NEOADJUVANT TREATMENT OF ONTRUZANT® (SB3) IN PATIENTS WITH HER2-POSITIVE EARLY BREAST CANCER: AN OPEN-LABEL, MULTICENTER, PHASE IV STUDY

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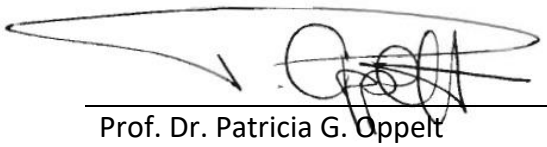
Version of Report:	1.0
Previous Reports	none
Protocol Version for this Report	Protocol Version 1.1 dated 15-Apr-2021
Investigational Medicinal Product	Ontruzant® (SB3)
Studied Indication	Neoadjuvant treatment of HER2-positive breast cancer
Trial Design	One-arm, open-label
Development Phase	IV
Date of First Patient Enrolled	12-Jul-2021
Date of Last Patient Enrolled	17-Mai-2023
Date of Study Completion	23-Jan-2024

This study was performed in compliance with Good Clinical Practice according to ICH E6 (GCP).

1 Signatures

We confirm that this Clinical Study Report describes the conduct and results of the clinical trial NeoOn - Neoadjuvant treatment of Ontruzant® (SB3) in patients with HER2-positive early breast cancer: An open-label, multicenter, phase IV study.



Prof. Dr. Patricia G. Oppelt
Sponsor 22-JAN-2024

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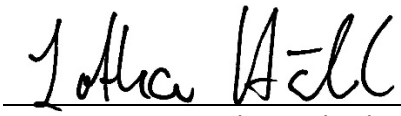

Priv.-Doz. Dr. Lothar Häberle
Statistician 22-JAN-2024

2 Synopsis

Study Title	NeoOn – Neoadjuvant treatment of Ontruzant® (SB3) in patients with HER2-positive early breast cancer: An open-label, multicenter, phase IV study
Trial Phase	Phase IV
Sponsor	Institut für Frauengesundheit GmbH Universitaetsstrasse 21-23, 91054 Erlangen, Germany
Coordinating Investigator	Prof. Dr. Peter A. Fasching Department of Gynecology and Obstetrics Erlangen University Hospital Universitätsstraße 21-23, 91054 Erlangen *Coordinating investigator according to AMG* Prof. Dr. Diana Lüftner Department for Hematology, Oncology and Tumor Immunology Charité Campus Benjamin Franklin, Berlin Hindenburgdamm 30, 12200 Berlin Prof. Dr. Andreas Schneeweiss National Center for Tumor Diseases (NCT), Head of Division Head of Division Gynecologic Oncology, Heidelberg University Hospital (UKHD) Fellow of the German Cancer Research Center (DKFZ) Im Neuenheimer Feld 460, 69120 Heidelberg
Clinical Indication	Neoadjuvant treatment of HER2-positive breast cancer
Trial Type	Interventional
Investigation Type	Drug
Route of administration	Intravenous
Trial Blinding	Unblinded, open-label
Purpose and Rationale	The treatment of patients with HER2 positive early breast cancer has continuously improved over the last decades. Up to now, trastuzumab has been approved in combination with chemotherapy (CTX) not only for the adjuvant but also for the neoadjuvant treatment of early breast cancer patients. A high rate of pathological complete response (pCR) in the neoadjuvant setting was shown in several trials and observational studies with CTX+ trastuzumab (Fasching et al. 2019; Gianni et al. 2012). The efficacy is dependent

