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Trastuzumab botidotin vs trastuzumab emtansine (T-DM1) in HER2-positive unresectable or metastatic breast cancer: Results from a randomized phase III study

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Background

Trastuzumab botidotin (A166) is a HER2-directed ADC developed using a stable, protease-cleavable valine-citrulline linker conjugated to the anti-microtubule agent Duo-5. In a phase 1 study, A166 showed promising activity in heavily pretreated patients (pts) with HER2+ breast cancer (BC). Here, we first report the results from a phase 3 study (NCT06968585).

Methods

Pts with HER2+ unresectable or metastatic BC who had received at least one prior anti-HER2 therapy were randomized (1:1) to receive A166 (4.8 mg/kg Q3W) or T-DM1 (3.6 mg/kg Q3W) until disease progression or unacceptable toxicity. The primary endpoint was PFS by BICR per RECIST v1.1.

Results

A total of 365 pts were randomized (median age 55 years; 73.4% with visceral metastases; 53.4% received ≥2 prior anti-HER2 therapies; 55.9% had prior pyrotinib). As of 26 April 2025, median follow-up was 14.9 mo. Median PFS was significantly longer in A166 than in T-DM1 (11.1 mo vs 4.4 mo; HR 0.39 [95% CI 0.30-0.51], p<0.0001). PFS benefit with A166 was consistently observed regardless of prior lines of anti-HER2 therapy (HR 0.36 for 1 prior line; HR 0.39 for ≥2 prior lines). ORR by BICR was 76.9% vs 53.0%, and mDOR was 12.2 mo vs 5.7 mo. Although OS data were immature, a trend toward benefit was observed in A166 (HR 0.62; 95% CI, 0.38-1.03). Grade ≥3 TEAEs occurred in 69.8% of pts in A166 and 63.7% in T-DM1. The most common grade ≥3 TEAEs (≥5%) were corneal disorder, dry eye, and vision blurred in A166, and platelet count decreased, neutrophil count decreased, hypokalemia, and GGT increased in T-DM1. Among A166-treated pts who experienced any-grade ocular AEs, instrumental activities of daily living (ADL) limitations occurred in 37 (20.3%) pts, and self-care ADL limitations in 13 (7.1%) pts; these resolved in 32 (86.5%) and 12 (92.3%) pts, respectively. TEAEs led to discontinuation in 1.1% of pts in A166 and 3.8% in T-DM1. No TEAE led to death in A166, compared with 1.1% in T-DM1.

Conclusions

A166 demonstrated statistically significant and clinically meaningful improvement in PFS compared with T-DM1, with a manageable safety profile in pts with HER2+ unresectable or metastatic BC. These results position A166 as a potential new therapeutic option for HER2+ disease.

Clinical trial identification

NCT06968585.

Legal entity responsible for the study

Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd.

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Disclosure

X. Jin, J. Ge: Financial Interests, Institutional, Full or part-time Employment: Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd. All other authors have declared no conflicts of interest.