

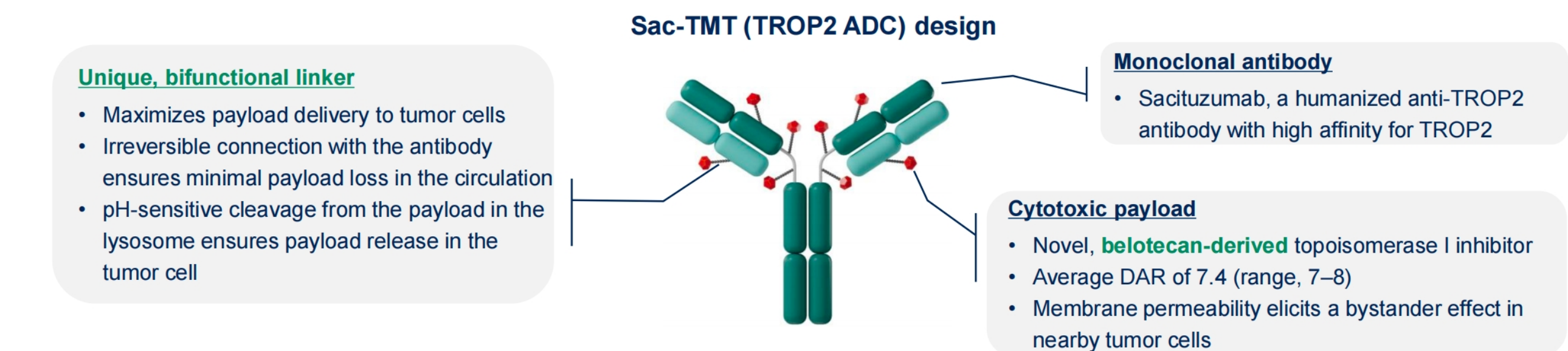
Sacituzumab Tirumotecan in EGFR-Mutated NSCLC patients with ≥3 metastatic sites: subgroup analysis of OptiTROP-Lung04

Wenfeng Fang¹, Lin Wu², Xiangjiao Meng³, Yu Yao⁴, Wei Zuo⁵, Wenxiu Yao⁶, Yanyan Xie⁷, Yu Zhang⁸, Jiawei Cui⁹, Yongchang Zhang¹⁰, Xingya Li¹¹, Wu Zhuang¹², Jian Fang¹³, Qiming Wang^{14, 15}, Wei Jiang¹⁶, Kai Li¹⁷, Yina Diao^{18, 19}, Junyou Ge^{18, 19}, Yunpeng Yang¹, Li Zhang^{*1}
¹Sun Yat-sen University Cancer Center, Guangzhou, China; ²Hunan Cancer Hospital/The Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University, Changsha, China; ³Shandong Cancer Hospital and Institute, Shandong First Medical University, Jinan, China; ⁴The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China; ⁵The First Affiliated Hospital of Nanchang University, Nanchang, China; ⁶Sichuan Cancer Hospital, Chengdu, China; ⁷The People's Hospital of Guangxi Zhuang Autonomous Region, Nanning, China; ⁸Mianyang City Center Hospital, Mianyang, China; ⁹The First Hospital of Jilin University, Changchun, China; ¹⁰Hunan Cancer Hospital, Changsha, China; ¹¹The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China; ¹²Fujian Cancer Hospital, Fuzhou, China; ¹³Beijing Cancer Hospital, Beijing, China; ¹⁴The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Zhengzhou, China; ¹⁵Institute of Cancer Research, Henan Academy of Innovations in Medical Science, Zhengzhou, China; ¹⁶Guangxi Medical University Cancer Hospital, Nanning, China; ¹⁷Tianjin Medical University Cancer Institute & Hospital, Tianjin, China; ¹⁸Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd., Chengdu, China; ¹⁹National Engineering Research Center of Targeted Biologics, Chengdu, China

Correspondence: Li Zhang

INTRODUCTION

- Sacituzumab tirumotecan (sac-TMT) is a novel antibody-drug conjugate targeting trophoblast cell surface antigen 2 (Trop-2) with a unique bifunctional linker that maximizes delivery of a belotecan-derivative topo I inhibitor payload to tumor cells.



