

Phase 1b/2a Legubicin Trial, a Doxorubicin and Legumain-Cleavable Tetrapeptide Conjugate, #PT2.01.02 for Pretreated Non-Small Cell Lung Cancer Patients

Ye Guo¹, Jin Li¹, **Yuping Sun**², Linlin Wang², Meili Sun³, Hua Li³, Yu Zhang⁴, Sheng Hu⁵, Cheng Liu⁶, Yuan Liu⁶, Hui Sun⁶, Wenyue Jin⁶, Fei Yang⁶, Hongqiang Xia⁶, Peng Wu⁷

¹Shanghai East Hospital, School of Medicine, Tongji University, Shanghai/CN, ²Cancer Hospital of Shandong First Medical University, Jinan/CN, ³Jinan Central Hospital, Jinan/CN, ⁴Nanjing Chest Hospital, The Affiliated Brain Hospital of Nanjing Medical University, Nanjing/CN, ⁵Hubei Cancer Hospital, Wuhan/CN, ⁶Affinity (Shanghai) Biopharmaceutical Co., Ltd., Shanghai/CN, ⁷Shanghai Zenith Data Technology Co., Ltd., Shanghai/CN.

Contact: sunyp@sd-cancer.com; heying@affinity.net.cn

Research supported by: Affinity (Shanghai) Biopharmaceutical Co., Ltd.

BACKGROUND

- Doxorubicin (DOX)** is a potent, broad-spectrum anthracycline cytotoxic agent used in numerous aggressive malignancies, but its clinical value is restricted by cardio- and hematotoxicity, limiting its max cumulative dose and long-term use;
- Application in NSCLC:** to enhance targeted DOX activation while reducing cardiac and hematologic toxicity via advanced delivery mechanisms;
- Legubicin** is a tumor microenvironment-activated (TMEA) albumin-drug conjugate (ALDC) with DOX as payload and a tetrapeptide linker selectively cleaved by legumain, a highly specific protease widely over-expressed in solid tumors;
- Legubicin** is designed to enhance tumor-selective activation, reduce systemic toxicity including cardiac exposure, and preserve antitumor activities.

DESIGN

- Based on phase 1 dose-escalation & early expansion results, this phase 1b/2a expansion further enrolled advanced NSCLC patients, prioritizing adenocarcinoma and squamous cell carcinoma, who had received ≥ 3 prior lines or had no standard treatment options;
- Patients received legubicin 270 mg/m² IV Q2W (4-week cycle) or Q3W (3-week cycle).

Table 1. Key eligibility criteria for prioritized subtypes

NSCLC subtype	Prior therapy ≥ 3 prior lines or no standard of care (SOC)
Adeno-carcinoma & Squamous NSCLC	- Driver-positive*: prior targeted therapy and platinum chemotherapy; - EGFR exon20 insertion or driver-negative: prior platinum chemotherapy and PD-1 /PD-L1 therapy;

* Driver-positive: EGFR, ALK, NTRK, BRAF, ROS1, MET exon 14 skipping, or RET-positive;

Key primary endpoints:

ORR, DCR, PFS; Incidence of AEs and serious AEs;

Key secondary endpoints: OS, PK, PD;

Objective: Evaluate safety, tolerability, and efficacy of different dosing frequencies of single-agent legubicin in advanced solid tumor patients failing SOC.

RESULTS

Patient and tumor characteristics

As of October 23, 2025, 38 patients (median age 60 years; men 60.5%) had received legubicin 270 mg/m² Q2W (n=36) or Q3W (n=2) and were included in the efficacy and safety analyses. All patients had stage III (2.6% [1/38]) or IV disease (97.4% [37/38]), 13.2% (5/38) had brain metastases, and 92.1% (35/38) received ≥ 3 lines of prior systemic treatment.

