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

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INTRODUCTION

HER2-positive advanced breast cancer (ABC) is an aggressive tumor with high recurrence rates and high incidence of brain metastases (BM). Tucatinib is a highly selective HER2 tyrosine kinase inhibitor. In the pivotal HER2CLIMB trial, tucatinib + trastuzumab + capecitabine demonstrated significant overall and progression-free survival (OS, PFS) benefit compared to placebo + trastuzumab + capecitabine in heavily pretreated patients (trastuzumab, pertuzumab and trastuzumab-emtansine)[1,2]. Thereby, risk of death, disease progression, or development of BM was reduced by 27%, 43% or 45% respectively[1,2,6]. Also, intracranial response rates in patients with BM were higher in the tucatinib compared to the placebo treatment group[4–6]. Since February 2021, tucatinib is approved in the European Union for patients with HER2-positive ABC pretreated with at least two anti-HER2 treatment regimens in any setting. Yet, real-world data from clinical routine and 1st and 2nd treatment lines are scarce. Here, we present the current study design of the non-interventional study TRACE, which will collect real-world data of tucatinib + trastuzumab + capecitabine, including patients underrepresented or excluded from the pivotal trial like elderly patients or patients treated with tucatinib in early ABC treatment lines. Moreover, prospective data on tucatinib combination therapy after prior therapy with trastuzumab-deruxtecan (T-DXd) in Germany and Austria will be gathered.

CONCLUSION

The non-interventional study TRACE will provide important 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 for patients with HER2-positive ABC over a period of five years. The primary focus of TRACE is HRQoL. Furthermore, effectiveness and safety in real-world will be assessed and preplanned subgroup analyses will fill important knowledge gaps between the pivotal trial and routine clinical practice.

METHODS

TRACE (NCT05253911) is a non-interventional, multicenter, prospective and international study currently conducted in Germany and Austria. In total, 300 patients with HER2-positive ABC scheduled to be treated with tucatinib + trastuzumab + capecitabine according to summary of product characteristics (SmPC) are planned to be enrolled. Patients will be enrolled into two cohorts depending on the actual treatment line (1st / 2nd and 3rd / 4th line). Details on study design are shown in **Figure 1**.

Within 36 months, patients will be enrolled by 60 German (start of enrollment: May 2022) and 10 Austrian sites (start of enrollment: October 2023). Key in- and exclusion criteria are listed in **Figure 2**.

The validated questionnaires EQ-5D-5L, EORTC QLQ-C30 and QLQ-BR23 will be used to rate patient reported outcomes on health-related quality of life (HRQoL). Questionnaires will be filled out before start of treatment at baseline, every 2 months during study treatment and thereafter every 3 months. For each patient, HRQoL will be gathered for a maximum of 24 months. Moreover, detailed information on treatment reality during tucatinib + trastuzumab + capecitabine treatment will be documented and patients will be followed up concerning subsequent therapies, disease progression and survival. Documentation will end for all patients at the latest 24 months after finalization of enrollment (i.e. LPI) (**Figure 3**).

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. Effectiveness and safety, physician's 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) will be assessed as secondary endpoints. Health economic parameters will be exploratively evaluated. Data will be analyzed descriptively. TRACE will be complemented by a decentral biobank for future translational research. TRACE will gain valuable real-world insights into treatment with tucatinib + trastuzumab + capecitabine in early (1st and 2nd) and later (3rd and 4th) palliative treatment and will fill important knowledge gaps as shown in **table 1.**

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

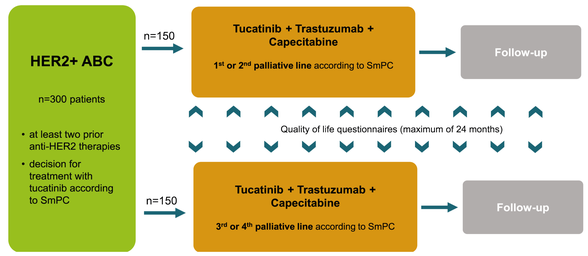

Figure 1: Study design
TRACE plans to enroll 300 patients with locally advanced or metastatic HER2-positive breast cancer who were pretreated with at least two anti-HER2 treatment regimens and who were scheduled to receive tucatinib + trastuzumab + capecitabine (= study treatment) according to summary of product characteristics (SmPC). Patients will be enrolled into two cohorts, depending on palliative treatment line. 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

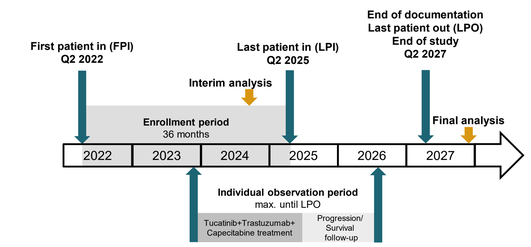

Figure 3: Expected time schedule
Enrollment started in May 2022 and is planned to last for 36 months. The individual observation period involves an intense treatment observation period from first administration of any study treatment (i.e., tucatinib + trastuzumab + capecitabine) until final discontinuation 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. HRQoL: Health-related quality of life, LPI: Last patient in.