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Phase I/II Study of iza-bren (BL-B01D1) as Monotherapy in Patients with Locally Advanced or Metastatic EGFR Mutated NSCLC

Presented by: Wenfeng Fang[1]

H. Zhao[2], Y. Zhao[2], Y. Ma[2], Y. Huang[2], Y. Yang[2], L. Chen[2], X. Hou[2], Y. Wang[3], S. Xiao[4], H. Zhu[5], Y. Zhu[5], L. Zhang[2]

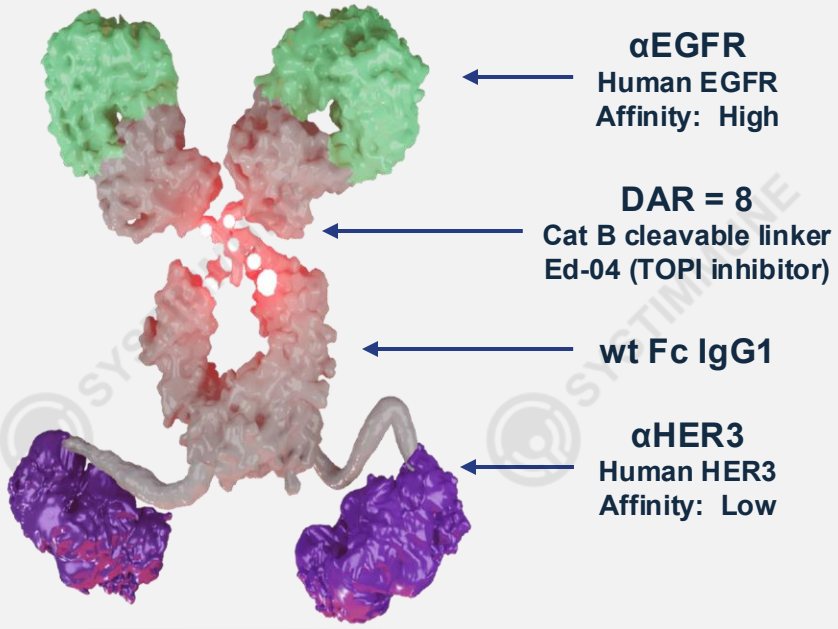
[1]Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Guangzhou, China; [2]Sun Yat-sen University Cancer Center, Guangzhou, China; [3]West China Hospital Sichuan University, Sichuan, China; [4]Baili-Bio (Chengdu) Pharmaceutical Co., Ltd., Sichuan, China; [5]SystImmune, Inc., Redmond, WA, United States

Take-Home Points

- Iza-bren (BL-B01D1), a potential first-in-class antibody-drug conjugate targeting EGFR and HER3, demonstrated promising antitumor activity in previously treated EGFR-mutated advanced NSCLC.
- Safety profile of iza-bren was manageable and most common toxicities related to iza-bren were hematologic.
- Iza-bren is being evaluated in two phase III studies in patients with EGFR-mutated advanced NSCLC after 3rd generation EGFR-TKI failure (NCT06382116 & NCT07100080).

Background

Iza-bren (BL-B01D1)



