

4R0
Target switching with conserved-payload novel ADCs in patients with metastatic breast cancer following prior ADC therapy (SWITCH): A prospective, open-label, phase 2 platform trial

X. Liu¹, Y. Yang¹, F. Liang², C. Chen¹, Y. Liu¹, F. Yang¹, S. Zhao¹, L. Chen¹, W. Zhang¹, Q. Liang³, Y. Shen³, Y. Jiang¹, L. Fan¹, Z. Shao¹

¹ Department of Breast Surgery, Fudan University Shanghai Cancer Center, Shanghai, China, ² Department of Biostatistics, Zhongshan Hospital Affiliated to Fudan University, Shanghai, China³ Department of Clinical Research & Development, Jiangsu Hengrui Pharmaceutical Co., Ltd., Shanghai, China

Background

Resistance to antibody-drug conjugates (ADCs) is an inevitable challenge in metastatic breast cancer (MBC), but the optimal post-progression sequencing strategy remains unclear. The SWITCH trial evaluated the efficacy and safety of a “target/payload switching” strategy using novel ADCs in patients with ADC-refractory MBC.

Methods

SWITCH is a prospective, open-label, phase 2 platform trial. Patients with human epidermal growth factor receptor 2-negative (HER2-negative) MBC who progressed on at least one prior ADC were enrolled. Based on prior treatment history, participants were randomly assigned to four novel ADC cohorts: SHR-A1811 (Cohort A), SHR-A1921 (Cohort B), SHR-A2009 (Cohort C), or SHR-A2102 (Cohort D), all carrying a topoisomerase I inhibitor (TOP1i) payload. The primary endpoint was investigator-assessed objective response rate (ORR).

Results

Between Oct 21, 2024, and Dec 30, 2025, 58 HER2-negative patients were screened, 54 of whom were randomly assigned (Cohort A: n=10; B: n=12; C: n=12; D: n=20). The population was heavily pretreated, with the majority (94.4%) having prior exposure to TOP1i-based ADCs. Confirmed ORRs were limited across all cohorts: 0% in Cohort A, 8.3% in Cohort B, 0% in Cohort C, and 5% in Cohort D. Responses were observed only in patients switching from the microtubule inhibitor-based ADC disitamab vedotin (RC48) to a TOP1 inhibitor-based ADC, whereas no responses occurred after switching between ADCs with the same payload class despite antigen switching. Treatment-related adverse events were consistent with known profiles of each ADC and manageable.

Conclusions

Rechallenging ADC-refractory MBC with novel agents targeting alternative antigens yielded limited responses, which suggested that payload cross-resistance was a primary driver of resistance. Diversified payload mechanisms in subsequent ADC sequencing were important to restore therapeutic sensitivity.

Clinical trial identification

NCT06649331.

Legal entity responsible for the study

Fudan University Shanghai Cancer Center.

Funding

National Major Science and Technology Projects of China; National Natural Science Foundation of China.

Disclosure

All authors have declared no conflicts of interest.