER2 signaling by preventing proteolytic processing of the extracellular HER2 domain and, eventually, activation of HER2. Hence, inhibition of HER2 proteolysis and activation by trastuzumab results in inhibition of proliferation. Furthermore, trastuzumab also mediates antibody-dependent cell-mediated cytotoxicity (ADCC).

2.2.3 Docetaxel

The taxane Docetaxel is approved for the treatment of breast cancer, non-small cell lung cancer, prostate cancer, adenocarcinoma of the stomach and head and neck cancer (docetaxel is available as generical medicinal product. Information summarized here refers to the SmPC Taxotere® 20-160 mg, Sanofi-Aventis Deutschland GmbH, version May 2015). In breast cancer it may be administered as per approval status for the treatment of nodal positive and nodal negative operable breast cancer in combination with cyclophosphamide and doxorubicine, with the restriction that nodal negative patients with operable disease must be eligible for primary treatment of early stage breast cancer according to internationally defined criteria. Furthermore, it is approved for the combination treatment together with doxorubicine in patients with locally advanced or metastatic breast cancer who did not receive previous chemotherapy.

Docetaxel monotherapy is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of anthracycline- or alkylating agent-containing chemotherapy. Furthermore, docetaxel is approved in combination with trastuzumab for the treatment of patients with HER2 overexpressing metastatic breast cancer, who did not receive previous chemotherapy for metastatic disease, as well as in combination with capecitabine for the treatment of patients with locally advanced or metastatic breast cancer after failure of anthracycline-containing chemotherapy.
Docetaxel is a member of the taxane drug class. It mediates its antineoplastic action by increasing the polymerization rate of tubulin to stable microtubuli and simultaneous inhibition of depolymerization, thereby significantly reducing the availability of free tubulin within the cell. This effect leads to the destruction of the cellular microtubular network, which is crucial for cell division. Hence, the mechanism of action of a taxane docetaxel results in cytotoxicity.

2.3 Study Rationale

Despite the clear benefit of a combination therapy of pertuzumab plus trastuzumab plus docetaxel when compared with a combination therapy of trastuzumab and docetaxel the study populations of the CLEOPATRA [32, 33] trial might be slightly different from a patient population, in which pertuzumab, plus trastuzumab plus chemotherapy or trastuzumab plus chemotherapy are applied in routine clinical practice.

This non-interventional approach aims to confirm the clinically relevant outcomes shown in the phase III CLEOPATRA study in patients with advanced HER2-positive breast cancer [32, 33] in routine practice. Docetaxel is recommended as chemotherapy, however, any treatment choice or change in regimen is performed at the discretion of the treating physician.

Data on efficacy, safety, tolerability and quality of life will be documented for this purpose. Following the recommendations as laid down in guidelines for treatment of breast cancer, the quality of life of patients will be assessed on a regular basis [38].
3 Study Objectives and Outcome Measures

3.1 Primary Objective

<table>
<thead>
<tr>
<th>Primary Objective</th>
<th>Outcome Measure</th>
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<tbody>
<tr>
<td>The primary objective of this study is to assess the progression free survival rate at month 12 for both treatment cohorts in routine clinical practice. i.e. therapy with either pertuzumab plus trastuzumab plus chemotherapy or trastuzumab plus chemotherapy.</td>
<td>Probability of a patient to experience no progress or death for any cause between the date of the first therapy until month 12 in routine clinical practice of study site calculated using the Kaplan-Meier method.</td>
</tr>
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3.2 Secondary Objectives

<table>
<thead>
<tr>
<th>Secondary Objectives</th>
<th>Outcome Measure</th>
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<tbody>
<tr>
<td>• to assess efficacy between the two treatment cohorts as assessed by</td>
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<tr>
<td>○ progression free survival (PFS) and</td>
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</tr>
<tr>
<td>○ overall response rate (ORR)</td>
<td>Progression free survival (PFS) is defined as the time interval from start of therapy until progression proven with clinical measures according to expertise and daily clinical routine or death from any cause, whichever comes first.</td>
</tr>
<tr>
<td>• to assess quality of life based on the evaluation of the EORTC QLQ-C30 and EORTC QLQ-BR23 questionnaires</td>
<td>Quality of life (QoL) will be assessed by the EORTC QLQ-C30 (Version 3.0) and EORTC QLQ-BR23 (Version 1.0) questionnaires until disease progression under first line treatment either with chemotherapy and trastuzumab or chemotherapy, trastuzumab and pertuzumab. The minimum target return rate for PRO questionnaires should be 70% defined as at least 70% of patients having completed the PRO questionnaires at all collection time points.</td>
</tr>
</tbody>
</table>
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| • to evaluate the safety and tolerability of the study treatments (all AEs of all grades, all serious adverse events) | Incidence of adverse events and serious adverse events will be reported according to NCI Common Toxicity Criteria Version 4.03. |
4 Study Population

The study will be conducted as an open registry, therefore there will be no restriction in the number of patients to be included. The assignment of the patient to a particular treatment falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the non-interventional study.