- The phase III OptiTROP-Lung04 study demonstrated superior survival outcomes with sac-TMT compared with platinum-based chemotherapy in patients (pts) with advanced or metastatic EGFR-mutated (EGFRm) non-small cell lung cancer (NSCLC) after progression on EGFR-TKIs¹.

- Pts with high tumor burden, commonly defined by the presence of ≥3 metastatic sites (mets)², represent a clinically challenging population with poor outcomes following EGFR-TKI failure.

- This subgroup analysis evaluated the efficacy and safety of sac-TMT in pts with ≥3 metastatic sites.

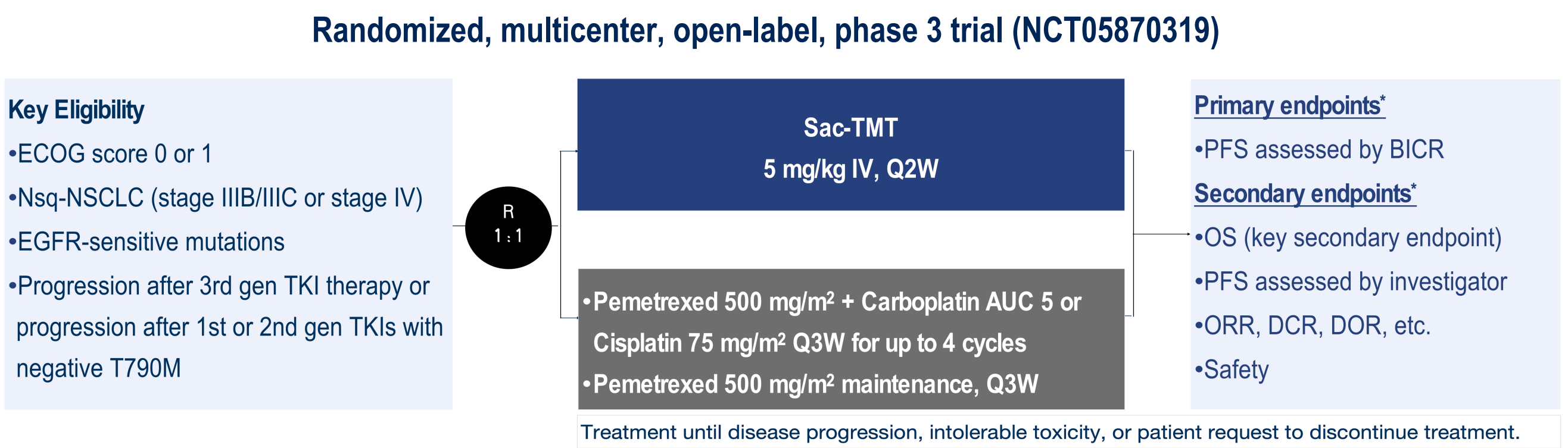
METHODS

Design

- OptiTROP-Lung04 study is a multicenter, open-label, randomized phase III trial. Eligible pts with locally advanced or metastatic nonsquamous EGFRm NSCLC who progressed after EGFR-TKI therapy were randomized 1:1 to receive sac-TMT 5 mg/kg Q2W or pemetrexed plus platinum-based chemotherapy (**Figure 1**).

- The primary endpoint was progression-free survival (PFS) assessed by blinded independent central review (BICR) per RECIST v1.1. Secondary endpoints included overall survival (OS), objective response rate (ORR), disease control rate (DCR), and safety. This subgroup analysis assessed PFS, OS, ORR, DCR and safety in pts with ≥3 metastatic sites at baseline.

Figure 1. Study Design of OptiTROP-Lung04 Study



- Stratification factors:**
 1. Prior EGFR-TKI therapy (3rd gen TKI in 1st line vs in 2nd line vs no 3rd gen TKI)
 2. Brain metastases (yes vs no)

RESULTS

Patient Characteristics

- As of July 6, 2025, 188 patients were enrolled in each treatment group in the overall study. Among them, 128 patients (68.1%) in the sac-TMT group and 126 patients (67.0%) in the chemotherapy group had ≥3 metastatic sites at baseline and comprised the subgroup population for this analysis. (**Table 1**).