	on a variety of mechanisms including the blocking of the important PI3K/Akt and MAPK pathways, and ADCC (antibody dependent cellular toxicity). Recently the biosimilar Ontruzant® (SB3) has been introduced into the treatment of HER2 positive breast cancer as a biosimilar. Efficacy and toxicity have been shown to be equivalent to the first approved antibody, however, data from the real-world setting have not been published like it has for the originally approved antibody (Fasching et al. 2019). Therefore, the aim of this study was to establish safety and efficacy for Ontruzant® in the real-world setting. Patients could be included if they were treated with Ontruzant® in the neoadjuvant setting. Additionally, the study was be accompanied by a comprehensive immune monitoring program and biomarker program to explore immune oncology potential for the neoadjuvant treatment.
Primary Objectives	Pathological complete response (pCR) rate, defined as the complete absence of tumor cells (ypT0; ypN0) after neoadjuvant study treatment of HER2-positive early breast cancer patients treated with Ontruzant® (SB3).
Secondary Objectives	• To evaluate the pCR with other definitions of pCR (e.g., ypT0/is; ypN0) • To evaluate the safety and tolerability of Ontruzant® • Clinical response, as assessed by routine ultrasound or mammography • To assess the frequency of possible combination partners administered together with Ontruzant® • To evaluate changes in health-related quality of life (QoL) assessments
Translational Objectives	• To assess the antibody-dependent cell mediated cytotoxicity (ADCC) • To evaluate the impact of FcγR genotypes on ADCC and pCR • To assess molecular characterization
Study Design and Treatment	This was a multicenter, phase IV, one-arm, open-label study of Ontruzant® (SB3) in combination with a standard chemotherapy as neoadjuvant treatment for patients with early HER2 positive breast cancer. All patients received either an anthracycline free treatment regimen comprising 6 cycles of Ontruzant® i.v. q21d in combination with standard chemotherapy; initial dose of Ontruzant® i.v. was 8 mg/kg b.w. followed by 5 cycles of Ontruzant® i.v. 6 mg/kg b.w. q21d. Alternatively, patients received a sequential anthracycline-taxane containing treatment regimen comprising 4 cycles with an anthracycline followed by 4 cycles of Ontruzant® i.v. q21d in combination with a taxane-based standard chemotherapy; initial dose of Ontruzant® i.v. was 8 mg/kg b.w. followed by 3 cycles of Ontruzant® i.v. 6 mg/kg b.w. q21d. The decision for a specific treatment regimen resided with the investigator.

	Clinical and bioptic tumor assessment were performed during baseline and during surgery. Study treatment was applied until state-of-the-art surgery, onset of unacceptable toxicities, progression or withdrawal of consent. A safety follow-up was planned for 30 days after the last administration of study medication.
Inclusion Criteria	In order to be eligible for participation in this trial subject had to fulfil all of the following criteria: 1. Written informed consent prior to beginning of trial specific procedures. 2. Subject must be female and aged ≥ 18 years on day of signing informed consent. 3. ECOG 0-1. 4. Histologically confirmed, early HER2 positive breast cancer determined by core biopsy of breast tumor lesion. 5. Measurable tumor lesion with a size of ≥ 1 cm assessed by sonography or magnetic resonance imaging (MRI) within ≤ 28 days prior to entry. In case of inflammatory disease, the extent of inflammation will be measured. 6. Indication for chemotherapy. 7. Multicentric and/or multifocal disease as well as synchronous bilateral breast cancer was eligible as long as one measurable lesion meets all inclusion criteria. The investigator had to determine which lesion will be used for tumor evaluation before initiation of treatment. 8. Complete staging within 8 weeks prior to entry with no evidence of distant disease, including bilateral mammography, breast ultrasound, chest-X-ray (or chest CT-scan), liver ultrasound (or liver CT-scan or liver MRI) and bone scan. 9. Subjects had to provide a core biopsy from tumor lesion before first chemotherapy and after last neoadjuvant study treatment for biomarker analyses. 10. Adequate organ function defined as: o Absolute neutrophile count ≥1500/µL o Platelets ≥100 000/µL o Hemoglobin ≥10.0 g/dL or ≥6.2 mmol/L o Creatinine ≤1.5 × ULN OR measured or calculated creatinine clearance ≥30 mL/min for participant with creatinine levels

	>1.5 × institutional ULN (GFR can also be used in place of creatinine or CrCl) o Total bilirubin ≤1.5 ×ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN o AST (SGOT) and ALT (SGPT) ≤2.5 × ULN o International normalized ratio (INR) OR prothrombin time (PT) ≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants o LVEF > 50 % 11. Female subjects of childbearing potential must have a negative urine pregnancy test within 72 h prior to study entry and be willing to use highly effective method of contraception for course of the study through 7 months after the last dose of trial treatment.
Exclusion Criteria	The subject had to be excluded from participating in the trial in following cases: 1. Concurrent participation in a study with an investigational agent/device or within 14 days of study entry or 5 half-lives of the respective investigational agent/device, whichever was longer. 2. Known hypersensitivity to Ontruzant® or any of the drug excipients. 3. Prior chemotherapy, radiation therapy or small molecule therapy for any reason. 4. Previous malignant disease being disease-free for less than 3 years (except in situ carcinoma of the cervix and basal cell carcinoma of the skin). 5. Pregnancy or breast-feeding. 6. Prior neoadjuvant therapy. 7. Active infection requiring systemic therapy. 8. History of (non-infectious) pneumonitis that required steroids or current pneumonitis. 9. Active autoimmune disease or other diseases that required systemic treatment with corticosteroids or immunosuppressive drugs (physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency is allowed). 10. History of primary or acquired immunodeficiency (including allogenic organ transplant). 11. Active or prior documented inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis).

