STUDY DESIGN OF THE NON-INTERVENTIONAL STUDY TRACE IN GERMANY AND AUSTRIA

TUCATINIB IN PATIENTS WITH LOCALLY ADVANCED OR METASTATIC HER2-POSITIVE BREAST CANCER WHO RECEIVED AT LEAST TWO PRIOR ANTI-HER2 TREATMENT REGIMENS

Arnd Nusch[1]
Moritz Angerer[2]
Janine Kreiss-Sender[3]
Julia Radosa[4]
Christoph Uleer[5]
Denise Wrobel[6]
Marija Balic[7]
Daniel Egle[8]
Nadia Harbeck[9]
Volkmar Müller[10]
Eva Schumacher-Wulf[11]
Rebecca de Buhr[12]
Martin Glasstetter[12]
Johanna Hanselmann[12]
Cathrin Salb[12]
Norbert Marschner[12]
Katja Gratzke[12]
Rupert Bartsch[13]
Anja Welt[14]

1 Praxis für Hämatologie und Onkologie, Ratingen, Germany
2 Schwerpunktpraxis Hämatologie & Internistische Onkologie, Fürth, Germany
3 Frauenärztliche Gemeinschaftspraxis, Braunschweig, Germany
4 Universitätsklinikum des Saarlandes, Homburg (Saar), Germany
5 Praxisgemeinschaft Gynäkologische Onkologie & spezielle operative Gynäkologie, Hildesheim, Germany
6 Sozialstiftung Bamberg Klinik für Frauenheilkunde und Geburtshilfe, Bamberg, Germany
7 LKH-Univ. Klinikum Graz, Graz, Austria
8 Medizinische Universität Innsbruck, Innsbruck, Austria
9 Klinikum der Universität München, München, Germany
10 Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany
11 Mamma Mia – Die Krebsmagazine, atp Verlag GmbH, Köln, Germany
12 iOMEDICO AG, Freiburg im Breisgau, Germany
13 Medizinische Universität Wien, Wien, Austria
14 Universitätsklinikum Essen Innere Klinik (Tumorforschung), Essen, Germany

References
1. Murthy, R. K. et al. Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer. N. Engl. J. Med. 382, 597–609 (2020).

2. Curigliano, G. et al. Tucatinib versus placebo added to trastuzumab and capecitabine for patients with pretreated HER2+ metastatic breast cancer with and without brain metastases (HER2CLIMB): final overall survival analysis. Ann. Oncol. 33, 321–329 (2022).

3. Lin, N. U. et al. Intracranial Efficacy and Survival With Tucatinib Plus Trastuzumab and Capecitabine for Previously Treated HER2-Positive Breast Cancer With Brain Metastases in the HER2CLIMB Trial. J. Clin. Oncol. (2020) doi:10.1200/JCO.20.00775.

4. Lin, N. U. et al. Tucatinib versus placebo added to trastuzumab and capecitabine for patients with previously treated HER2+ metastatic breast cancer with brain metastases (HER2CLIMB). J. Clin. Oncol. 38, 1005–1005 (2020).

5. Lin, N. U. et al. Abstract PD4-04: Updated results of tucatinib vs placebo added to trastuzumab and capecitabine for patients with previously treated HER2-positive metastatic breast cancer with brain metastases (HER2CLIMB). Cancer Res. 82, PD4-04-PD4-04 (2022).

6. Lin, N. U. et al. Tucatinib vs Placebo, Both in Combination With Trastuzumab and Capecitabine, for Previously Treated ERBB2 (HER2)-Positive Metastatic Breast Cancer in Patients With Brain Metastases: Updated Exploratory Analysis of the HER2CLIMB Randomized Clinical Trial. JAMA Oncol. 9, 197 (2023).

