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Sacituzumab tirumotecan (sac-TMT) vs investigator's choice of chemotherapy (ICC) in previously treated locally advanced or metastatic hormone receptor-positive, HER2-negative (HR+/HER2-) breast cancer (BC): Results from the randomized, multi-center phase III OptiTROP-Breast02 study

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Background

Sac-TMT is a TROP2 ADC developed with a novel linker to conjugate the payload, a belotecan-derivative topoisomerase I inhibitor. Sac-TMT has shown promising activity in pre-treated patients (pts) with HR+/HER2- mBC in the phase 1/2 trial (*Ouyang et al.,JHO, 2025*). Here, we first report the PFS results from the phase 3 OptiTROP-Breast02 study (NCT06081959).

Methods

Pts with HR+/HER2- BC who had progression on CDK4/6 inhibitors and received at least one prior line of chemotherapy in the advanced/metastatic setting were randomized (1:1) to receive sac-TMT 5 mg/kg Q2W or ICC (eribulin, vinorelbine, capecitabine, or gemcitabine). The primary endpoint was PFS assessed by blinded independent central review (BICR).

Results

A total of 399 pts (median age 54 yrs; 53% HER2-zero; 96% visceral mets; 57% with ≥2 prior lines of chemotherapy) were randomized (sac-TMT: 200; ICC: 199). At data cut-off (22 Jan 2025), 113 pts in sac-TMT and 61 in ICC remained on treatment. Median PFS was significantly longer in sac-TMT than in ICC (8.3 vs. 4.1 mo; HR, 0.35; 95% CI, 0.26-0.48; P<0.0001). The 6-mo PFS rates with sac-TMT were 61.4% vs 25.7% with ICC. Clinical benefit was seen in sac-TMT independent of HER2 expression (HR for PFS in HER2-zero: 0.39, 95% CI, 0.26-0.57; in HER2-low: 0.31, 95% CI, 0.20-0.48). ORR was also superior with sac-TMT to ICC (41.5% vs 24.1%). Although the OS data were not mature at a median follow-up of 7.4 mo, there was a trend that favored sac-TMT over ICC (HR, 0.33; 95% CI, 0.18-0.61). Grade ≥ 3 TRAEs occurred in 62.0% and 64.8% of pts in sac-TMT and ICC with the most common being neutrophil count decreased (44.5% vs 51.5%) and WBC decreased (31.0% vs 31.6%); TRAE led to discontinuation in 0% and 0.5% of pts; pneumonitis occurred in 1.5% and 1.0% of pts (all grade 1-2) in sac-TMT and ICC, respectively.

Conclusions

Sac-TMT demonstrated significantly improved PFS compared to ICC, with manageable safety profile in pts with previously treated HR+/HER2- BC including both HER2-zero and HER2-low, positioning it as a new therapeutic option for this population.

Clinical trial identification

NCT06081959.

Legal entity responsible for the study

Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd.

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Disclosure

G. Liu, Y. Diao, 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.