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Sacituzumab tirumotecan (sac-TMT) vs platinum-based chemotherapy in EGFR-mutated (EGFRm) non-small cell lung cancer (NSCLC) following progression on EGFR-TKIs: results from the randomized, multi-center phase III OptiTROP-Lung04 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 demonstrated significant survival benefits over docetaxel in EGFRm NSCLC after failure of EGFR-TKI and platinum-based chemotherapy (*Fang et al.,BMJ 2025*). Here, we first report the final PFS analysis and preplanned interim OS analysis results from the phase 3 OptiTROP-Lung04 study (NCT05870319).

Methods

Patients (pts) were randomized (1:1) to receive sac-TMT monotherapy (5 mg/kg Q2W) or chemotherapy (pemetrexed 500 mg/m^2 + carboplatin AUC 5 or cisplatin 75 mg/m^2 Q3W for 4 cycles followed by maintenance of pemetrexed). The primary endpoint was PFS assessed by blinded independent review committee (BIRC) with OS as a key secondary endpoint tested hierarchically.

Results

A total of 376 pts (median age 59.5 yrs; 39.6% male; 79.3% ECOG PS 1; 94.7% prior 3rd-generation EGFR TKI) were randomized to the sac-TMT (n=188) or chemotherapy (n=188) groups. At a median follow-up of 18.9 mo, 21.3% of pts (sac-TMT) vs 1.6% (chemotherapy) remained on treatment. Sac-TMT demonstrated highly statistically significant and clinically meaningful improvements in PFS and OS compared to chemotherapy (Table). Grade ≥ 3 TRAEs occurred in 49.5% and 52.2%, and TRSAEs in 7.4% and 17.0% of pts in sac-TMT and chemotherapy arms, respectively. No drug-related interstitial lung disease/pneumonitis occurred in either arm.Table: LBA5

	Sac-TMT (n=188)	Chemotherapy (n=188)
Median PFS (BIRC), mo (95% CI)	8.3 (6.7 - 9.9)	4.3 (4.2 - 5.5)
HR (95% CI)	0.49 (0.39 - 0.62)	
P-value	<0.0001	
12-mo PFS rate, %, (95% CI)	32.3 (25.5 - 39.2)	7.9 (4.4 - 12.8)
Median OS, mo (95% CI)	NR (21.5 - NE)	17.4 (15.7 - 20.4)

	Sac-TMT (n=188)	Chemotherapy (n=188)
HR (95% CI)	0.60 (0.44 - 0.82)	
P-value	0.0006	
Adjusted median OS*, mo (95% CI)	NR (21.5 - NE)	17.2 (15.4 - 18.9)
HR (95% CI)	0.56 (0.41 - 0.77)	
P-value	0.0002	
ORR (BIRC), % (95% CI)	60.6 (53.3, 67.7)	43.1 (35.9, 50.5)
Median DOR (BIRC), mo (95% CI)	8.3 (6.2 - 10.0)	4.2 (3.0 - 4.4)

Data cutoff: Jul 06, 2025. P-value was presented as one-sided. *censored at the date of initiation of subsequent anti-tumor ADC drug therapy.

Conclusions

Sac-TMT is the first TROP2 ADC to significantly improve PFS and OS over platinum-based chemotherapy, with manageable safety in EGFR-TKI resistant NSCLC, positioning it as a potential new standard of care for this population.

Clinical trial identification

NCT05870319.

Legal entity responsible for the study

Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd.

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Disclosure

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