4.1 Inclusion Criteria

• Adult breast cancer patients (age ≥18 years)
• Patients with metastatic or locally advanced, unresectable HER2-positive breast cancer proven by clinical measures (i.e. standard imaging) in first line treatment (Locally recurrent disease must not be amenable to resection with curative intent)
• Patients who are eligible for treatment with trastuzumab plus chemotherapy or pertuzumab plus trastuzumab plus chemotherapy as first line therapy, administered intravenously in a three weekly frequency, according to each center’s medical practice. The first line anti-HER2 treatment must not have started more than 28 days before study entry.
• No prior chemotherapy or HER2-directed therapy for metastatic or locally advanced disease, prior therapy for early breast cancer (eBC) is allowed
• Signed informed consent prior to onset of documentation.

4.2 Exclusion Criteria

• Patients who are not eligible for observation due to severe comorbidities or unavailability according to the treating physician
5 Study Design

PerFECT is a non-interventional, multi-center study according to AMG section 4 (23) sentence 3 [39] designed to document representative epidemiological data under real life conditions of patients with the diagnosis of metastatic or locally recurrent, unresectable HER2-positive breast cancer, who are treated either with pertuzumab plus trastuzumab plus chemotherapy or trastuzumab plus chemotherapy as first line therapy, administered intravenously/subcutaneously in a three weekly frequency. Docetaxel is recommended as chemotherapy, however, any treatment choice or change in regimen is performed at the discretion of the treating physician. The assignment of the patient to a particular treatment falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the non-interventional study. Primary objective is the progression free survival rate at 12 months in routine clinical practice. Enrollment of patients may only be initiated following approval of the IEC responsible for the lead investigator. The study will be conducted at up to 80 initial study centers distributed over Germany. The endpoint of study is reached when 50% of patients recruited until January 2018 have progressed.

Study Procedures and Examinations:

5.1 Time Schedule

- IRB Submission: December 2015 (planned)
- FPI: May 2016
- LPI: January 2018 (planned)
- LPO: January 2020 (planned)
- Interim analysis: April 2018 (planned)/Data cut off January 2018 (planned)
- Final clinical study report: July 2020 (planned)
5.2 Study Documentation

Table 1 Documentation schedule

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Follow Up Documentation every 3 months</th>
<th>Time point of Progression* / End of Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICF</td>
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<td></td>
<td></td>
</tr>
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<td>Demography/medical history</td>
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<td>Status of tumor/relapse/metastasis</td>
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<td>Current anti-neoplastic treatment</td>
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<tr>
<td>and relevant concomitant medication</td>
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<td></td>
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<td>Patient Reported Outcomes (PRO):</td>
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<td>EORTC QLQ-C30¹ and EORTC QLQ-BR23¹</td>
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<td></td>
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<td>X²</td>
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</tr>
<tr>
<td>Progression status form</td>
<td></td>
<td></td>
<td>X³</td>
</tr>
</tbody>
</table>

*Progression following either pertuzumab plus trastuzumab plus chemotherapy or trastuzumab plus chemotherapy as first line therapy

¹PRO questionnaires are only completed until disease progression under treatment with either pertuzumab, trastuzumab and chemotherapy or trastuzumab and chemotherapy including the time point of Progression/End of Treatment visit (EoT) visit due to any other reason than withdrawal of consent or death.

²AEs/SAEs/pregnancies are assessed during treatment period and for 90 days following last administration of treatment (EoT).

³Patients who discontinue treatment due to other reasons than disease progression are followed on a regular three-monthly basis to assess progression status (progression status form). At the time point of progression the EoS form has to be completed.
5.2.1 Data Source/Data Collection Process

All data will be collected using an eCRF database. Data will be reviewed for clarifications and/or corrections of inconsistent or missing data. The following data will be assessed at baseline:

- Age, weight, height, race
- Dosing of medication
- Cancer related medical history (first cancer diagnosis, localization of first tumor, histology, date of first/previous metastasis/progression(s))
- Other relevant medical history
- Prior antineoplastic treatment, incl. surgery, radiotherapy and chemotherapy
- ECOG performance status
- Patient reported outcomes (EORTC QLQ-C30 and EORTC QLQ-BR23)

As per approval status and laid down in the respective SmPCs of the administered medications in their most current versions, the following special assessments are recommended and documented if performed:

- Left Ventricular Ejection Fraction Assessment
  LVEF assessment is recommended for patients treated with pertuzumab before onset of treatment and, for patients in the metastatic setting, afterwards every three cycles (SmPC Perjeta®, Roche Pharma AG).