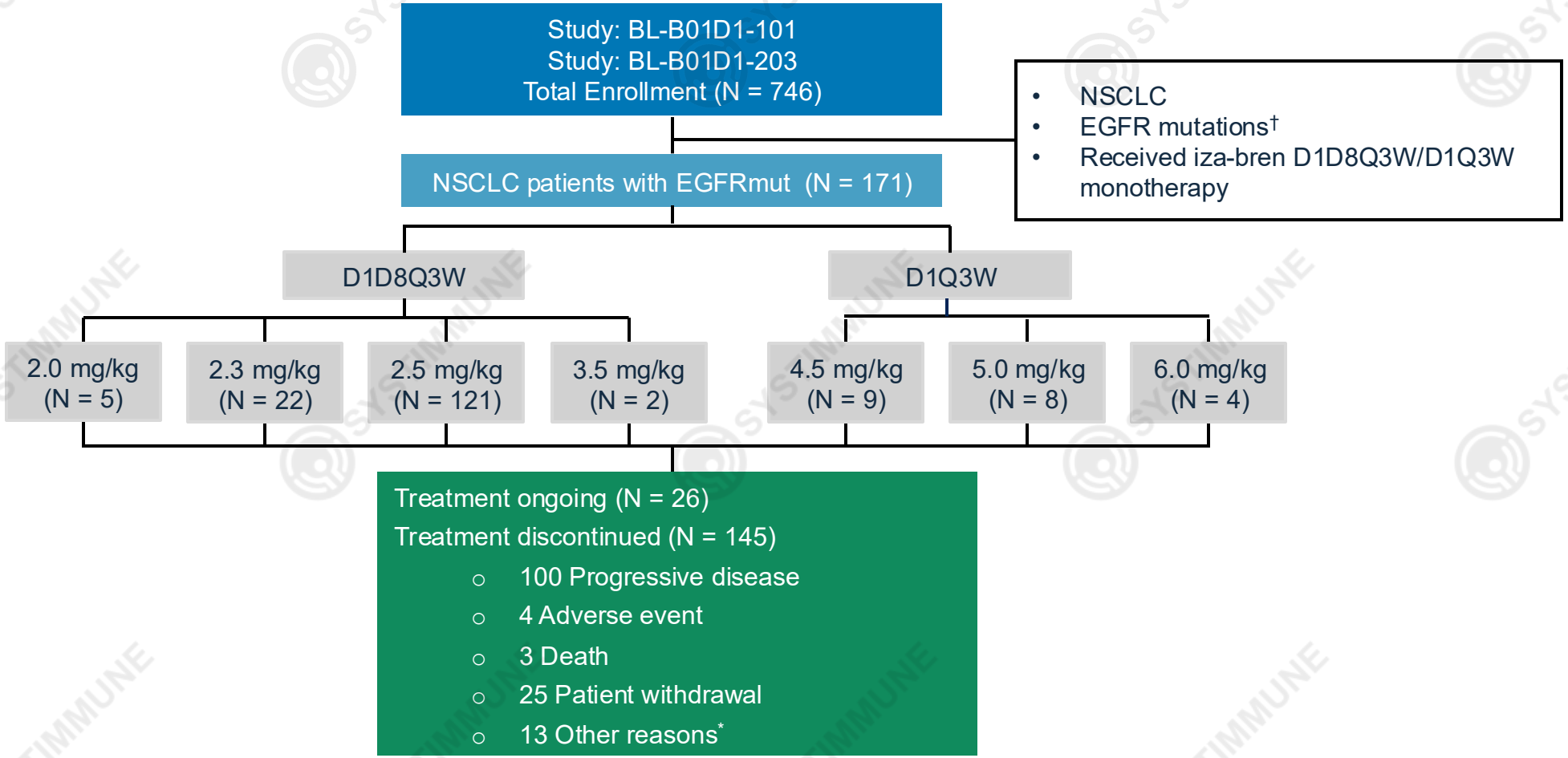
- Third generation (3G) EGFR-TKI is one of the standard first-line therapy for patients with EGFRmt NSCLC, and most patients inevitably developed drug resistance. Subsequent therapeutic options following 3G EGFR-TKI remain limited.
- Iza-bren is a potential first-in-class ADC comprised of an EGFR x HER3 bispecific antibody conjugated to a novel topo-I inhibitor payload (Ed-04) via a stable tetrapeptide-based cleavable linker.
- Iza-bren has shown promising clinical activity and a manageable safety profile in solid tumors including pretreated EGFRmt NSCLC[1].

Here, we report the latest efficacy and safety results of iza-bren as monotherapy in pretreated EGFRmt NSCLC from two phase I/II studies (NCT05194982, NCT05880706).

wt: wild type; **Cat B:** cathepsin B; **TOPI:** Topoisomerase I.

[1] Ma, Yuxiang et al. The Lancet Oncology, Volume 25, Issue 7, 901-911.

Study Design & Patient Disposition



†: Including EGFR exon19del, L858R, T790M, Exon 20ins, etc.
*: Including 5 with treatment delay >28 days; 5 discontinued per investigator decision; 2 started new anti-cancer therapy; 1 non-compliant.