- Baseline characteristics were generally balanced between both groups, including age, disease stage, prior EGFR-TKI exposure, smoking history and baseline brain metastases, etc.

Table 1. Patient Demographics and Baseline Characteristics

	Sac-TMT (N = 128)	Chemotherapy (N = 126)
Age		
Median (range)	60.0 (31, 75)	60.0 (33, 75)
≥65 yr , n (%)	35 (27.3)	40 (31.7)
Sex, n (%)		
Male	49 (38.3)	63 (50.0)
Smoking history, n (%)		
Current or former smoker	33 (25.8)	38 (30.2)
Never smoked	95 (74.2)	88 (69.8)
ECOG score, n (%)		
0	21 (16.4)	25 (19.8)
1	107 (83.6)	101 (80.2)
Disease stage, n (%)		
IIIB	1 (0.8)	0
IV	127 (99.2)	126 (100)
Liver metastases, n (%)	21 (16.4)	30 (23.8)
Brain metastases, n (%)	26 (20.3)	30 (23.8)
EGFR mutation subtype†, n (%)		
L858R	61 (47.7)	47 (37.3)
19-Del	68 (53.1)	80 (63.5)
Other	6 (4.7)	5 (4.0)
T790M mutation status, n (%)		
Negative	31 (24.2)	27 (21.4)
Positive	23 (18.0)	22 (17.5)
Unknown	74 (57.8)	77 (61.1)

Previous third-generation EGFR-TKI , n (%)		
First-line therapy	79 (61.7)	85 (67.5)
Second-line therapy	41 (32.0)	35 (27.8)
Never received	8 (6.3)	6 (4.8)

†The sum of percentages exceeds 100 because of overlapping mutations in some patients. The subcategory "Other" includes other EGFR mutations co-occurring with exon 21 L858R substitution or exon 19 deletion.

Efficacy

- Sac-TMT was associated with longer PFS than chemotherapy.
 - Median PFS was 7.4 months for sac-TMT versus 4.3 months for chemotherapy (hazard ratio [HR], 0.51; 95% confidence interval [CI], 0.38-0.67) (**Figure 2**).

- Consistent improvement was observed in OS (HR, 0.49; 95%CI, 0.34-0.70), ORR (61.7% vs 43.7%) and DCR (86.7% vs 77.8%) (**Figure 3 & Table 2**).