- Assessment of cardiac function
  Assessment of cardiac function including anamnesis, physical examination and electrocardiogram (ECG), echocardiogram (ECHO) and/or multigated acquisition scan (MUGA) or magnetic resonance imaging (MRI) is recommended for patients for whom trastuzumab treatment is indicated before onset of therapy. Cardiac assessments performed at treatment start should be repeated every three months during treatment and every six months for the 24 months following treatment discontinuation (SmPC Herceptin® i.v., Roche Pharma AG).

- Laboratory Assessments
  In patients treated with docetaxel full blood count shall be frequently assessed (SmPC Taxotere®20-160 mg, Sanofi-Aventis Deutschland GmbH).
  Other chemotherapies may require different or additional lab assessments.

5.2.2 Core Study Documentation

Data entry is expected at a frequency of 3 months, within the routine treatment. In addition to the above listed parameters, data entry will comprise the following information:

- Tumor response as assessed by physician (incl. evaluation method)
- Tumor and metastasis status (TNM, HER2, ER/PR, number of metastasis and localization)
- Adverse events will be assessed according to the Common Terminology
Criteria for Adverse Events (CTCAE) version 4.03.

- Patients who discontinue treatment due to other reasons than disease progression are followed up on a regular three-monthly basis to assess progression status. No other assessments are performed for those patients. 90 days safety follow-up must be adhered to for these patients, as well. At the time point of progression the EoS form has to be completed for each patient.

5.2.3 Patient-Reported Outcomes

Patient reported outcomes will be assessed via the validated questionnaires EORTC QLQ-C30 (version 3.0), a tool to assess quality of life in cancer patients, and the disease-specific supplementary questionnaire EORTC QLQ-BR23 (version 1.0) [34, 41] until disease progression under treatment either with pertuzumab, trastuzumab and chemotherapy or trastuzumab and chemotherapy. PROs will not be assessed for patients after discontinuing treatment prior disease progression. The minimum target return rate for PRO questionnaires should be 70%, defined as at least 70% of patients having completed PRO questionnaires at all collection time points.

Questionnaires will be handed out to the patients as paper copies. Questionnaires must be completed by the patient on site prior to any assessment and are collected to site personnel following completion. The patients shall take no questionnaires home. Baseline PRO questionnaires must be captured before initiation of treatment. Patient reported outcome (PRO) assessment shall strictly follow the "Guidelines for assessing quality of Life in EORTC clinical trials" [42]:

- As it is preferable to reduce all sources of potential bias it is recommended that questionnaires are completed prior to seeing the physician. This has the advantage that it may prompt the patient to discuss any worrying symptoms.
- PRO assessments should be timed to yield maximum information about changes in QoL due to both treatments and changing disease status.
- Timing schedules should be similar across both treatment arms.
- To reduce the administrative burden and thus improve compliance, assessment times should coincide with the clinical care schedule dictated by the treatment regimens.
- However, assessments should be timed to reflect the expected profile of treatment burden and toxicity.
- It is usually recommended that patients’ completed questionnaires regarding their QoL are not shown to their physician or other personnel responsible for their treatment. If this is the case, it should be emphasized to the patient at the time of seeking informed consent that it is their responsibility to communicate any problems or symptoms to their doctor. They should be reminded of this throughout the trial. No intervention can be offered to patients who only disclose their symptoms by completing questionnaires.
5.2.4 Study Completion/Interruption/End of Study (EoS)

Each patient remains in the study until disease progression, death or withdrawal of informed consent. In case of change in therapy regimen (trastuzumab and/or pertuzumab) due to any reason other than disease progression patients are followed up on a regular three-monthly basis to assess progression status. No other assessments are performed for those patients. At the time point of progression the EoS form has to be completed. At study completion and/or study treatment discontinuation due to disease progression, withdrawal of consent or death, the documentation shall be updated as usual and PRO questionnaires shall be obtained from the patient, as applicable. Additionally, an end of study (EoS) form has to be completed at the time point of progression, to capture the reason for end of study. Data capture within PerFECT can be discontinued by the patient at any time without giving reasons by withdrawal of informed consent or by death. If the patient is enrolled in a different clinical study in which investigational therapeutic procedures are performed or investigational therapies are administered then the patient will be excluded from the study. There are no further criteria leading to premature discontinuation of observation. This prospective non-interventional study ends when the last patient has experienced disease progression. As the study is designed as an open registry without limitations in patient number, the "last patient" will prospectively be identified.