Data cutoff: June 30, 2025

Baseline Characteristics

	Total (N = 171)	D1D8Q3W				D1Q3W		
		2.0 mg/kg (N = 5)	2.3 mg/kg (N = 22)	2.5 mg/kg (N = 121)	3.5 mg/kg (N = 2)	4.5 mg/kg (N = 9)	5.0 mg/kg (N = 8)	6.0 mg/kg (N = 4)
Median (range) age, years	57.0 (35.0, 82.0)	58.0 (40.0, 69.0)	61.5 (37.0, 72.0)	57.0 (37.0, 82.0)	39.0 (39.0, 39.0)	54.0 (42.0, 71.0)	60.5 (35.0, 73.0)	61.0 (53.0, 67.0)
Male, n (%)	72 (42.1)	3 (60.0)	10 (45.5)	51 (42.1)	1 (50.0)	2 (22.2)	3 (37.5)	2 (50.0)
Median (range) baseline sum of diameters, mm	45.5 (10.0, 181.0)	64.7 (52.0, 120.0)	41.5 (18.0, 133.0)	42.0 (10.0, 181.0)	64.5 (16.0, 113.0)	58.0 (27.0, 94.0)	40.5 (26.0, 91.0)	63.0 (42.0, 117.0)
ECOG-PS Score, n (%)								
0	14 (8.2)	0	1 (4.5)	9 (7.4)	0	2 (22.2)	1 (12.5)	1 (25.0)
1	157 (91.8)	5 (100)	21 (95.5)	112 (92.6)	2 (100)	7 (77.8)	7 (87.5)	3 (75.0)
EGFR exon19del mutation, n (%)	91 (53.2)	3 (60.0)	10 (45.5)	65 (53.7)	1 (50.0)	5 (55.6)	6 (75.0)	1 (25.0)
EGFR L858R mutation, n (%)	67 (39.2)	2 (40.0)	12 (54.5)	44 (36.4)	0	4 (44.4)	2 (25.0)	3 (75.0)
Brain metastasis at baseline, n(%)	61 (35.7)	2 (40.0)	3 (13.6)	44 (36.4)	1 (50.0)	6 (66.7)	3 (37.5)	2 (50.0)
Prior line of therapy, n (%)								
1L	44 (25.7)	1 (20.0)	12 (54.5)	30 (24.8)	1 (50.0)	0	0	0
2L	53 (31.0)	3 (60.0)	8 (36.4)	36 (29.8)	0	2 (22.2)	4 (50.0)	0
3L and above	74 (43.3)	1 (20.0)	2 (9.1)	55 (45.5)	1 (50.0)	7 (77.8)	4 (50.0)	4 (100)
Prior line of chemotherapy, n (%)								
0L	74 (43.3)	1 (20.0)	16 (72.7)	50 (41.3)	1 (50.0)	0	5 (62.5)	1 (25.0)
1L	60 (35.1)	3 (60.0)	4 (18.2)	42 (34.7)	1 (50.0)	5 (55.6)	3 (37.5)	2 (50.0)
2L	18 (10.5)	1 (20.0)	1 (4.5)	16 (13.2)	0	0	0	0
3L and above	19 (11.1)	0	1 (4.5)	13 (10.7)	0	4 (44.4)	0	1 (25.0)
Prior 3G EGFR-TKI, n (%)	158 (92.4)	5 (100)	22 (100)	110 (90.9)	1 (50.0)	9 (100)	7 (87.5)	4 (100)
Prior PBC, n (%)	90 (52.6)	4 (80.0)	1 (4.5)	69 (57.0)	1 (50.0)	9 (100)	3 (37.5)	3 (75.0)
Prior anti-PD(L)-1, n (%)	31 (18.1)	0	0	25 (20.7)	1 (50.0)	4 (44.4)	0	1 (25.0)

Most patients were pretreated with 3G EGFR-TKI; predominant EGFR mutations in our population were exon19del and L858R.

Data cutoff: June 30, 2025

Summary of Efficacy

	Total (N = 171)	2.5 mg/kg D1D8Q3W		
		Total (N = 121)	Post any TKI & chemo naïve* (N = 50)	Post 3G TKI & chemo naïve (N = 46)
Median (range) LoT	2 (1-10)	2 (1-10)	2 (1-5)	2 (1-5)
BOR, n (%)				
PR	99 (57.9)	68 (56.2)	33 (66.0)	30 (65.2)
Confirmed PR	81 (47.4)	59 (48.8)	28 (56.0)	25 (54.3)
PR pending confirmation[1]	3 (1.8)	1 (0.8)	1 (2.0)	1 (2.2)
SD	40 (23.4)	30 (24.8)	12 (24.0)	12 (33.3)
PD	26 (15.2)	19 (15.7)	4 (8.0)	3 (6.5)
NE[2]	6 (3.5)	4 (3.3)	1 (2.0)	1 (2.2)
ORR, % (95%CI)	57.9 (50.1, 65.4)	56.2 (46.9, 65.2)	66.0 (51.2, 78.8)	65.2 (49.8, 78.6)
cORR, % (95%CI)	**47.4** (39.7, 55.1)	48.8 (39.6, 58.0)	**56.0** (41.3, 70.0)	**54.3** (39.0, 69.1)
DCR, % (95%CI)	81.3 (74.6, 86.8)	81.0 (72.9, 87.6)	90.0 (78.2, 96.7)	91.3 (79.2, 97.6)
Median DoR, mo (95%CI)	8.5 (6.9, 11.2)	8.5 (6.5, 12.7)	13.7 (5.5, 19.5)	12.7 (5.5, NR)
Median PFS, mo (95% CI)	**6.9** (5.5, 9.6)	6.9 (5.5, 9.7)	**12.5** (6.9, 18.0)	**12.5** (6.9, 18.0)
Median OS, mo (95% CI)	**24.8** (18.5, NR)	24.8 (18.0, NR)	**NR** (NR, NR)	**NR** (NR, NR)
Median FU for OS, mo (95% CI)	20.5 (18.3, 21.9)	21.9 (20.3, 22.7)	20.5 (15.8, 21.9)	20.5 (15.8, 21.9)

- In total of 171 patients, the cORR was 47.4%, mPFS was 6.9 mo, mOS was 24.8 mo.
- In post any TKI and chemo naïve patients at 2.5 mg/kg D1D8Q3W, the cORR was 56.0%, mPFS was 12.5 months, mOS was not reached.
- The efficacy in post 3G TKI and chemo naïve patients was comparable to that in post-TKI and chemo naïve patients.