Figure 2. PFS as assessed by BICR of Pts with ≥3 mets

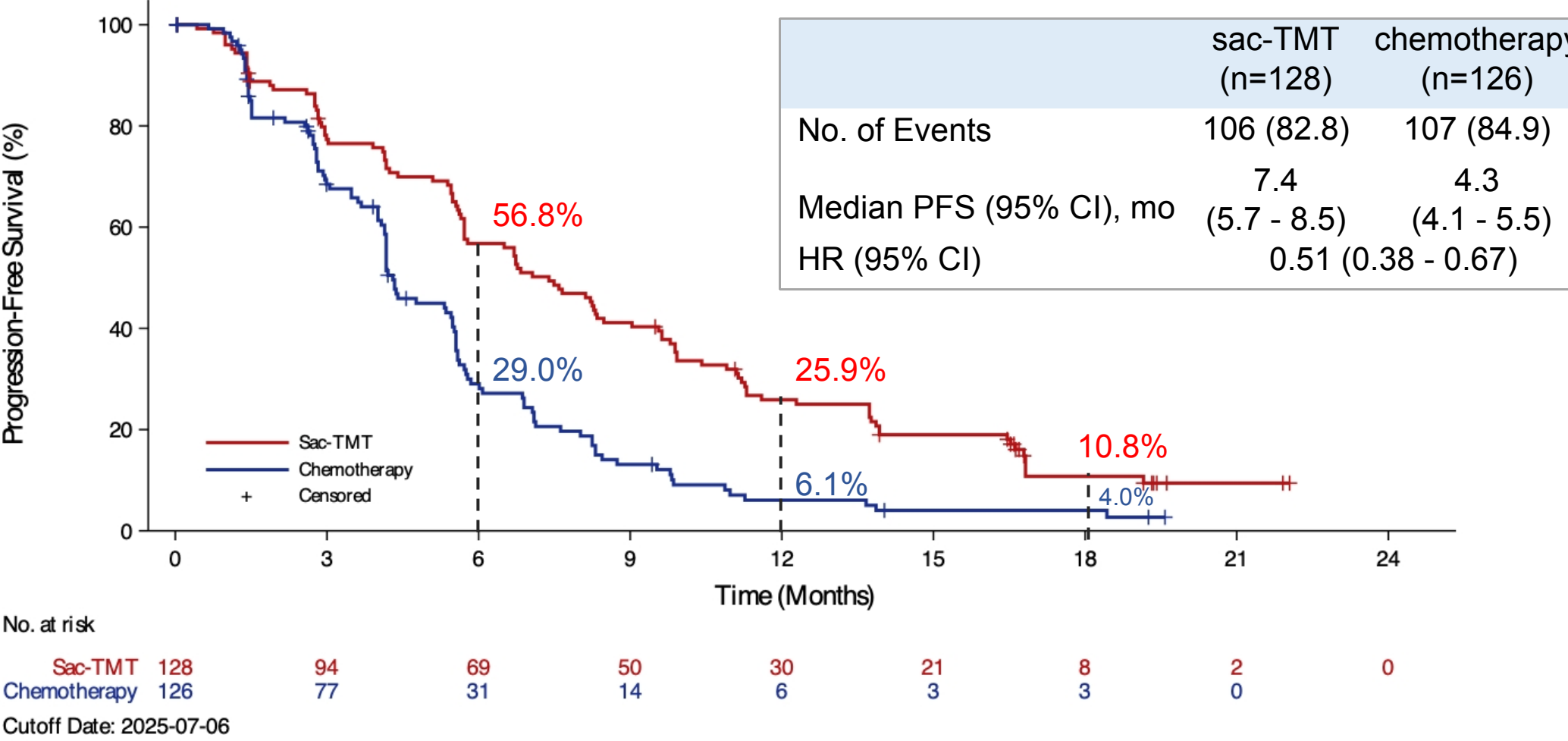


Figure 3. OS of Pts with ≥3 mets

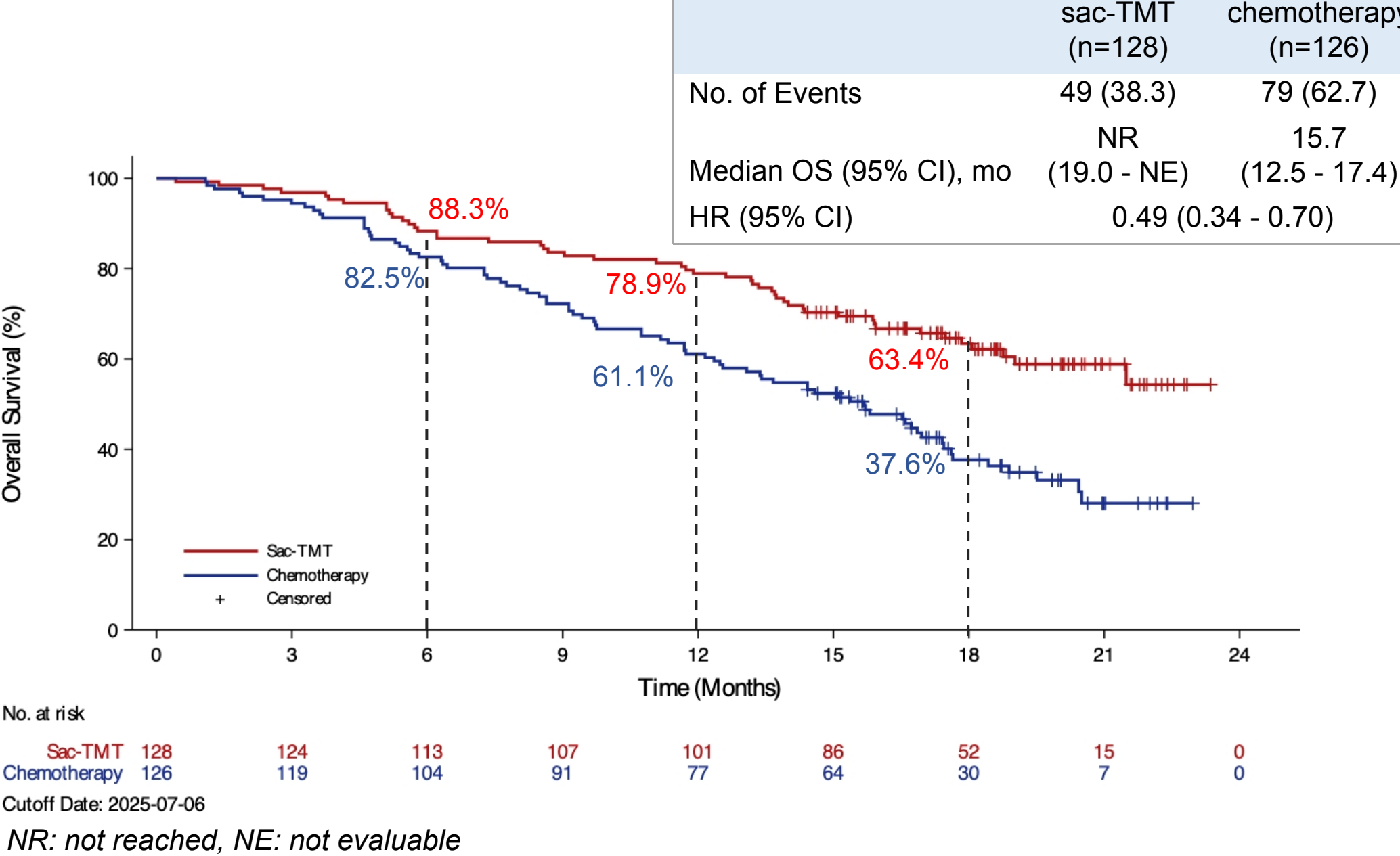


Table 2. ORR and DCR as assessed by BICR of Pts with ≥3 mets

	Sac-TMT (N = 128)	Chemotherapy (N = 126)
ORR (CR+PR), n (%)	79 (61.7)	55 (43.7)
95%CI	52.7, 70.2	34.8, 52.8
DCR (CR+PR+SD), n (%)	111 (86.7)	98 (77.8)
95%CI	79.6, 92.1	69.5, 84.7