5.3 Treatment, Dosage and Administration

Patients are treated either with commercially available, prescribed pertuzumab (Perjeta®, Roche Pharma AG) plus trastuzumab (Herceptin® i.v. or s.c., Roche Pharma AG) plus chemotherapy or trastuzumab plus chemotherapy as first line therapy in a three weekly frequency. All treatments are prescribed and performed according to each center’s medical practice. Any treatment choice or change in regimen is performed at the discretion of each treating physician. The substances are administered sequentially and must not be mixed within the same infusion bag/bottle. No preferred order of administration is defined, if trastuzumab and pertuzumab are given as a combination treatment. Chemotherapy shall be administered after pertuzumab and trastuzumab (SmPC Perjeta®, Roche Pharma AG, version July 2015).

5.3.1 Pertuzumab

As per approval status (SmPC Perjeta®, Roche Pharma AG, version July 2015), patients with metastatic breast cancer shall be treated with pertuzumab and trastuzumab until disease progression or occurrence of uncontrollable toxicity. Pertuzumab (trade name Perjeta®, Roche Pharma AG) is available as 420 mg concentrate for preparation of an infusion solution.
The initial infusion is administered intravenously (i.v.) over a duration of 60 minutes, followed by maintenance i.v. doses every three weeks over a duration of 30 to 60 minutes. Recommended initial dose is 840 mg, recommended maintenance doses are 420 mg. Dose modification of pertuzumab is not recommended. An observation period of 30 to 60 minutes following each pertuzumab infusion is recommended before a sequential trastuzumab or docetaxel infusion.

5.3.2 Trastuzumab

Trastuzumab for intravenous administration (trade name Herceptin® i.v., Roche Pharma AG) is available as 150 mg powder for preparation of a 21 mg/ml infusion solution. When given as a combination treatment with pertuzumab, an initial dose of 8 mg per kg body weight, administered as an i.v. infusion, followed by maintenance doses of 6 mg/kg every 3 weeks, is recommended (SmPC Perjeta®, Roche Pharma AG, version July 2015). Trastuzumab for subcutaneous administration (trade name Herceptin®SC, Roche Pharma AG, version February 2016) is available in a 5 ml vial containing 600 mg trastuzumab. The recommended dose of trastuzumab when given subcutaneously (s.c) is 600 mg, independently of body weight. This dose is administered s.c. over a duration of 2 – 5 minutes every 3 weeks. Dose reduction of trastuzumab, when given in combination with pertuzumab, is not recommended. Discontinuation of trastuzumab treatment shall lead to likewise discontinuation of pertuzumab treatment (SmPC Perjeta®, Roche Pharma AG, version July 2015).

5.3.3 Docetaxel and other chemotherapies

In order to depict a real-life setting the assignment of the patient to a particular treatment falls within current practice. Therefore, the choice for a particular chemotherapy is performed at the discretion of each treating physician. When Docetaxel is given as a combination treatment with pertuzumab, an initial dose of 75 mg per m² body surface, repeated every three weeks, is recommended (SmPC Perjeta®, Roche Pharma AG, version July 2015). When given in combination with pertuzumab and trastuzumab, docetaxel dose should be modified according to the SmPC/routine clinical practice of study site. In the pivotal trial docetaxel was administered one day after the initial trastuzumab dose. Following doses of docetaxel were given immediately after trastuzumab administration, provided that the previous trastuzumab doses had been well tolerated (SmPC Herceptin® i.v., Roche Pharma AG, version July 2015). When pertuzumab treatment is discontinued within the triple regimen, trastuzumab and docetaxel may be further administered until disease progression or occurrence of uncontrollable toxicity (SmPC Perjeta®, Roche Pharma AG, version July 2015). When administered as a double combination treatment with trastuzumab, the recommended docetaxel dose is 100 mg/ m² every three weeks (SmPC Taxotere®20-160 mg, Sanofi-Aventis Deutschland GmbH, version May 2015).
6 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

6.1 Definitions

**Adverse event (AE):** Any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment i.e. any unfavorable and unintended sign, symptom or disease temporally associated with the use of a medicinal product whether or not considered related to the medicinal product.

**Adverse drug reaction (ADR):** A response to a drug which is noxious and unintended and which the causal relationship between the drug and the occurrence is suspected.

**Serious adverse event (SAE):** Any untoward medical occurrence that at any dose; results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect or is an important medical event in the physician’s judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above).

**Serious adverse drug reaction (SADR):** An unintended response to a medicinal product which is fatal, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity or is a congenital anomaly/birth defect and which the causal relationship between the drug and the occurrence is suspected. SADR includes the following:

- Suspected transmission of an infectious agent by the study medicine (STIAMP), as defined below: Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term only applies when a contamination of the study medicine is suspected.