Patients who received at least one dose of iza-bren were included in the analysis.

*: Patients with prior TKI treatment and no prior chemotherapy.

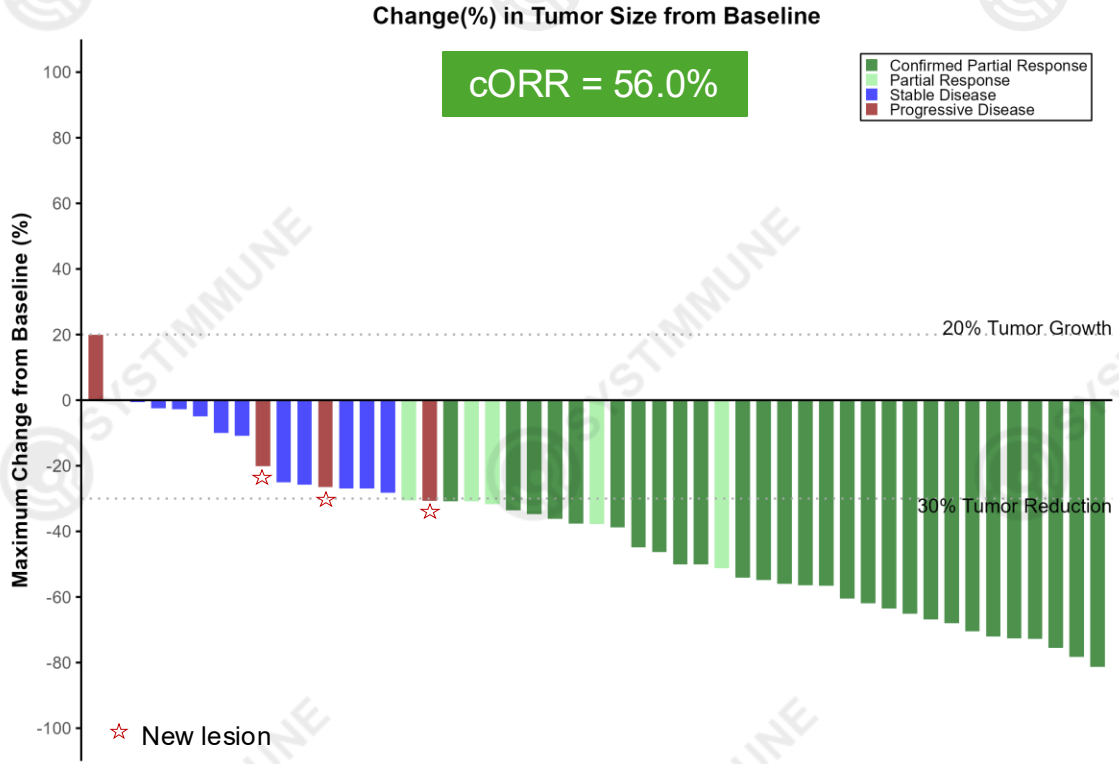
[1] Patients still on study with tumor assessment of PR and not reach to the next time point of tumor assessment;