Acknowledgements:
The TRACE study is financially supported by Pfizer Pharma GmbH
(initially by Seagen Germany GmbH)

Conflicts of Interest:
Janine Kreiss-Sender: Advisory board: Astra Zeneca, Daiichy Sankyo, Lilly. Lecture honoraria: Astra Zeneca, NCD, Novartis. Study honoraria: Astra Zeneca, Axios, Daiichy Sankyo, GBG, NOSGO, Roche, WSG. Trainings: Daiichy Sankyo, Lilly, Stemline. **Julia Radosa:** Advisory board membership: AGE, AGO Trafo. Advisory Role and/or Lecture Honoraria: Astra Zeneca, Clovis, Daiichi-Sankyo, Eisai, Exact Science, Gedeon Richter, Lilly, MSD, Novartis, Pierre Fabre, Pfizer, Roche, Seagen, Stemline, Theramex. Travel grants: Daiichi-Sankyo, Medac, Pierre Fabre, Pfizer, Seagen.
Christoph Uleer: Honoraria for lectures: Ärztekammer Niedersachsen. Honoraria for advisory board activities: Medi-Seminar GmbH, Seagen Germany GmbH, Eisai GmbH, Novartis Pharma GmbH, Lilly GmbH, Heraclin GmbH, Exact Siences, Daiichi Sankyo Deutschland GmbH, NJD Kongress GmbH. Participation in clinical trials: GBG Forschungs GmbH, palleos healthcare GmbH, MMF GmbH, Roche AG, Pfizer Pharma GmbH, Novartis Pharma GmbH, Westdeutsche Studiengruppe GmbH, Pierre Fabre Pharma GmbH, iOMEDICO AG, Onco Medical Consult GmbH, AstraZeneca GmbH, Universitätsklinikum Ulm, AGO Research GmbH. Traveling expenses: CoMed GmbH **Denise Wrobel:** Honoraria for lectures: Novartis, Roche, Pierre Fabre. Travel grants from Novartis, Pfizer, Teva, Roche and Pierre Fabre **Marija Balic:** Advisory board memberships, Lecture Honoraria, Consulting fees, and travel grants: Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Celgene, Daiichi-Sankyo, Eli Lilly, Gilead, Lenis, MSD, Novartis, Pfizer, Roche, Seagen, Stemline. Research funding: AstraZeneca, Eli Lilly, Novartis, Pierre Fabre, Pfizer, Seagen, Stemline. **Daniel Egle:** Honoraria: AstraZeneca, Daiichi-Sankyo, Gilead, Lilly, Pfizer, Roche, Seagen, Sirius. Grant: Sirius **Nadia Harbeck:** Advisory Role and/or Lecture Honoraria: AstraZeneca, Daiichi-Sankyo, Gilead, iOMEDICO, Lilly, MSD, Novartis, Pierre Fabre, Pfizer, Roche, Sandoz, Sanofi, Seagen, Viatris . Co-Director: Westdeutsche Studiengruppe (WSG) **Volkmar Müller:** Advisory Role: Amgen, ClinSol, Daiichi-Sankyo, Eisai, Gilead, Hexal, Lilly, MSD, Novartis, Pierre Fabre, Roche, Sanofi, Seagen. Lecture Honoraria: Amgen, AstraZeneca, Daiichi-Sankyo, Eisai, Gilead, GSK, high5 Oncology, Medac, Medscape, MSD, Novartis, Onkowissen, Pfizer, Roche, Seagen, Teva. Research Support: AstraZeneca, Genentech, Novartis, Roche, Seagen. Travel grants: Daiichi-Sankyo, Pfizer, Roche. **Norbert Marschner:** Consulting and expert activities: AstraZeneca, Bayer, Beigene, BMS, Clovis, Daiichi-Sankyo, Deloitte, Eusapharm, EISAI, GSK, IPSEN, J&J, Lilly, MSD, Mylan, Novartis, Oncopeptides, Onkovis, Pfizer, Pierre Fabre, Roche, Sanofi, Seagen, Servier. Ownership of shares, stock or funds: iOMEDICO. Research support or other financial relations: Abbvie, Amgen, AstraZeneca, Bayer, Beigene, BMS, Clovis, Daiichi-Sankyo, Deloitte, Eusapharm, EISAI, Gilead, GSK, IPSEN, J&J, Lilly, Morphosys, MSD, Mylan, Novartis, Oncopeptides, Onkovis, Pfizer, Pierre Fabre, Roche, Sanofi, Seagen, Servier. Employment or management position: iOMEDICO **Rupert Bartsch:** Advisory Role: AstraZeneca, Daiichi-Sankyo, Eisai, Eli Lilly, Gilead, Gruenenthal, MSD, Novartis, Pfizer, Pierre Fabre, Puma, Roche, Seagen, Stemline. Lecture Honoraria: AstraZeneca, Daiichi-Sankyo, Eisai, Eli Lilly, Gilead, Gruenenthal, MSD, Novartis, Pfizer, Pierre Fabre, Roche, Seagen, Stemline. Research Support: Daiichi-Sankyo, MSD, Novartis, Roche. **Anja Welt:** Advisory Role: MSD, Novartis, Pfizer, Roche, Seagen. Honoraria: Amgen, AstraZeneca, Daiichi-Sankyo, Eisai, iOMEDICO, Interplan, Lilly, MSD, MC1, Pfizer, Roche. Research support: Novarti. Employment or management position: Chief Medical Officer Universitätsklinikum Essen