	12. Known history or positive antibody test for any of the following infections: Human immunodeficiency virus (HIV), History of acute or chronic Hepatitis B or Hepatitis C, had received a live-virus vaccination within 30 days of planned treatment start. Seasonal flu vaccines that do not contain live virus were permitted. 13. Known congestive heart failure > NYHA I and/or coronary heart disease, angina pectoris, previous history of myocardial infarction, uncontrolled or poorly controlled arterial hypertension (e.g. blood pressure >160/90 mmHg under treatment with two or more antihypertensive drugs), rhythm disorders with clinically significant valvular heart disease. 14. Pre-existing motor or sensory neuropathy of a severity grade ≥2 by National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v5.0. 15. Any other condition in opinion of the investigator that would interfere with applied systemic treatment or other trial procedures.
Investigational Products	Ontruzant® (SB3)
Non-Investigational Products	Standard neoadjuvant chemotherapy (Physician's choice)
Supportive treatment	Supportive treatment during systemic therapy was recommended according to guidelines (ASCO/ESMO). No additional supportive treatment was required for investigational medication
Number of Subjects	Planned: 98 patients Total registered: 104 patients Total enrolled: 103 patients
Number of Recruiting sites	Planned: 12 Active: 3
Duration of Participation	Maximum time of participation for a subject from signed informed consent until completion of the trial was 6-8 months.
Date of First patient Enrolled	12-Jul-2021
Date of Study Completion	17-Mai-2023
Date of Data Entry Complete	22-Jul-2024

Criteria for Efficacy Evaluation	Efficacy analysis was performed in the full analysis set and the per protocol set. The full analysis set (FAS) or efficacy population included all patients meeting the in- and exclusion criteria enrolled into the NeoOn clinical trial who have received at least one full cycle of trial treatment (SB3+CTX or SB3+CTX-T). The per protocol set (PPS) or efficacy population included all patients meeting the in- and exclusion criteria enrolled into the NeoOn clinical trial who have received full 6 cycles of SB3+CTX or 4 cycles SB3+CTX-T, depending on treatment schedule.
Criteria for Safety Evaluation	Safety analysis was performed in the safety analysis set. The safety analysis set (SAS) consisted of all patients who have received at least one dose of trial treatment SB3, regardless of compliance with the trial protocol.
Statistical Methods	This was a phase IV study to evaluate the efficacy and safety of trastuzumab with standard neoadjuvant chemotherapy (CTX). Primary study aim was the assessment of pCR. In a controlled study, a pCR rate of about 45 % was shown for patients treated with Ontruzant® (Pivot, Bondarenko, Nowecki, Dvorkin, Trishkina, Ahn, Vinnyk, et al. 2018). In a large clinical real-world registry pCR rates of about 30% were observed for such patients (Fasching et al. 2019). We wanted to show that the pCR rate is greater than 30 %. The null hypothesis stating that the pCR rate is at most 30.0% was tested with a one-sided exact binomial test with significance level α = 2.5% (type I error). In case of a significant test result, the two-sided 95% confidence interval (CI) for the observed pCR rate did not cover 30%. More precisely, the lower bound of the CI was greater than 30%. A sample size calculation said that 88 patients would be required to achieve a power of 80% (i.e., type II error: β = 20%). The drop-out rate was expected to be 10%, finally resulting in 98 patients in total.
Efficacy Results	Efficacy analysis was performed in the FAS comprising of 99 patients who had received at least one full cycle of trial treatment with SB3+CTX and in the PPS comprising of 91 patients who had received six full cycle of trial treatment with SB3+CTX. All patients received additional pertuzumab. Within the FAS pCR rate (ypT0 ypN0) was 59.4% (95% CI: 48.9% to 69.3%) which is significantly higher than the assumed 30% (*P < 0.000001*). Furthermore, the pCR rate (ypT0/is and ypN0) was 68.8% (95% CI: 58.5% to 77.8%). Within the PPS pCR rate (ypT0 ypN0) was 58.9% (95% CI: 48% to 69.2%). In addition, pCR rate (ypT0/is and ypN0) was 68.9% (95% CI: 58.3% to 78.2%). The best overall response as assessed by imaging was summarized for the trial. In the FAS a complete response via imaging was