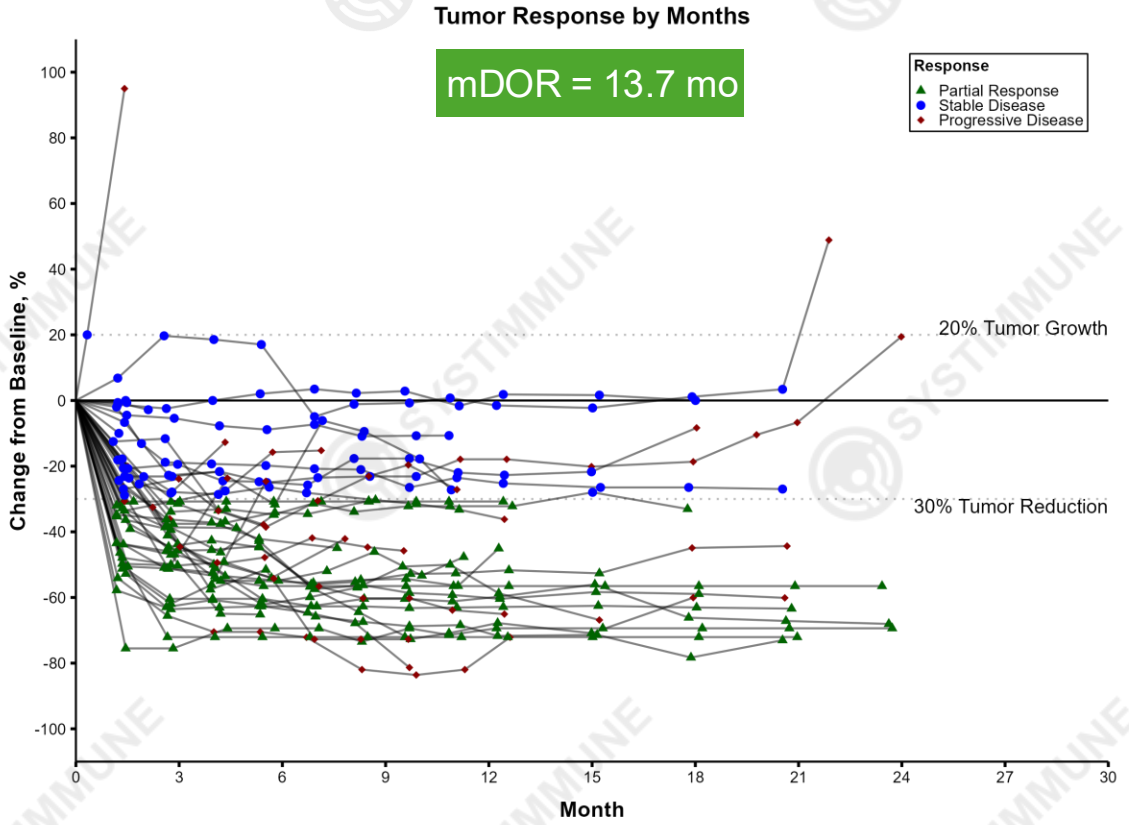
[2] Including patients without post-baseline tumor assessment.

CI: confidence interval; **cORR:** confirmed objective response rate; **PR:** partial response; **SD:** stable disease; **PD:** progressive disease; **NE:** not evaluable: FU: follow-up

Data cutoff: June 30, 2025

Depth & Duration of Response – Post TKI & chemo naïve (N = 50)