Figure 1. Patient enrollment and dosing

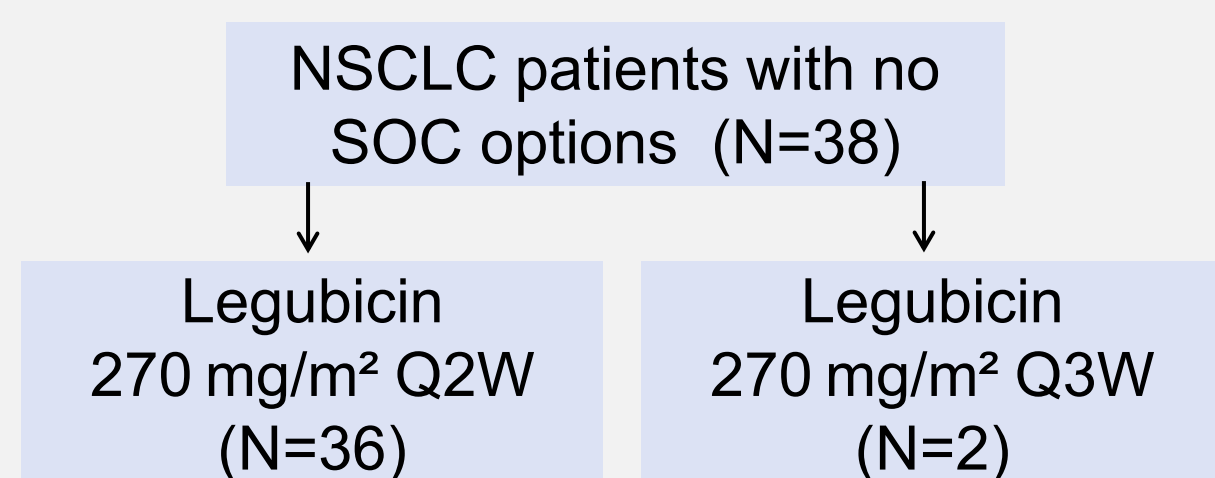


Table 2. Patient demographic and baseline characteristics

Characteristics	N=38
Age, Median (range), years	60 (23,75)
Male, n (%)	23 (60.5)
Race, n (%)	
Asian	38 (100)
ECOG PS 1, n (%)	36 (94.7)
Histology, n (%)	
Adenocarcinoma	33 (86.8)
Squamous cell carcinoma	5 (13.2)
Number of prior lines of systemic therapy, n (%)	
≥ 3 lines	35 (92.1)
≥ 5 lines	18 (47.4)
Clinical stage, n (%)	
III	1 (2.6)
IV	37 (97.4)
Metastases at baseline, n (%)	
Brain	5 (13.2)
Liver	8 (21.1)
Pleura	16 (42.1)
Bone	17 (44.7)
Lymph node	23 (60.5)
Missing	3 (7.9)

Anti-tumor efficacy

- Under legubicin monotherapy, 3 patients had a partial response and 23 had stable disease, with an ORR of 7.9% and a DCR of 68.4%. At the data cutoff (Nov 6, 2025), 27 PFS events occurred. mPFS was 4.4 months (95%CI, 3.9-6.4), and mOS was 15.0 months (95%CI, 9.7-NR). For lung adenocarcinoma patients who received ≥ 3 lines, mPFS was 5.3 months (95%CI, 3.9-7.1) and mOS 17.3 months (95%CI, 12.0-NR).

