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Ruzaltatug rezetecan, a HER3-directed ADC, vs platinum-based chemotherapy (PBC) in EGFR-mutated advanced NSCLC progressing after EGFR-TKI: Interim analyses (IA) from the phase 3 HERON-Lung01 trial

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Background

Ruzaltatug rezetecan (SHR-A2009) is a novel ADC composed of a fully human anti-HER3 IgG1 mAb, cleavable peptide linker and DNA topoisomerase I inhibitor payload. In a previous phase 1 trial, SHR-A2009 showed promising antitumor activity and manageable safety in pretreated *EGFR*-mutated NSCLC, supporting pivotal investigation.

Methods

In this phase 3 study, patients (pts) with *EGFR*-mutated (Ex19del/L858R) advanced nonsquamous NSCLC progressing after EGFR–TKI were randomized 1:1 to receive SHR-A2009 (8 mg/kg, IV, Q3W) or PBC (pemetrexed 500 mg/m^2 + carboplatin AUC 5 or cisplatin 75 mg/m^2 Q3W for 4 cycles, followed by maintenance pemetrexed). Crossover to SHR-A2009 from PBC arm was allowed after disease progression. The primary endpoint was progression-free survival (PFS) per blinded independent central review (BICR).

Results

A total of 498 pts were randomized (SHR-A2009, n=250; PBC, n=248). At the prespecified PFS IA (data cutoff, Apr. 15, 2026), median follow-up was 7.7 mo. BICR-assessed PFS was significantly longer with SHR-A2009 vs PBC (median, 8.3 vs 5.4 mo; HR 0.47 [95% CI 0.36–0.60]; 1-sided P <0.0001). PFS benefits persisted across all prespecified subgroups, regardless of presence of brain metastases or *EGFR* mutation type. Overall survival was immature but favored SHR-A2009 (HR 0.70; 95% CI, 0.43–1.14), despite substantial post-progression crossover (19.4%) from PBC arm. Objective response rate (60.0% vs 34.3%), disease control rate (92.8% vs 83.1%) and median duration of response (8.5 vs 4.4 mo) per BICR were also improved with SHR-A2009. Grade ≥3 treatment-related adverse events (TRAEs) occurred in 40.7% with SHR-A2009 vs 38.9% with PBC, most commonly decreased neutrophil count (25.8% vs 19.2%), decreased WBC count (11.7% vs 12.1%) and anaemia (6.0% vs 10.9%). Interstitial lung disease occurred in 6 pts (2.4%; grade 1–2, n=5; grade 3, n=1) with SHR-A2009. TRAEs led to dose discontinuation in 1.2% with SHR-A2009 and 1.3% with PBC.

Conclusions

SHR-A2009 significantly improved PFS vs PBC, with a manageable safety profile, supporting it as a new standard-of-care option for advanced *EGFR*-mutated NSCLC progressing after EGFR-TKI.

Clinical trial identification

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Legal entity responsible for the study

Jiangsu Hengrui Pharmaceuticals.

Funding

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Disclosure

Y. Wu: Financial Interests, Personal, Invited Speaker: AstraZeneca, BMS, Boehringer Ingelheim, BeOne, Hengrui, Merck, MSD, Pfizer, Roche; Financial Interests, Personal, Advisory Board: AstraZeneca, MSD, Amgen, Daiichi Sankyo; Financial Interests, Coordinating PI: AstraZeneca, Boehringer Ingelheim, BMS, Hengrui, Merck, MSD, Pfizer, Roche, Eli Lilly; Financial Interests, Steering Committee Member: Sanofi, Yunhan; Non-Financial Interests, Leadership Role: Chinese Thoracic Oncology Group (CTONG); Non-Financial Interests, Other, WCLC 2020 Conference Chair: IASLC; Non-Financial Interests, Leadership Role, Past President: Chinese Society of Clinical Oncology (CSCO); Non-Financial Interests, Other, Editorial Board member of Ann Oncology and ESMO Open: ESMO. J. Zhang: Financial Interests, Personal, Full or part-time Employment: Hengrui. F. Qiu: Financial Interests, Personal, Full or part-time Employment: Hengrui. L. Yang: Financial Interests, Personal, Full or part-time Employment: Hengrui. All other authors have declared no conflicts of interest.

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