**Adverse events of special interest (AESI):** AEs of special interest for this study are limited to the following:

- Cases of potential medicine-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law:

  The finding of an elevated ALT or AST (> 3 · the ULN) in combination with either an elevated total bilirubin (> 2 · the ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to
be an indicator of severe liver injury. Therefore, physicians must report as an AESI the occurrence of either of the following:

- Treatment-emergent ALT or AST > 3 · ULN in combination with total bilirubin > 2 · the ULN
- Treatment-emergent ALT or AST > 3 · ULN in combination with clinical jaundice

**Special Situations:** The following events are considered as Special Situations for safety reporting even in the absence of an Adverse Event (AE):

- **Pregnancy:** This refers to situation where the embryo or fetus may have been exposed to a Roche medicinal product(s), either through maternal exposure or transmission of a medicinal product via semen following paternal exposure
- **Breastfeeding:** This refers to a situation in infants following exposure to a medicinal product from breast milk
- **Lack of efficacy:** This refers to a situation of lack of therapeutic efficacy of a medicinal product
- **Overdose:** This refers to the administration of a quantity of a medicinal product given per administration or cumulatively, which is above the maximum recommended dose according to the authorized product information
- **Misuse:** This refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the authorized product information
- **Abuse:** This corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects
- **Off-label use:** This relates to situations where the medicinal product is intentionally used for a medical purpose not in accordance with the authorized product information
- **Medication error:** This refers to any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the healthcare professional, patient or consumer
- **Occupational exposure:** This refers to the exposure to a medicinal product as a result of one’s professional or non-professional occupation
- **Pediatric and elderly population:** Reasonable attempts should made to obtain and submit the age or age group of the patient when a case is reported by a healthcare professional, or consumer in order to be able to identify potential safety signals specific to a particular population
Furthermore, the following event shall be recorded and reported following the respective timelines:

- **Quality Defects and Falsified Medicinal Products**: Reports of suspected or confirmed falsified medicinal product or quality defect of a medicinal product, with or without an associated AE, should be forwarded to the sponsor as per non-serious timelines. If the associated AE fulfills the seriousness criteria, the event should be reported to the sponsor immediately (i.e., no more than 24 hours after learning of the event).

All patients will be monitored for AEs during the study. Assessments may include monitoring of any or all of the following parameters in accordance with standard clinical practice: the patient’s clinical symptoms, laboratory, pathological, radiological or surgical findings, physical examination findings, or other appropriate tests and procedures.

### 6.2 Evaluation of Adverse Events

The treating physician will evaluate all adverse events as to seriousness, severity, causality, duration, action taken and outcome.

#### Seriousness

A serious adverse event (SAE) is any AE occurring at any dose that:

- Results in death;
- Is life-threatening (i.e., in the opinion of the physician, the patient is at immediate risk of death from the AE);
- Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay);
- Results in persistent or significant disability/incapacity (a substantial disruption of the patient’s ability to conduct normal life functions);
- Is a congenital anomaly/birth defect;
- Constitutes an important medical event.

Important medical events are defined as those occurrences that may not be immediately life threatening or result in death, or hospitalization, or disability, but may jeopardize the patient or require medical or surgical intervention to prevent one of the other outcomes listed above. Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

#### Severity/ intensity

For both AEs and SAEs, the physician must assess the severity/intensity of the event according to CTCAE grading (version 4.03.):

**Grade 1 = Mild – transient or mild discomfort; no limitation in activity; no medical intervention/therapy required**
**PerFECT - Pertuzumab in First Line Treatment of HER2-positive metastatic breast Cancer patients: A cohort study of patients treated either with docetaxel and Trastuzumab or docetaxel, trastuzumab and pertuzumab**

**Grade 2** = Moderate – mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required

**Grade 3** = Severe – marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible

**Grade 4** = Life-threatening – extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable

**Grade 5** = Death - the event results in death

**Causality**

The physician must determine the relationship between the administration of drug and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

**Not suspected:** The temporal relationship of the AE to drug administration makes a causal relationship unlikely or remote, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.

**Suspected:** The temporal relationship of the AE to drug administration makes a causal relationship possible, and other medications, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.

For known pertuzumab, trastuzumab or docetaxel side-effects, please rely on the most current versions of the summaries of product characteristics (SmPCs).

**Duration**

For both AEs and SAEs, the physician will provide a record of the start and stop dates of the event.

**Action Taken**

The Physician will report the action taken with study medication as a result of an AE or SAE, as applicable (e.g., discontinuation or reduction of study medication, as appropriate) and report if concomitant and/or additional treatments were given for the event.

**Outcome**

The Physician will report the outcome of the event for both AEs and SAEs. For each AE, the physician will provide information on severity, seriousness, start and stop dates, relationship to study medication, action taken regarding study medication and outcome.
6.3 Pregnancies/Breastfeeding in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the physician if they become pregnant during the study or within 7 months after the last dose of pertuzumab plus trastuzumab treatment or trastuzumab. Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state), are considered immediately (within 24 hours) reportable events. Pertuzumab and/or trastuzumab treatment is to be discontinued immediately.