Arnd Nusch, Moritz Angerer, Eva Schumacher-Wulf, Rebecca de Buhr, Martin Glasstetter, Johanna Hanselmann, Cathrin Salb, Katja Gratzke: Declared no conflicts of interests.

DGHO Jahrestagung 2024
11. - 14. Oktober, Basel
Posternummer: P639

INTRODUCTION

HER2-positive advanced breast cancer (ABC) is associated with an aggressive tumor behavior, poor response rates to chemotherapy, high relapse rates, and high incidences of brain metastases (BMs). Tucatinib, a highly selective HER2 tyrosine kinase inhibitor, in combination with trastuzumab and capecitabine has demonstrated a significant overall and progression-free survival (OS, PFS) benefit compared to placebo + trastuzumab + capecitabine in patients pretreated with trastuzumab, pertuzumab and trastuzumab emtansine (T-DM1) in the pivotal HER2CLIMB trial[1,2]. For patients with BMs, intracranial response rates were higher with the tucatinib combination compared to the placebo combination[3–5]. Moreover, the risk of developing new BMs or death was reduced by 45.1% in all patients in the tucatinib-combination group vs. the placebo-combination group.[6] Since February 2021, the tucatinib combination is approved by the EMA for patients with HER2-positive ABC who have received at least two prior anti-HER2 treatment regimens. TRACE will gather valuable real-world data of treatment with tucatinib + trastuzumab + capecitabine in early (1st and 2nd) and later (3rd and 4th) palliative treatment in Germany and Austria. The non-interventional study will address important knowledge gaps such as effectiveness and therapy management of tucatinib in comorbid patients of higher age, in first and second line, after pretreatment with anti-HER2 targeted therapies not included in the pivotal trial (**Table 1**).

CONCLUSION

The non-interventional study TRACE will provide important real-world insights into tucatinib + trastuzumab + capecitabine treatment of patients with HER2-positive ABC with focus on QoL. Besides, effectiveness and safety will be assessed in real-world settings and preplanned subgroup analyses will help fill important knowledge gaps between the pivotal clinical trial and routine clinical practice.

METHODS

The prospective observational study TRACE (NCT05253911) will enroll 300 patients with HER2-positive ABC scheduled to receive tucatinib + trastuzumab + capecitabine according to summary of product characteristics (SmPC). 150 patients each (with up to 30 Austrian patients per cohort) will be enrolled in the 1st/2nd line cohort and the 3rd/4th line cohort (**Figure 1**).

Patients will be enrolled by 60 German (start of recruitment in May 2022) and 10 Austrian sites (start of recruitment in October 2023).

Key in- and exclusion criteria are listed in **Figure 2**.

Primary endpoint of TRACE is time to deterioration and change from baseline in all scores of the EQ-5D-5L, EORTC QLQ-C30, and QLQ-BR23 questionnaires.

Secondary endpoints include effectiveness and safety, physician decision making, patient and disease characteristics, details on tucatinib treatment (e.g., type and reason for modifications, temporary treatment interruptions for local intracranial treatment), and therapy management (e.g., usage of antidiarrheals), as well as treatment sequences (e.g., prior and subsequent antineoplastic therapies).

Additionally, health economic parameters will be exploratively evaluated.

Furthermore, a decentral biobank will be established for future translational research.