Figure 2. Kaplan-Meier curve of PFS

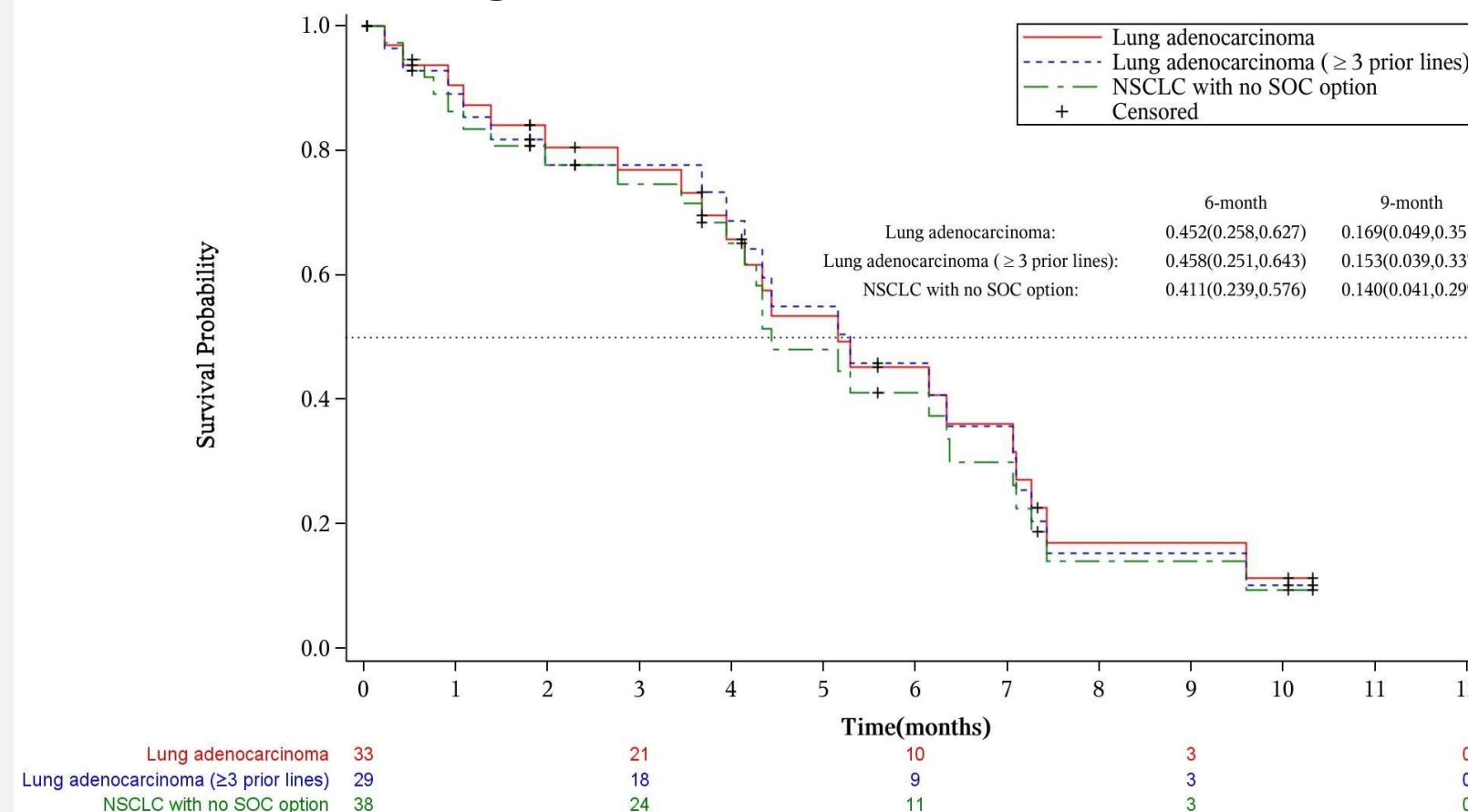


Figure 3. Kaplan-Meier curve of OS

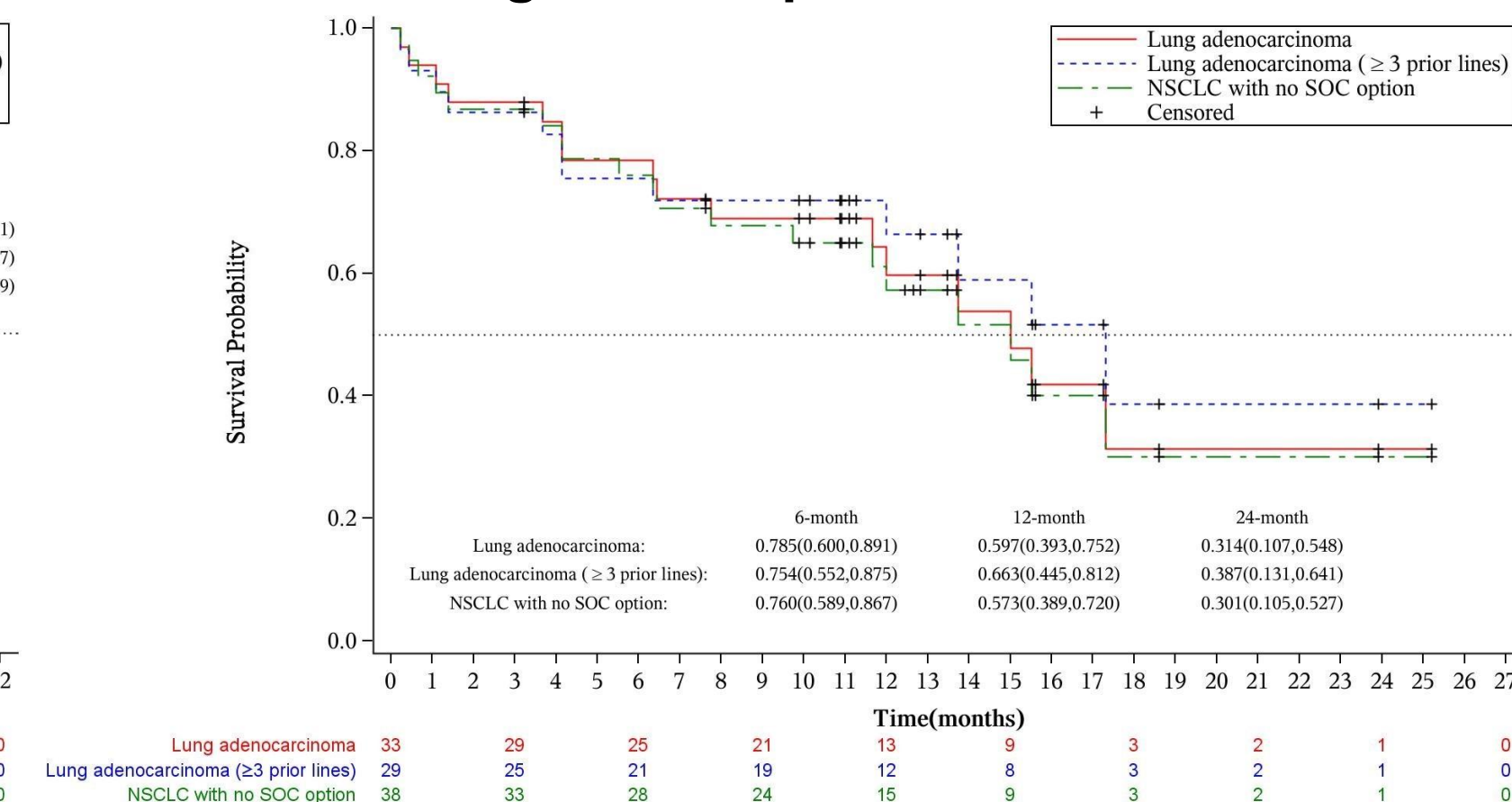


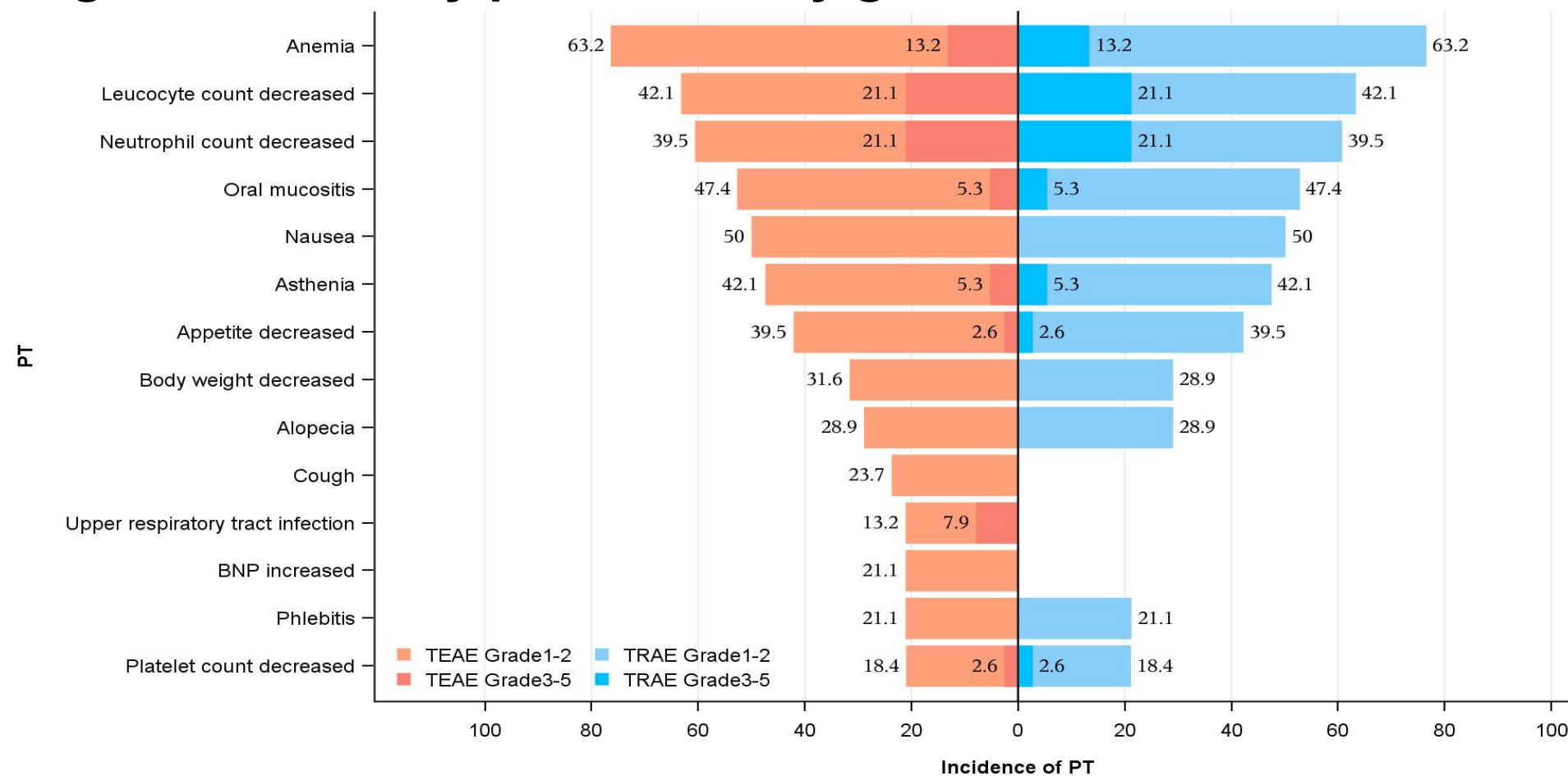
Table 3. Efficacy comparison in NSCLC patients without SOC

Endpoint	Historical meta-analysis ¹	Legubicin monotherapy
mPFS, months	3.0 (95%CI, 2.9-3.8)	4.4 (95%CI, 3.9-6.4)
mOS, months	10.3 (95%CI, 9.5-10.8)	15.0 (95%CI, 9.7-NR)

Safety analysis

- 60.5% of patients received ≥ 6 cycles of legubicin monotherapy; median treatment duration was 16.4 weeks, and median cumulative legubicin exposure was 3,317 mg (~1,746 mg DOX equivalent, or ~2.4x maximum cumulative DOX dose of 450 mg/m², assuming a BSA of 1.62 m²);

Figure 4. Butterfly plot of AEs by grade with incidence $\geq 20\%$



Legubicin showed longer mPFS and OS vs historical meta-analysis in heavily pretreated NSCLC patients without SOC, suggesting clinically meaningful disease control and potential long-term survival benefit.

Grade ≥ 3 TEAEs occurred in 65.8% of patients and SAEs in 34.2%. Treatment discontinuation (5.3%) and study withdrawal (7.9%) due to TEAEs were infrequent;

Most TRAEs were grade 1–2 and resolved with routine supportive care. Most common grade ≥ 3 TRAEs were hematotoxicity (leukocyte and neutrophil count decrease (21.1% each) and anemia (13.2%)), and GI toxicity (oral mucositis (5.3%));

Grade ≥ 3 cardiac TRAEs were rare, occurring in 1 patient (2.6%), and resolving with symptomatic treatment.

Conclusion: Legubicin 270 mg/m² (Q2W and Q3W) exhibited a favorable safety profile and clinically significant antitumor activity in heavily pretreated advanced NSCLC patients who had no standard treatment options. PFS and OS trends compared favorably with historical controls despite prolonged, high cumulative anthracycline exposure.