The patient may be referred to an obstetrician-gynecologist or another appropriate healthcare professional for further evaluation.

The physician will follow the patient until completion of the pregnancy, and must notify the study sponsor and Roche Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the pregnancy report form.

If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion) and meets any of the serious criteria, the physician should report the abnormal outcome as an SAE to the study sponsor and Roche Drug Safety within 24 hours of the physician’s knowledge of the event using the eCRF-embedded SAE form (see section 5.5).

All neonatal deaths that occur within 90 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 90 days that the physician suspects to be related to the in utero exposure to pertuzumab and/or plus trastuzumab plus chemotherapy treatment, should also be reported to the study sponsor and Roche Drug Safety within 24 hours of the Physician’s knowledge of the event using the eCRF-embedded SAE form. Follow-up information may be obtained within the first year after birth.

Suspected adverse reactions that occur in infants following exposure to a medicinal product from breast milk should also be reported.

6.4 Pregnancies in Female Partners of Male Patient

Male patients will be instructed through the Informed Consent Form to immediately inform the physician if their partner becomes pregnant during the study or within 7 months after the last dose of study medicinal product. A Pregnancy Report should be completed by the physician immediately (i.e., no more than 24 hours after learning of the pregnancy) and sent to the Study Sponsor and Roche Drug Safety. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study medicine. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. Once the authorization has been signed, the investigator will update the Pregnancy Report with additional information on the course and outcome of the pregnancy. A physician who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to
support an informed decision in cooperation with the treating physician and/or obstetrician.

6.5 Progression of Underlying Disease

Events that are clearly consistent with the expected pattern of progression of the underlying disease are not considered as adverse events, however, they are captured in the eCRF. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an AE. This exception from reporting includes events of disease progression with a fatal outcome which are clearly attributable to disease progression.

6.6 Deaths

All deaths that occur during the protocol-specified AE reporting period regardless of relationship to study medication must be recorded in the AE section of the eCRF.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the SAE section of the eCRF. Generally, only one such event should be reported. The term “sudden death” should only be used for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without preexisting heart disease, within 1 hour after the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, “unexplained death” should be recorded on the SAE section of the eCRF. If the cause of death later becomes available (e.g., after autopsy), “unexplained death” should be replaced by the established cause of death. Disease progression and breast cancer specific death are not considered as SAE, however are documented in the eCRF.

6.7 Patient-Reported Outcome Data

As laid down in the "Guidelines for assessing quality of Life in EORTC clinical trials" [42], no intervention can be offered to patients who only disclose their symptoms by completing questionnaires. Patients will be reminded regularly to directly communicate any kind of problems and symptoms to the physician. Furthermore, the administered questionnaires exclusively aim at the assessment of quality of life and will be analyzed in an aggregated fashion on the level of the patient population and not on an individual patient level. Therefore no individual patient allocation is possible.

6.8 Reporting of Serious Adverse Events, Non-Serious Adverse Drug Reactions and Pregnancies

The physician must record all AEs and special situations in the eCRF and in the patient’s source documents from the time the patient signs the informed consent until the end of his or her treatment period and for 90 days following last
administration of treatment. Serious adverse events, related and not related (SAE, SADR), AESI and special situations need to be reported within 24 h after learning of the event.

Any serious adverse event or non-serious adverse event experienced after the patients treatment period and 90 days thereafter should only be reported to the corresponding Marketing Authorisation Holder if the physician suspects a causal relationship to pertuzumab or trastuzumab or chemotherapy.

The physician is required to ensure that the reported data is accurate and consistent. This requirement applies to all AEs (regardless of relationship to pertuzumab plus trastuzumab plus chemotherapy treatment or trastuzumab plus chemotherapy treatment).

Recording of SAE, SADR, AESI and special situations within 24 h after learning of the event in the eCRF consequently involves immediate reporting of these events to the sponsor using the respective eCRF pages and the printout SAE report form provided in the eCRF.

Completed SAE Report Forms have to be faxed to:

   **Safety-Fax: 07071 5681491**

Reporting is based on a fax-to-mail solution. By using the fax-number above, the report will be sent to the study sponsor and Roche Drug Safety in parallel, i.e. the site only has to send the report once. This instruction pertains to initial as well as any follow-up reports.

Study sponsor pharmacovigilance contact details:

Institut für Frauengesundheit GmbH (IFG)
Universitätsstraße 21-23
91054 Erlangen

If the eCRF SAE Form is not accessible, the event must be reported by using the replacement SAE Report Form provided in the Physician Folder and faxed to the safety-fax number above, in order to provide it to the trial sponsor and Roche Drug Safety. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the documentation at the study site.