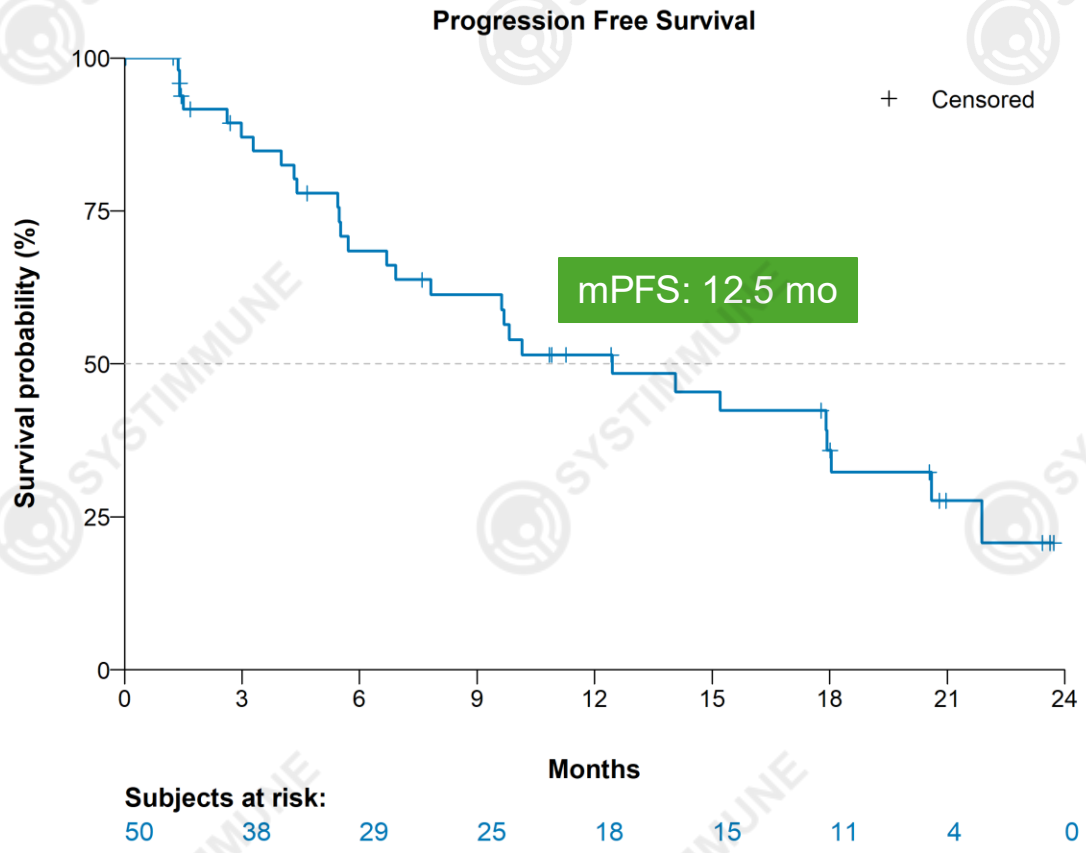


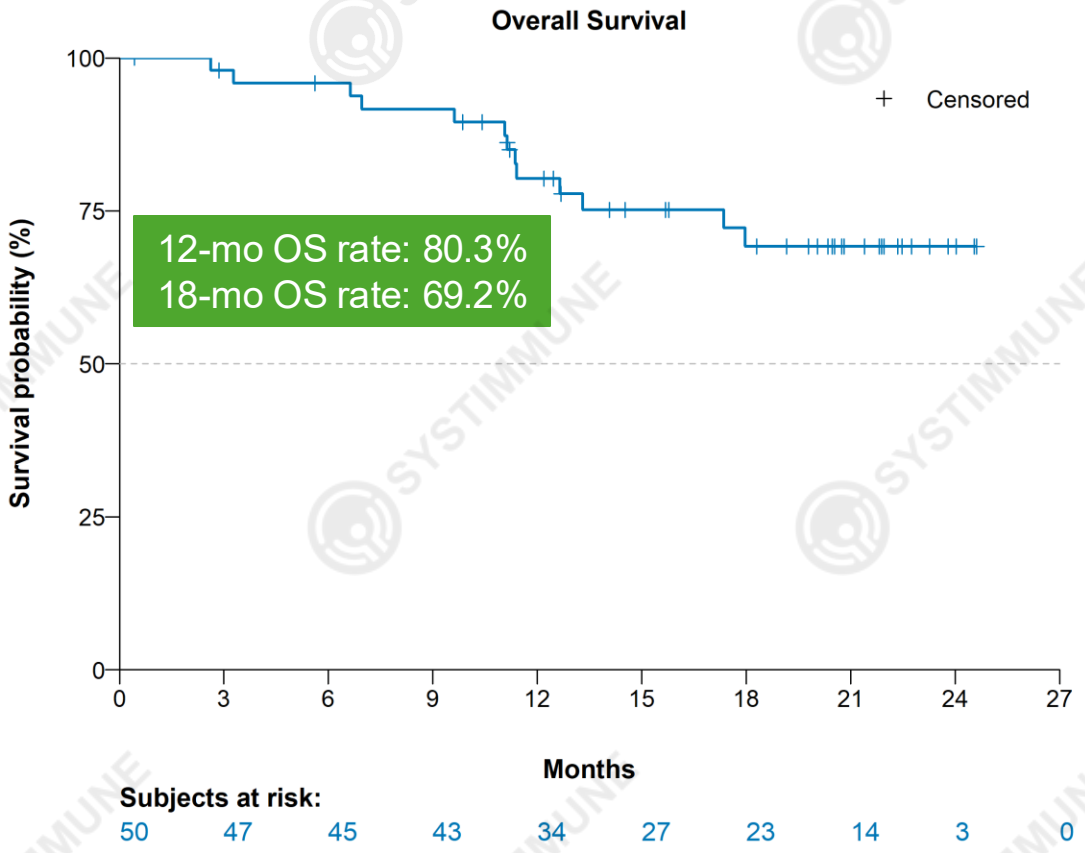


94.0% of patients with tumor shrinkage and the median (range) shrinkage (%) was -38.9 (-81.3, -0.7).

Data cutoff: June 30, 2025

PFS & OS – Post TKI & chemo naïve (N = 50)



