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Sacituzumab tirumotecan (sac-TMT) plus pembrolizumab (P) versus chemotherapy (chemo) plus pembrolizumab (P) as first-line (1L) treatment for PD-L1-negative advanced non-squamous (nsq) NSCLC: Randomized phase 3 OptiTROP-Lung06 study

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Background

Pembrolizumab plus chemotherapy is the standard 1L treatment for PD-L1-negative advanced nsq-NSCLC without actionable genomic alterations, but outcomes remain suboptimal. Sac-TMT, a TROP2-directed ADC, previously showed encouraging activity with PD-1 blockade in 1L PD-L1-positive NSCLC (*Xiong et al., Lancet, 2026*). We report the results from the preplanned interim PFS analysis of OptiTROP-Lung06 (NCT06711900).

Methods

Eligible patients (pts) had treatment-naïve, locally advanced or metastatic nsq-NSCLC without *EGFR/ALK* alterations and PD-L1 tumor proportion score (TPS) <1% using the 22C3 assay. Pts were randomized 1:1 to receive sac-TMT 4 mg/kg Q2W + P 400 mg Q6W or chemo + P. The primary endpoint was PFS per RECIST 1.1 assessed by blinded independent central review (BICR); OS was secondary.

Results

A total of 455 pts (median age 63 yrs; 72.1% male; 82.4% ECOG 1; 91.6% stage IV) were randomized to receive sac-TMT + P (n=229) or chemo + P (n=226). As of Jun 9, 2026, median follow-up was 9.7 mo. Sac-TMT + P showed a highly statistically significant and clinically meaningful improvement in PFS by BICR compared with chemo + P (median: 15.0 vs 5.7 mo; HR, 0.49; 95% CI 0.36-0.65; *p*<0.0001). OS data were immature, but a favorable trend was observed in the sac-TMT + P group (HR, 0.58; 95% CI 0.38-0.88). ORR by BICR was 50.2% vs 47.3%, and median DoR was 13.6 vs 6.8 mo (HR 0.47, 95% CI 0.29-0.77). Grade ≥3 TEAEs were less frequent with sac-TMT + P than with chemo+ P (47.6% vs 60.6%), including neutrophil count decreased (19.7% vs 28.8%), white blood cell count decreased (9.6% vs 16.4%), anemia (6.1% vs 20.4%), and platelet count decreased (3.9% vs 14.6%). Sac-TMT-associated AEs were manageable; grade ≥3 stomatitis occurred in 2.2%.

Conclusions

Sac-TMT+ P significantly prolonged PFS versus chemo + P, with longer response duration and a manageable safety profile. To our knowledge, this is the first randomized phase 3 study showing superior PFS with a TROP2-directed ADC plus PD-1 blockade versus an immunotherapy-plus-chemo standard therapy in NSCLC, supporting sac-TMT +P as a potential 1L treatment option for this population.

Clinical trial identification

NCT06711900; first posted on Dec 02, 2024.

Legal entity responsible for the study

Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd., Chengdu, China.

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Disclosure

C. Zhou: Financial Interests, Personal, Invited Speaker: Eli Lilly, Sanofi, BI, Roche, MSD, Qilu, Hengrui, Innovent Biologics, C-Stone, LUYE Pharma, TopAlliance Biosciences Inc, Amoy Diagnostics, Allist, Dizal; Financial Interests, Personal, Advisory Role: Innovent Biologics, Hengrui, Qilu, TopAlliance Biosciences Inc. L. Yin: Financial Interests, Personal, Full or part-time Employment: Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd. Y. Qing: Financial Interests, Personal, Full or part-time Employment: Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd. X. Jin: Financial Interests, Personal, Full or part-time Employment: Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd. J. Ge: Financial Interests, Personal, Full or part-time Employment: Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd. All other authors have declared no conflicts of interest.

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