The physician should provide information by fully completing the relevant sections of the SAE form and may include brief summaries of relevant documents (e.g. hospital records) and not attach large volumes of supporting information. Any follow up data must be detailed in a subsequent SAE report form, and sent to the study sponsor and Roche Drug Safety.
All SAEs and AEs that have not resolved upon treatment discontinuation must be followed up to at least 90 days after end of treatment until recovered, recovered with sequela, not recovered (death due to another cause) or death (due to the SAE).

In addition, reasonable attempts should be made to obtain and submit the age or age group of the patient, in order to be able to identify potential safety signals specific to a particular population.

6.9 Safety Reporting Requirements for other drugs than trastuzumab or pertuzumab

Although adverse event information is not being actively solicited for non-studied medicinal products, the physician/consumers are reminded to report any adverse reactions (for which they suspect a causal role of a medicinal product) that come to their attention to the marketing authorization holder of the suspected medicinal product, or to the concerned competent authorities via the national spontaneous reporting system.
7 Statistical Considerations, Data Collection and Management

7.1 Statistical Considerations and Analysis Plan

This NIS will be considered as a registry. A registry is a complete collection of patient data for a given time period and for centers willing to participate. No formal statistical hypothesis and no formal sample size calculation will be performed. All efficacy and safety variables documented in this study will be analyzed by means of descriptive analysis. Continuous data will be summarized using mean, standard deviation, median, minimum and maximum. Categorical variables will be expressed as absolute and relative number. Progression-free survival rates will be calculated using the Kaplan-Meier method.

7.2 Data collection and management

7.2.1 Documentation

Each site will keep a patient log file allocating patient name (and, if necessary to unambiguously identify a patient, further personal data like date of birth to be entered optionally in compliance with the principle of data reduction and data economy [43]) and date of registration to the eCRF patient number. This patient identification list will remain at the study site. Patients are registered for the study by the study site. Registration is performed electronically and pseudonymized. The patient is identified by a combination of site number and patient number, automatically generated by the software.
Once a patient is enrolled for the study, all data essential for the enrollment are captured in the eCRF (in-/exclusion criteria, informed consent). At study entry medical history up to the time of the study inclusion will be documented side effects of therapies will be documented prospectively.
Data is stored centrally with all applicable data protection and IT safety standards guaranteed by the central data management team of Institut für Frauengesundheit GmbH (IFG) (see also 7.2.4).

7.2.2 Documentation by Study Personnel

Each study site will specify adequately qualified personnel, which will be authorized for the remote data entry system to document the pre-specified variables. The eCRF must be signed by the principal physician, who will retrieve a different access level with the possibility to verify the correctness of the documented data at the end of documentation.
The central data management site will post queries to entries, which are not plausible. These are to be resolved by the study sites.
7.2.3 Data Management/Data Committee

Central data management and trial statistics are performed by

**Data management**
Institut für Frauengesundheit GmbH (IFG), Universitätsstraße 21-23, 91054 Erlangen

**Trial statistics**
Frauenklinik des Universitätsklinikums Erlangen, Universitätsstraße 21-23, 91054 Erlangen

will be responsible for the data management of this study, including quality checking of the data captured in the eCRF.

7.2.4 Electronic Case Report Forms

The eCRF will be developed, established and maintained by:

Institut für Frauengesundheit GmbH (IFG), Universitätsstraße 21-23, 91054 Erlangen

Sites will receive training and have access to a manual for appropriate eCRF completion. All eCRFs shall be completed by designated, trained site staff. The eCRF must be signed by the responsible physician, who will retrieve a different access level with the possibility to verify the correctness of the documented data at the end of documentation.

Data from paper PRO questionnaires will be entered into the eCRF system by site staff.

7.2.5 Data Quality Assurance

Sites will be responsible for data entry into the eCRF system. In the event of discrepant data, data management (IFG) will request data clarification from the sites via queries, which the sites will resolve electronically in the eCRF system. Correction/query resolution documentation will be documented in the eCRF system's audit trail.

CRO monitors will perform source data verification in compliance with the NIS monitoring plan. Before study initiation, the types of source documents that are to be generated and monitored will be clearly defined in the NIS monitoring plan. To facilitate source data verification, the physicians and institutions must provide the CRO monitors direct access to applicable source documents for NIS-related monitoring.

7.3 Archiving

In compliance with the professional code of conduct for physicians [44] the treating physician is obliged to archive the patient identification list and documentation of treatment within this registry for at least 10 years.
8 Compliance with Laws and Regulations

The non-interventional study will be conducted in compliance with all applicable legislation and regulations as well as established guidelines and recommendations, i.a. the FSA codex for the cooperation with healthcare professionals [45], the combined recommendations of German Federal Institute for Drugs and Medical Devices (BfArM) and German federal institute for vaccines and biomedicines (Paul-Ehrlich-Institut, PEI) for the registration of non-interventional studies [46] as well as the recommendations for non-interventional studies of the Association of Research-Based Pharmaceutical Companies (vfa) [47] in their most current available versions.

