STUDY DESIGN OF THE NON-INTERVENTIONAL STUDY TRACE

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

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Conflicts of Interest:
Welt A: Consultancy for Amgen, Roche, Novartis, Pfizer, Tesaro, Seagen; Honoraria from Roche, Eisai, Amgen, AstraZeneca, Pfizer, Daiichi Sankyo, Lilly, Iomedico, Interplan; Financial research support from Novartis, **Nusch A:** Honoraria from Roche, Novartis, AstraZeneca. **Losem C:** Consultancy for Amgen, Abbvie, BMS. Shareholder of iOMEDICO. **Zaiss M:** Honoraria from Astra Zeneca, Janssen, Celgene, Novartis, Hexal, Roche, Takeda, BMS, Vifor, Pfizer, Eisai. **Marschner N:** CEO of iOMEDICO, Consultancy for 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; Shareholder of iOMEDICO; Research funding from 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.
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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 novel 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 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 BM or death was reduced by 48% in all patients with or without brain metastasis in the tucatinib combination.[6] The tucatinib combination has recently been approved in European Union for HER2-positive ABC patients with at least two prior anti-HER2 treatment regimens(in any setting). However, real-world data without strict in- and exclusion criteria are still limited. Additionally, data on tucatinib in early treatment lines (1st and 2nd line) are scarce.

CONCLUSION

Over the next 5 years, TRACE will provide valuable real-world data not only on treatment with tucatinib + trastuzumab + capecitabine in the 1st to 4th line setting, but also on treatment reality and the changing treatment landscape of patients with HER2-positive ABC. TRACE will focus on HRQoL. Effectiveness and safety in real-world will also be assessed and preplanned subgroup analyses will fill important knowledge gaps.

METHODS

The prospective non-interventional 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 will be enrolled into the 1st / 2nd line and the 3rd / 4th line cohort (**Figure 1**).

Patients will be enrolled within 36 months by 60 sites across Germany (start of enrollment in May 2022). Key in- and exclusion criteria are listed in **Figure 2**.

Patient reported outcomes (PRO) on health-related quality of life (HRQoL) will be assessed by 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, 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**).

Primary endpoint 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 are on 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 evaluated. Descriptive statistics will be used to analyze data. Furthermore, a decentral biobank will be established for future translational research.

TRACE will provide important real-world insights into tucatinib + trastuzumab + capecitabine treatment and will address important data gaps such as effectiveness and therapy management of tucatinib in comorbid patients of higher age, in first and second line, after extended adjuvant therapy and after different prior antineoplastic therapies.

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 summary of product characteristics (SmPC) either in 1st / 2nd palliative treatment line (cohort 1) or 3rd / 4th palliative treatment line (cohort 2).
- Patients in cohort 2 must have been diagnosed with locally advanced and unresectable or metastatic disease at primary diagnosis.
- 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

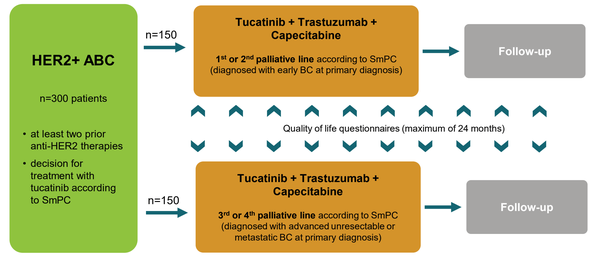

Figure 1: Study design
300 patients with locally advanced or metastatic HER2-positive breast cancer pretreated with at least two anti-HER2 treatment regimens and with decision for treatment with tucatinib + trastuzumab + capecitabine (=observed study treatment) according to summary of product characteristics (SmPC) will be enrolled within 36 months in two cohorts, depending on palliative treatment line. Treatment will be observed during administration of any study treatment until end of treatment. Afterwards, all patients will be followed up until end of observation (i.e. end of study) which will be at the latest 24 months after last patient in. Patient-reported outcomes on quality of life will be collected for each patient for 24 months.

Figure 3

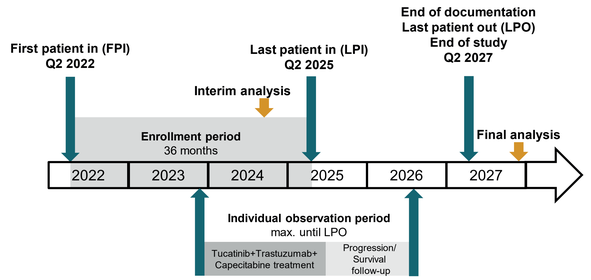

Figure 3: Expected time schedule
Enrollment started in May 2022 and will last for 36 months. The individual observation period involves an intense treatment observation period from first administration of any study treatment (i.e. tucatinib + trastuzumab + capecitabine) until final discontinuation of study treatment. According to SmPC of TUKYSA® (02/2021), tucatinib will be administered until disease progression or unacceptable toxicity. In case of isolated intracranial progression and reintroduction of study treatment after local intracranial therapy, documentation of treatment within TRACE should be continued. 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.