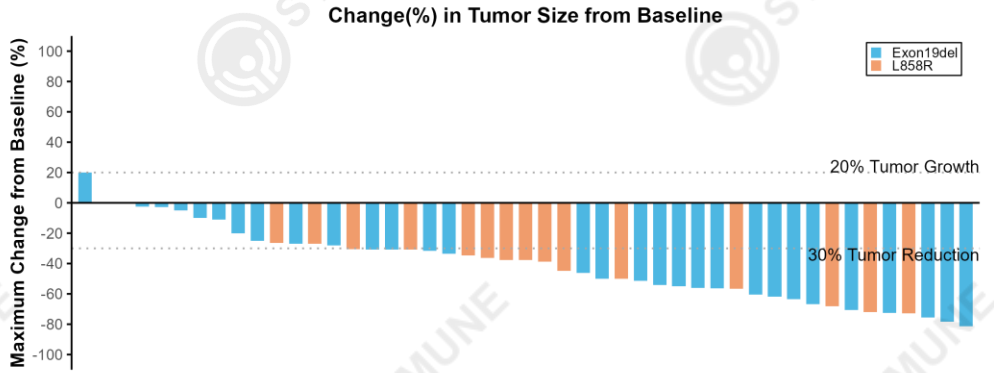


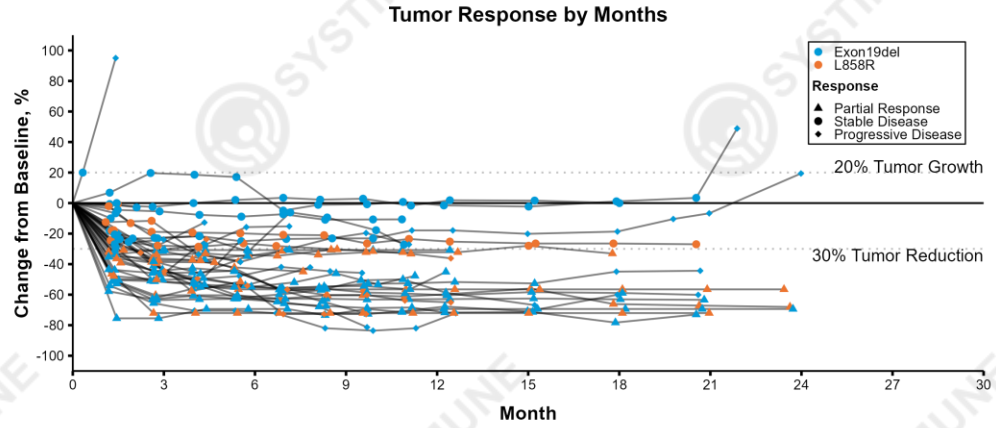
The mPFS in post TKI and chemo naïve patients was 12.5 mo, and the 18-mo OS rate was 69.2%.

Data cutoff: June 30, 2025

Efficacy of Post TKI & Chemo naïve Patients by EGFRmt Subtype

	EGFR Exon 19del (N = 31)	EGFR L858R (N = 17)
Median (range) LoT	2 (1-5)	1 (1-3)
BOR, n (%)		
PR	19 (61.3)	13 (76.5)
Confirmed PR	17 (**54.8**)	10 (**58.8**)
PR pending confirmation[1]	1 (3.2)	0
SD	9 (29.0)	2 (11.8)
PD	3 (9.7)	1 (5.9)
NE[2]	0	1 (5.9)
ORR, % (95%CI)	61.3 (42.2, 78.2)	76.5 (50.1, 93.2)
cORR, % (95%CI)	54.8 (36.0, 72.7)	58.8 (32.9, 81.6)
DCR, % (95%CI)	**90.3** (74.2, 98.0)	**88.2** (63.6, 98.5)
Median DoR, mo (95%CI)	13.7 (4.2, 19.4)	NR (3.1, NR)
Median PFS, mo (95% CI)	**14.1** (5.5, 17.9)	**12.5** (4.4, NR)
Median FU for PFS, mo (95% CI)	20.5 (11.3, NR)	20.5 (4.7, 23.4)
Median OS, mo (95% CI)	NR (17.3, NR)	NR (11.1, NR)
Median FU for OS, mo (95% CI)	20.3 (15.8, 21.9)	20.5 (9.9, 22.3)