8.1 Informed Consent

The informed consent form (ICF) must be signed and dated by the patient before participation in the study. A copy of each signed ICF must be provided to the patient or the patient’s legally authorized representative. All signed and dated ICFs must remain in the respective study/patient file and must be available for verification by CRO monitors.

8.2 Independent Ethics Committee

The NIS protocol as well as the ICF will be submitted to the ethics committee responsible for the lead investigator and for the sponsor:

Ethik-Kommission der Medizinischen Fakultät der Friedrich-Alexander-Universität Erlangen-Nürnberg, Krankenhausstraße 12, 91054 Erlangen

Ethik-Kommission der Medizinischen Fakultät der Eberhard-Karls-Universität und am Universitätsklinikum Tübingen, Gartenstraße 47, 72074 Tübingen

8.3 Protocol Amendments

Approval must be obtained from the IEC before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only. Any substantial amendments to the protocol require prior central and, if applicable, local ethics approval.

9 Amendment(s)

9.1 Rationale for Amendment 1:

The current protocol was updated to correct for minor inconsistencies of the previous version and to allow for documentation of individual routine treatment of patients in first line treatment of HER2-positive metastatic breast cancer treated either with trastuzumab or trastuzumab and pertuzumab.
10 Responsibilities

Sponsor
Universitätsklinikum Tübingen
Department für Frauengesundheit
Universitäts-Frauenklinik
Forschungsinstitut für Frauengesundheit Baden-Württemberg
Calwerstraße 7
72076 Tübingen

Coordinating investigator

Steering Board

Prof. Dr. med. T. Fehm
Universitätsklinikum Düsseldorf
Klinik für Frauenheilkunde und Geburtshilfe
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40225 Düsseldorf

Prof. Dr. med. A. Schneeweiss
Universitäts-Frauenklinik Neuenheimer Feld
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Prof. Dr. med. H. Tesch
Onkologie Betthanien Frankfurt
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Prof. Dr. med. S. Brucker
Universitätsfrauenklinik Tübingen
Calwerstraße 7
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PerFECT - Pertuzumab in First Line Treatment of HER2-positive metastatic breast cancer patients: A cohort study of patients treated either with docetaxel and Trastuzumab or docetaxel, trastuzumab and pertuzumab

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Universitätsklinikum Tübingen
Department für Frauengesundheit
Universitäts-Frauenklinik
Forschungsinstitut für Frauengesundheit Baden-Württemberg
72076 Tübingen

Data management/trial
Biostatistics Unit
Frauenklinik des Universitätsklinikums Erlangen
Universitätsstraße 21-23
91054 Erlangen

Pharmacovigilance  Institut für Frauengesundheit GmbH (IFG)
Universitätsstraße 21-23
91054 Erlangen

Study and project management:  ClinSol GmbH & Co.KG
Kantstraße 26
97074 Würzburg
11 Abbreviations

AE  Adverse event
AESI  Adverse event of special interest
CR  Complete response
EBC  Early breast cancer
eCRF  Electronic case report form
ECG  Electrocardiogram
EDC  Electronic data capture
EoT  End of treatment
EoS  End of study
FPI  First patient in
FPO  First patient out
HER2  Human epidermal growth factor receptor 2
ICF  Informed consent form
IEC  Independent ethics committee
IRB  Institutional review board
LVEF  Left Ventricular Ejection Fraction
LPI  Last patient out
MUGA  Multigated acquisition scan
MBC  Metastatic breast cancer
NIS  Non interventional study
ORR  Overall response rate
PD  Progressive disease
PFS  Progression free survival
PFSR  Progression free survival rate
PRO  Patient reported outcomes
QoL  Quality of life
SAE  Serious adverse event
SD  Stable disease
SmPC  Summary of medicinal product characteristics
STIAMP  Suspected transmission of an infectious agent by the study medicine
12 REFERENCES

19. Petru, E., et al., Austrian Arbeitsgemeinschaft fur Gynakologische Onkologie (AGO) guideline for prophylaxis with granulocyte colony-stimulating factors (G-CSF) in
PerFECT - Pertuzumab in First Line Treatment of HER2-positive metastatic breast Cancer patients: A cohort study of patients treated either with docetaxel and Trastuzumab or docetaxel, Trastuzumab and pertuzumab


45. FSA-Kodex zur Zusammenarbeit mit Fachkreisen. 08.05.2014; Available from: http://www.fsa-pharma.de/verhaltenskodizes/fachkreise/.