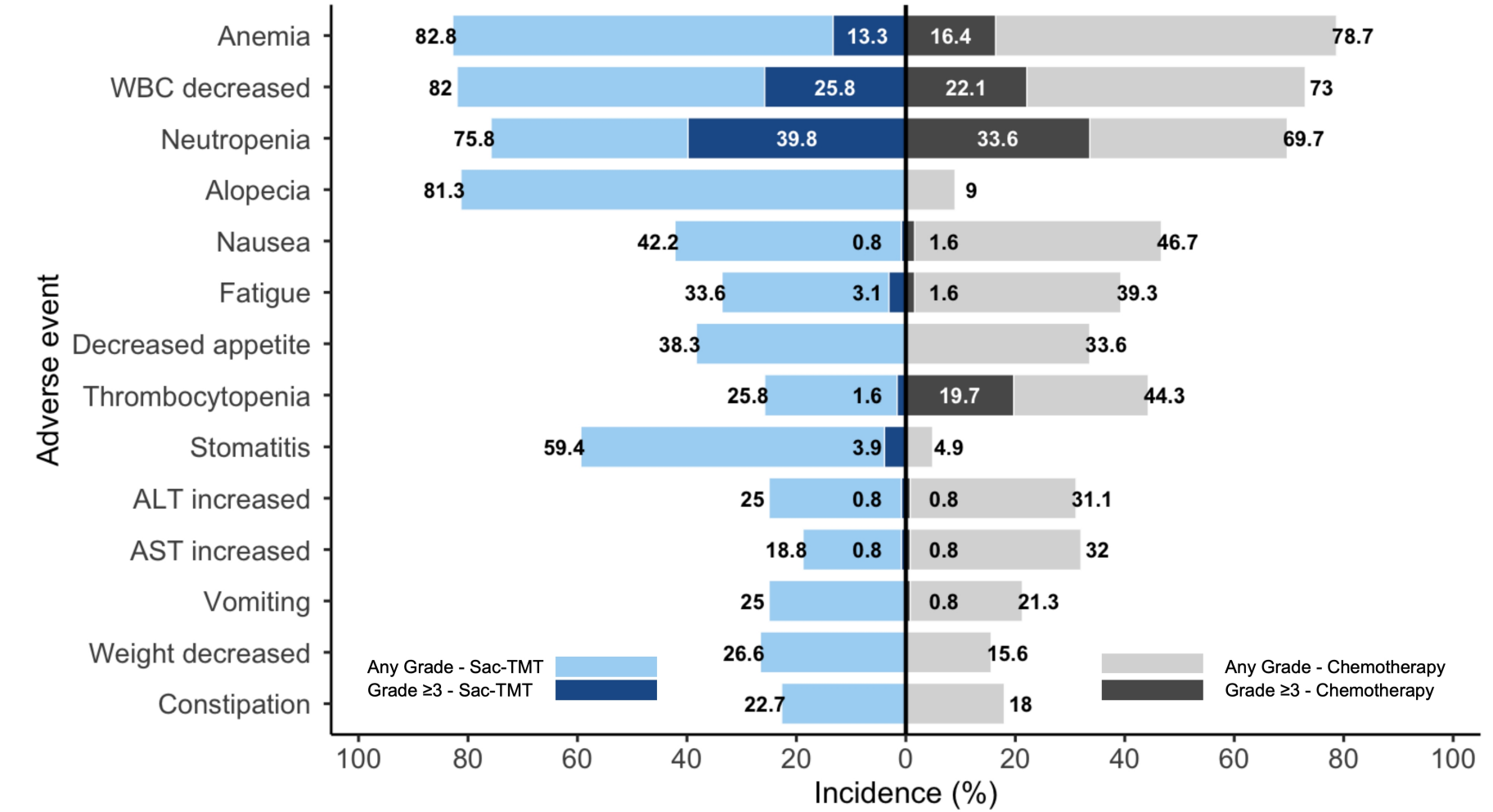
CR: complete response, PR: partial response, SD: stable disease

Safety

- Despite longer exposure with sac-TMT compared with chemotherapy (8.7 vs 4.4 months), toxicity was comparable: any TRAE, 100% vs 99.2%; grade ≥3 TRAE, 57.8% vs 55.7%; TRAE leading to dose reduction, 28.1% vs 23.8%; TRAE leading to treatment interruption, 36.7% vs 32.0%. No fatal TRAEs occurred with sac-TMT versus one with chemotherapy. No TRAEs led to treatment discontinuation in either group.

- TRAEs were predominantly hematologic in both groups, with stomatitis more frequent for sac-TMT (**Figure 4**).

Figure 4. Overview of TRAEs (All Grade ≥ 20%)



Safety analyses were based on the safety sets (sac-TMT, n=128; chemotherapy, n=122). TRAE: treatment related adverse events, WBC: white blood cell, ALT: alanine aminotransferase, AST: aspartate aminotransferase

DISCUSSION AND CONCLUSION

- For pts with high tumor burden (≥3 mets), sac-TMT provided substantial and clinically meaningful improvements in PFS, OS, ORR and DCR compared with platinum-based chemotherapy, with no new safety signals identified.

- These results support sac-TMT as an effective treatment option following EGFR-TKI failure in patients with extensive metastatic disease.

REFERENCES

- [1] N Engl J Med. 2026 Jan 1;394(1):13-26.
- [2] Cancer. 2009 Jul 1;115(13):2930-8.

ACKNOWLEDGMENTS

- The authors thank the patients and their families for their invaluable contribution and commitment, and the study team for their participation in the OptiTROP-Lung04 trial.

- This study was supported by Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd.

CONTACT INFORMATION

- Contact Dr Li Zhang at zhangli6@mail.sysu.edu.cn for questions or comments.