	achieved in 26 patients (27.7%), while 58 patients (61.7%) had a partial response. Five patients (5.3%) had a progressive disease. In the PPS complete response was observed in 23 patients (25.8%), partial response in 56 patients (62.9%). Five patients (5.6%) had a tumor progression by imaging. The best overall response as assessed by imaging was summarized for the trial. In the FAS 26 patients (27.7%) achieved a complete response and 62 patients (66%) partial response and 6 patients (6.4%) stable disease. In the PPS 23 patients (25.8%) achieved a complete response and 60 patients (67.4%) partial response. Quality of life was assessed during the course of the study. While a deterioration of quality of life could be observed during the treatment phase with SB3+CTX quality of life significantly improved during safety-follow up 120 days after the completion of trial treatment.
Safety Results	Safety analysis was conducted in the SAS comprising of patients who had at least received one dose of SB3, comprising of 99 patients. Reasons for irregular end of treatment was toxicity in 2 patients (2%), patient's wish in 1 patient (1%) or investigator's decision in 2 patients (2%). By database closure, a total of 1497 AEs and 48 SAEs had occurred in patients from the safety population. All patients from the SAS were affected by at least one AE, 26 patients were affected by a SAE. There were 112 AEs of grade 3 or grade 4 observed in 44 patients. No fatal events were observed during the trial. In total 907 AEs were considered related to trial treatment and therefore classified as ARs. 98 patients were affected by at least one AR. 14 SAEs were considered related to SB3 and therefore classified as SARs, which occurred in 11 patients. Of all AEs observed regardless of toxicity grade the most common were anemia (86.9%), diarrhea (83.8%) and polyneuropathy (75.8%) followed by neutropenia (56.6%), fatigue (54.5%), nausea (47.5%), skin toxicity (47.5%) and stomatitis (44.4%). Hepatotoxicity observed by increased transaminase levels were observed, e.g. increased AST (38.4%) and increased ALT (30.3%). Most common AEs related to SB3 were anemia (59.6%) diarrhea (76.8%), polyneuropathy (46.5%), neutropenia (46.5%), fatigue (46.5%), nausea (36.4%), skin toxicity (35.4%) stomatitis (32.3%), increased AST (27.3%), increased ALT (18.2%) and epistaxis (15.2%). The most commonly observed SAEs during this trial were diarrhea, which affected 7 patients (7.1%), followed by neutropenia, decreased blood potassium levels and acute kidney injury, observed in 4 patients (4%), respectively. Catheter site infections and a decrease in general condition were observed in 3 patients (3%) each.

	Any other SAEs occurred only once during the trial. The most common SARs were diarrhea (6.1%), decreased in general condition (3%) and neutropenia (2%).
Conclusion	Within the FAS considering patients who had received at least one full cycle of trial treatment with SB3+CTX the pCR rate was 59.4% (95% CI: 48.9% to 69.3%) which is significantly higher than the assumed 30% (*P < 0.000001*). Results from the bioequivalence trial leading to approval of SB3 showed a pCR rate of 45% for SB3 compared to 35.8% in the TZM arm (Pivot, Bondarenko, Nowecki, Dvorkin, Trishkina, Ahn, Im, et al. 2018). Further phase III clinical trials investigation trastuzumab biosimilars in the treatment of early HER2+ breast cancer showed pCR rates between 38% and event 62.4% (Buzdar et al. 2019; Gianni et al. 2010; Lammers et al. 2018; Stebbing et al. 2017; Untch et al. 2016; von Minckwitz et al. 2018). While pCR rates in this trial were significantly higher than the assumed 30%, it still falls within the expected range of pCR rates reported in other clinical trials in this indication with similar treatment approaches. Overall, the incidence of ARs and SARs reported in NeoOn and in the biosimilar study of SB3 were comparable. ARs and SARs observed in the trial were in line with the reference safety information. Results from the NeoOn clinical trial contribute to the observation that Ontruzant® (SB3) combined with pertuzumab and standard chemotherapy is a safe and effective treatment option for patients with early HER2+ breast cancer.
Date of CSR	22-JAN-2025