Patient reported outcomes (PRO) on health-related quality of life (HRQoL) will be assessed by the validated questionnaires EQ-5D-5L, EORTC QLQ-C30, and QLQ-BR23. HRQoL will be assessed at baseline before start of treatment, every 2 months during tucatinib + trastuzumab + capecitabine treatment, and every 3 months thereafter for a maximum of 24 months. Treatment reality of enrolled patients will be intensively documented during tucatinib + trastuzumab + capecitabine treatment and will be followed up regarding subsequent therapies, disease progression, and survival. Documentation of all patients will end at the latest 24 months after finalization of enrollment (i.e., last patient in, LPI) (**Figure 3**).

An international steering committee will accompany TRACE.

Descriptive statistics will be used to analyze data.

Key inclusion criteria

- Aged 18 years or older.
- Diagnosis of locally advanced or metastatic HER2-positive breast cancer, including patients with brain metastases.
- Prior therapy with at least two prior anti-HER2 treatment regimens.
- Decision for treatment with tucatinib in combination with trastuzumab and capecitabine according to current SmPC either in 1st / 2nd palliative treatment line (cohort 1) or 3rd / 4th palliative treatment line (cohort 2).
- Progression after or intolerance to last systemic anti-HER2-based therapy.
- Indication for treatment with tucatinib as assessed by the treating physician.
- Signed written informed consent.

Key exclusion criteria

- Contraindications according to current SmPC of tucatinib.
- Administration of study treatment in 5th or higher palliative therapy line.
- Onset of tucatinib treatment later than 22 days after start of therapy line.

Figure 2: Key in- and exclusion criteria
For a complete list of criteria please see https://clinicaltrials.gov/ct2/show/NCT05253911.

Figure 1

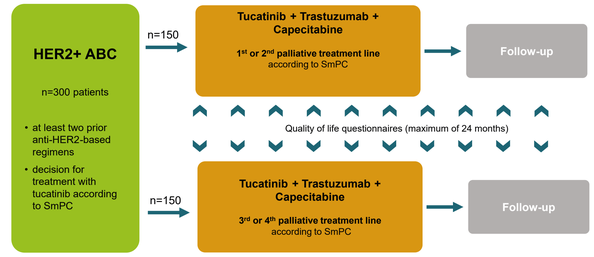

Figure 1: Study design
Treatment will be intensively documented during administration of any study treatment until end of treatment. Subsequently, patients will be followed up until end of study for a maximum of 24 months after enrollment of the last patient (= last patient in). For each patient, patient- reported outcomes (PRO) on health-related quality of life will be gathered for a maximum of 24 months.

Table 1

	HER2CLIMB	TRACE
Patients with higher age	× Median age 55 years	✓
Patients with ECOG ≥ 2	×	✓
Quality of life EQ-5D-5L, EORTC QLQ-C30 und QLQ-BR23	× EQ-5D-5L only	✓
Tucatinib in 1st and 2nd line	×	✓
Effectiveness of tucatinib after adjuvant neratinib	×	✓
Effectiveness of tucatinib after T-DXd	×	✓

Table 1: TRACE will complement valuable data not assessed in HER2CLIMB.

Figure 3

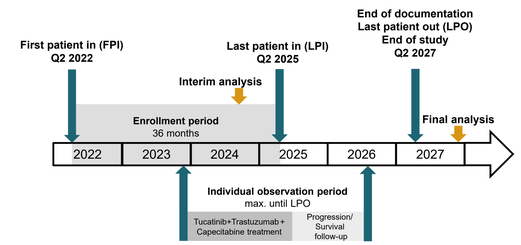

Figure 3: Expected time schedule
Enrollment started in May 2022 and will last for 36 months. The individual observation period involves an intense treatment observation period from first administration of any study treatment (i.e. tucatinib + trastuzumab + capecitabine) until final discontinuation of study treatment. After final discontinuation of study treatment, patients will be followed up for progression (in case study treatment was terminated for another reason than progression), subsequent antineoplastic treatment, overall survival and HRQoL. The documentation and follow-up period for all patients ends no later than 24 months after inclusion of the last patient (i.e. LPI). An interim analysis will be performed 12 months after inclusion of 50% of patients.
QoL: Quality of life, LPI: Last patient in.