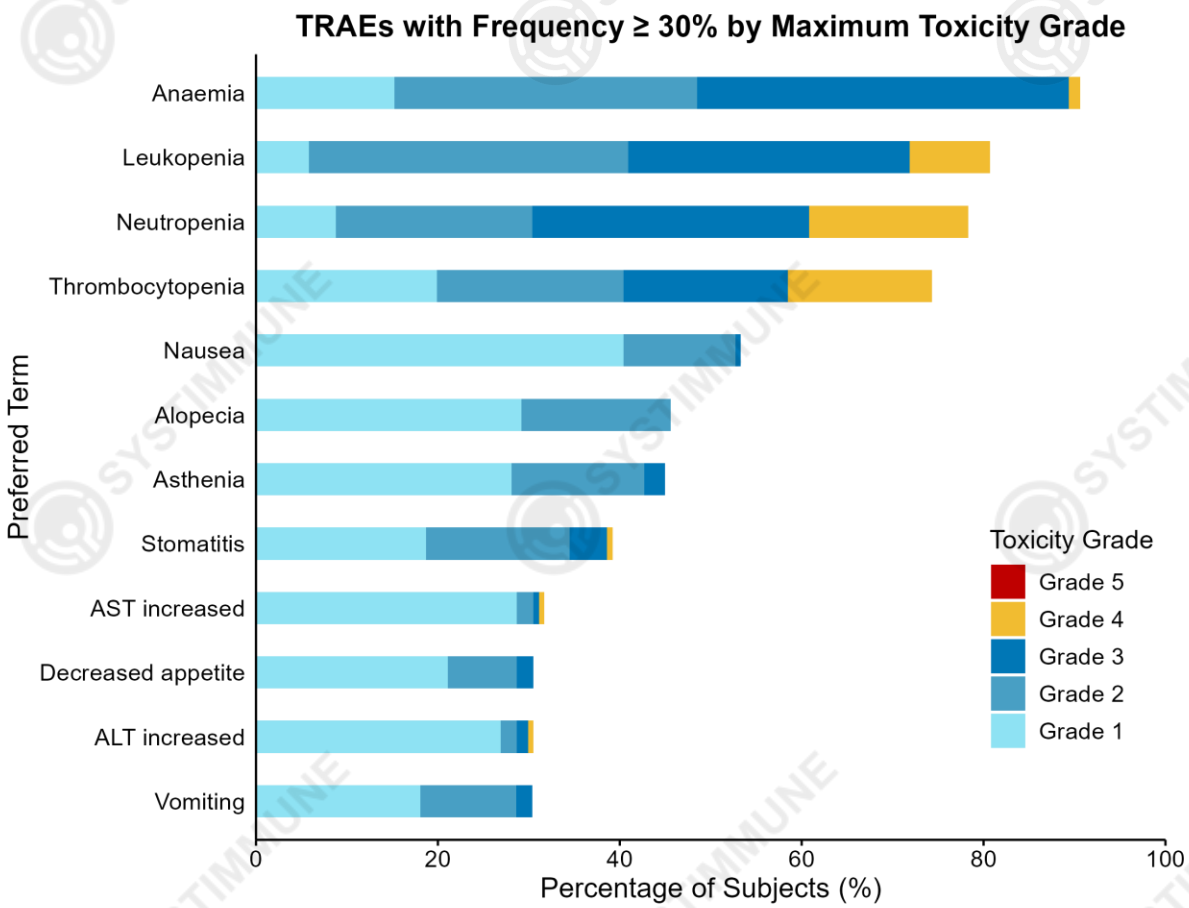


*: Two patients (1 EGFR S768I with confirmed PR and 1 EGFR T790M with SD) were not included.
[1] Patients still on study with tumor assessment of PR and not reach to the next time point of tumor assessment;
[2] Including patients without post-baseline tumor assessment.
CI: confidence interval; **cORR:** confirmed objective response rate; **PR:** partial response; **SD:** stable disease; **PD:** progressive disease; **NE:** not evaluable; **FU:** follow-up.

Data cutoff: June 30, 2025

Comparable efficacy was observed in patients with different EGFRmt subtypes.

TRAEs with Frequency ≥ 30% (N = 171)



- Most common Grade 3 and above AEs were hematologic toxicities*, which were effectively managed with standard supportive care, as demonstrated by the low rate (1.2%) of TRAE leading to drug discontinuation.
- Among patients with Grade 3 or above neutropenia, most patients had one or two episodes. The median time to resolution of Grade 3 or 4 neutropenia was 4-6 days.
- Febrile neutropenia rate was 1.8%.
- Primary G-CSF prophylaxis was not mandatory in this cohort.
- Only one case of Grade 1 interstitial lung disease (ILD) was observed (0.6%). No new safety signals were identified.

* Patients were frequently monitored with weekly CBC.

Data cutoff: June 30, 2025

Conclusions

- In heavily pre-treated EGFRmt NSCLC patients, iza-bren demonstrated promising efficacy with a manageable safety profile.
  - In total of 171 patients, ORR: 57.9%; cORR: 47.4%; mPFS: 6.9 mo; mOS: 24.8 mo.
  - In post-TKI and chemo naïve patients, ORR: 66.0%; cORR: 56.0%; mPFS: 12.5 mo; mOS was not reached.
  - In post-TKI and chemo naïve patients, comparable efficacy was observed in patients with different EGFRmt subtypes, which was consistent with total population.
- Two phase III registrational studies of iza-bren as monotherapy in EGFRmt NSCLC after progression on a 3G EGFR-TKI are ongoing in China (NCT06382116) and globally (IZABRIGHT-Lung01, NCT07100080).

Acknowledgements

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- Thanks to the investigators, study nurses, and other staffs for their contributions to this study.