137P - Trial Comparing the Safety, Efficacy and Immunogenicity of trastuzumab biosimilar candidate (TX05) with originator trastuzumab in HER2+ Early Breast Cancer

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Background

Biosimilars present patients with additional treatment options and may increase access by potentially lowering costs. TX05 is a trastuzumab biosimilar candidate manufactured in the United States. We report results of a Phase III study (TX05-03, *NCT03556358*) comparing the efficacy and safety of TX05 to originator trastuzumab (TRA) in patients with HER2+ early breast cancer (EBC). The neoadjuvant setting used in study TX05-03 is considered to be a homogeneous and sensitive patient population in which to establish no meaningful differences between TX05 and EU-TRA. In general, the patient population receiving HER2-based treatment is the same in the neoadjuvant and adjuvant settings, differing only in the timing of surgery.

Objectives

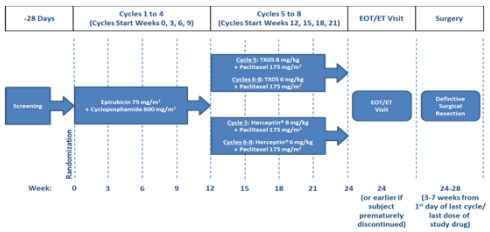
Primary: To demonstrate therapeutic equivalence of TX05 to TRA based on the pathologic complete response (pCR) rate following neoadjuvant chemotherapy. pCR is defined as absence of residual invasive cancer on hematoxylin and eosin evaluation of the complete resected breast specimen and all sampled regional lymph nodes following completion of neoadjuvant systemic therapy (ypT0/Tis ypN0).

Secondary: To compare objective response rate (ORR) between the 2 treatment arms; immunogenicity, safety and tolerability were also assessed.

Methods

TX05-03 was a randomized, double-blind, parallel group Phase III trial with patients enrolled at 124 centers in 10 countries (Belarus, Ukraine, Russia, Georgia, Hungary, Philippines, Mexico, Chile, Peru and India). Treatment included four 3-week cycles of epirubicin and cyclophosphamide followed by four 3-week cycles of paclitaxel and TX05 or TRA. 98.3 % (TRA) and 99.7% (TX05) of subjects completed all planned cycles of trastuzumab treatment, with all except one subject within 10% of the planned dose. The exposure to chemotherapy agents was also well balanced between the two arms in the study. Definitive surgery was completed 3 to 7 weeks after completion of treatment (Figure 1) , and pathologic complete response (pCR) in the per protocol population was defined as the primary study endpoint. Equivalence was concluded if the 95% CI of the risk ratio (TX05/TRA) was contained within the pre-defined interval [0.755, 1.325]. Secondary endpoints were objective response rate (ORR), immunogenicity and safety.

Figure 1: Study Design



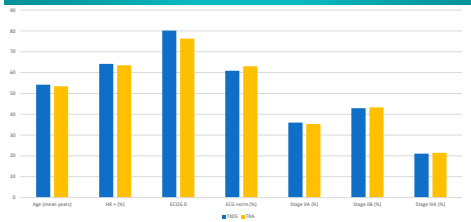
Results

809 subjects with human epidermal growth factor receptor positive (HER2+) invasive early breast cancer were randomized to receive either TX05 (n=404) or TRA (n=405). 794 patients received at least 1 dose of trastuzumab and were included in the modified intent-to-treat population (Figure 2). Overall, baseline characteristics of patients in the two treatment groups (TX05 and TRA) were highly similar. The mean difference in age (TX05 versus TRA) was 0.8 years. The ~~baseline~~ hormone receptor (HR) status was 64.2% HR positive in the TX05 group and 63.5% HR positive in the TRA group. In addition, the ECOG status, ECG status and tumor stage were also consistent between the two groups (Figure 3). Patients included in the per-protocol set received at least 1 dose of TX05 or TRA, had no major protocol deviations impacting efficacy and had an adequate surgical sample able to be assessed for pCR.

Figure 2: Treatment Randomization for TX05 and TRA

mITT: Modified Intent-to-Treat Population
PP: Per Protocol Population

Figure 3: Demographic and Baseline Characteristics of TX05 and TRA groups



The analysis of the primary endpoint (pCR) was based on independent, blinded central review of the pathology reports following definitive surgery. In the primary analysis, the proportion of subjects in the per protocol population meeting pCR criteria (primary efficacy endpoint) was highly similar between the TX05 and TRA groups (48.8% versus 45.3% of subjects, respectively; risk ratio: 1.0783). The 95% CI of the risk ratio (0.9185, 1.2659) was completely contained with the predefined interval, demonstrating therapeutic equivalence between TX05 and TRA (Figure 4). The similarities between treatment groups were also observed when the pCR outcome was based on local reporting (mITT) and when stratification factors were applied; subjects who were included in the mITT population, but did not have efficacy assessments were assessed as non-responders.

The secondary efficacy endpoint (ORR) was defined as the percentage of subjects (mITT population) having complete response (CR) or partial response (PR) at end of treatment. Assessments were done by the investigator in accordance with RECIST version 1.1. The RR and its 95% CI were estimated for ORR in the same way as for the primary efficacy variable. The ORR was also highly similar between the TX05 and TRA groups (84.3% versus 85.0%). The proportion of subjects with CR, partial response, stable disease, and PD was also highly similar based on the mITT population. In all sensitivity analyses, including a "tipping point" analysis, the 95% CI of the risk ratio was completely contained within the predefined interval, confirming the conclusions of the primary analysis (Table 1).

Figure 4: % subjects with pCR in the TX05 and TRA Groups for the PP and mITT Populations; RR = risk ratio TX05/TRA (95% CI)

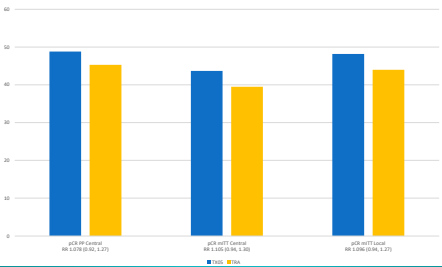


Table 1: Summary of Efficacy Analyses (TX05-03)

Endpoint	pCR positive (positive/total; %)		Review	Population	Risk Ratio (TX05/Her)	95% CI
	TX05	TRA				
pCR	164/336 (48.8)	153/338 (45.3)	central	PP	1.0783	0.9185, 1.2659
pCR, strat					1.0842	0.9283, 1.2662
pCR	172/394 (43.7)	158/400 (39.5)	central	mITT	1.1052	0.9369, 1.3037
pCR strat1					1.1100	0.9456, 1.3031
pCR	190/394 (48.2)	176/400 (44.0)	local	mITT	1.0960	0.9427, 1.2742
ORR	332/394 (84.3)	340/400 (85.0)	local	mITT	0.9913	0.934, 1.0519
ORR	293/336 (87.2)	297/338 (87.9)	local	PP	0.9924	0.9374, 1.0506

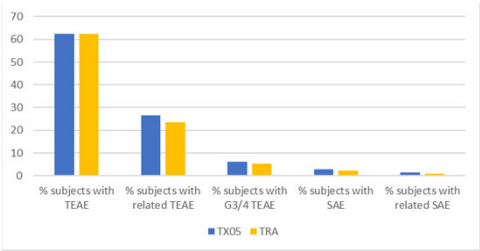
Safety

Because study drug (TX05/trastuzumab) was not introduced until Cycle 5 of treatment, the analyses of treatment emergent adverse events (TEAEs) was focused on Cycles 5 through 8 of treatment. Overall, 62.4% of subjects in the safety population experienced TEAEs during treatment with TX05 while 62.5% of subjects experienced TEAEs during treatment with TRA. The most frequently reported AEs during trastuzumab treatment were in the SOCs of musculoskeletal and connective tissue disorders, nervous system disorders, gastrointestinal disorders and general disorders, administration site conditions, and investigations. (Table 2). Overall, the safety profile of TX05 was similar to TRA (Figure 5).

Table 2 : Adverse Events by SOC

System Organ Class	TX05 N = 394 (n, %)	TRA N = 400 (n, %)
Musculoskeletal and connective tissue disorders	103 (26.1)	98 (24.5)
Nervous system disorders	87 (22.1)	88 (22.0)
Gastrointestinal disorders	50 (12.7)	57 (14.3)
General disorders and administration site conditions	48 (12.2)	55 (13.8)
Investigations	54 (13.7)	45 (11.3)
Blood and lymphatic system disorders	39 (9.9)	41 (10.3)
Skin and subcutaneous tissue disorders	33 (8.4)	27 (6.8)
Infections and infestations	27 (6.9)	25 (6.3)
Metabolism and nutrition disorders	12 (3.0)	13 (3.3)
Renal and urinary disorders	8 (2.0)	12 (3.0)
Cardiac disorders	10 (2.5)	7 (1.8)
Vascular disorders	12 (3.0)	4 (1.0)
Respiratory, thoracic and mediastinal disorders	10 (2.5)	5 (1.3)
Injury, poisoning and procedural complications	5 (1.3)	7 (1.8)
Immune system disorders	3 (0.8)	7 (1.8)
Psychiatric disorders	4 (1.0)	3 (0.8)
Hepatobiliary disorders	4 (1.0)	1 (0.3)
Reproductive system and breast disorders	3 (0.8)	1 (0.3)
Eye disorders	0	2 (0.5)
Ear and labyrinth disorders	0	1 (0.3)
Endocrine disorders	0	1 (0.3)
Neoplasms benign, malignant and unspecified	1 (0.3)	0
Pregnancy, puerperium / perinatal conditions	0	1 (0.3)
Social circumstances	0	1 (0.3)

Figure 5: Overview of TEAE in Safety Population by Treatment Group



Conclusions

- Overall, the TX05 study treatment was well-tolerated. The safety profile was consistent with the known profile of TRA with no significant safety findings seen in the study.
- The proportion of subjects meeting pCR criteria was highly similar between the TX05 and TRA groups (48.8% and 45.3% respectively; risk ratio: 1.0783; 95% CI: 0.9185, 1.2659) in the per protocol population based on central pathological review. As such, the primary efficacy endpoint was met.
- All sensitivity analyses, including evaluation of missing data by tipping point analysis, also supported the conclusions of the primary efficacy analysis.
- The ORR was also highly similar between the TX05 and TRA groups (84.3% and 85.0%, respectively mITT). The proportion of subjects with CR, partial response, stable disease, and PD was highly similar based on the mITT population. The PP population yielded comparable results. As such, the secondary efficacy endpoint was met.
- The results of this study support that there is no clinically meaningful difference between TX05 and EU-TRA in the treatment of subjects with HER2 positive EBC. A scientific bridge between EU-TRA, US-TRA, and TX05 has been established based on three-way PK similarity in a prior study. Together these results support the conclusion of no clinically meaningful difference between TX05 and US-TRA in the treatment of subjects with HER2 positive EBC.

Disclosures

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