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Phase 1 Global Study of Iza-bren (BL-B01D1), an EGFR x HER3 Bispecific Antibody-drug Conjugate (ADC), in Patients with Metastatic or Unresectable Non-Small Cell Lung Cancer (NSCLC) and Other Solid Tumors

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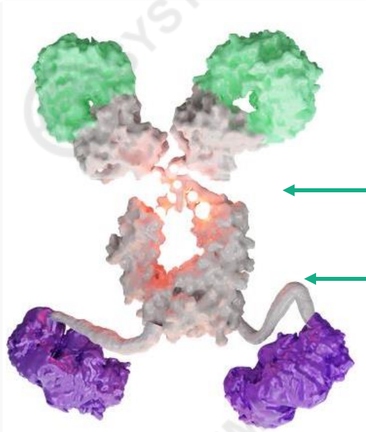
Declaration of interest

Iza-bren, an EGFR×HER3 bispecific ADC



- Iza-bren is a potential first-in-class ADC comprised of an EGFR x HER3 bispecific antibody conjugated to a novel topoisomerase 1 inhibitor payload (Ed-04) via a stable tetrapeptide-based cleavable linker.
- This is the first report of safety and efficacy results of dose escalation/finding phase from this global phase 1 BL-B01D1-LUNG-101 study (NCT05983432).
- Iza-bren was granted breakthrough therapy designation by U.S. FDA for patients with previously treated EGFR-Mutated NSCLC in August 2025 based on the data from China and this study.

Study Design

Key Eligibility Criteria

- Locally advanced or metastatic NSCLC or other solid tumors
- ECOG PS 0-1
- Measurable disease per RECIST v1.1

Escalation*

D1D8Q3W

- 3.0mg/kg
- 2.5mg/kg
- 2.0mg/kg
- 1.5mg/kg

D1Q3W

- 4.5mg/kg
- 4.0mg/kg
- 3.0mg/kg

Finding*

1.5, 2.0, 2.3, 2.5 mg/kg D1D8Q3W

3.0, 4.0, 4.5 mg/kg D1Q3W

Expansion

1.5, 2.0, 2.5 mg/kg D1D8Q3W

Endpoints

- Primary: Safety
- Secondary: PK, ORR, DCR, DOR, TTR, PFS, OS
- Exploratory: ADA, Biomarker

wt: wild type; **Cat B:** cathepsin B; **TOPI:** Topoisomerase I; ECOG PS: Eastern Cooperative Oncology Group performance status; RECIST: Response Evaluation Criteria in Solid Tumors; **PK:** Pharmacokinetics; **ORR:** Overall Response Rate; **DCR:** Disease Control Rate; **DOR:** Duration of Response; **PFS:** Progression Free Survival; **OS:** Overall Survival; **ADA:** Anti-drug Antibodies.
*Dose in the dose-escalation/ finding cohort was compensated per protocol.

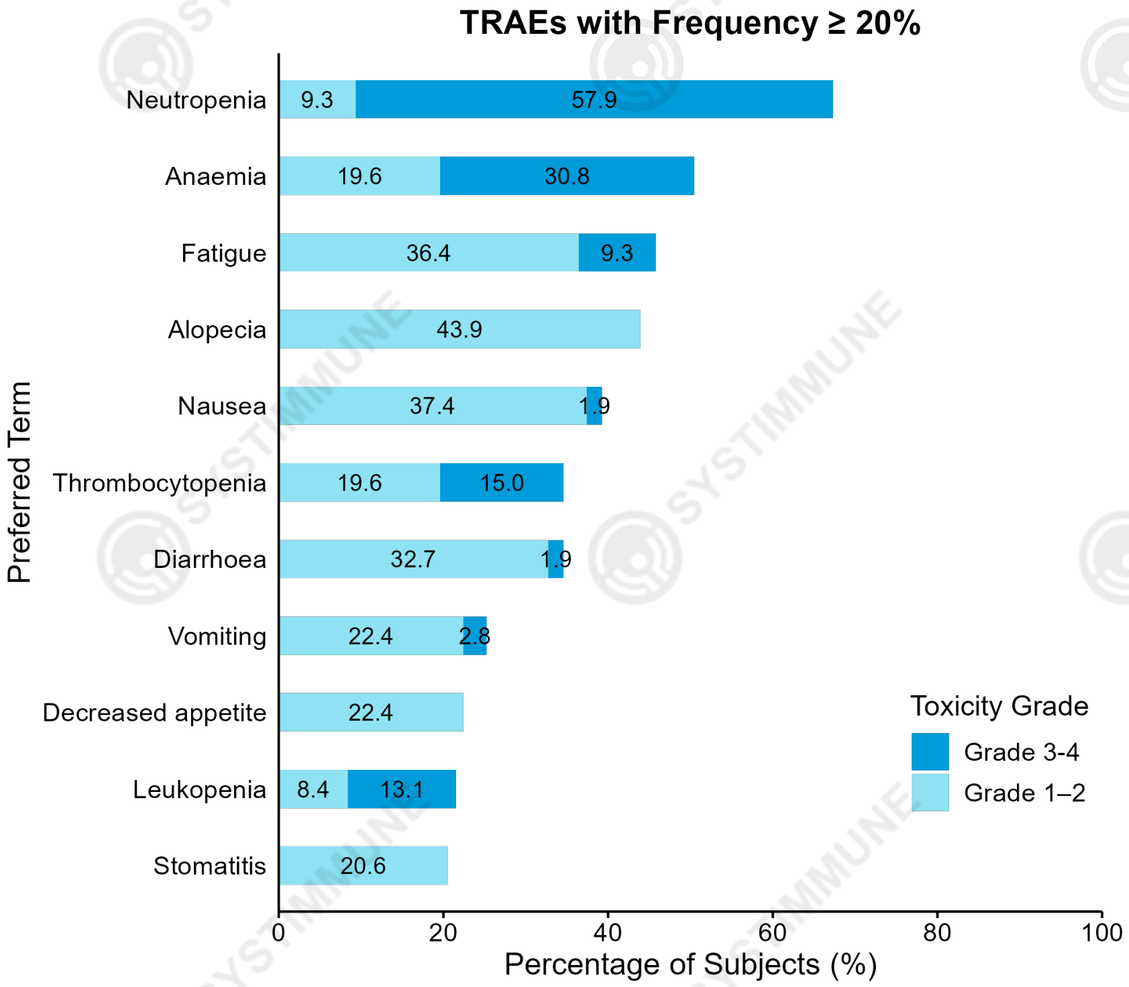
Baseline Characteristics

	Total (N = 107)	D1D8Q3W (mg/kg)				D1Q3W (mg/kg)		
		1.5 (N = 20)	2.0 (N = 21)	2.5 (N = 21)	3.0 (N = 3)	3.0 (N = 20)	4.0 (N = 12)	4.5 (N = 10)
Median (Q1, Q3) age, years	65.0 (57.0, 72.0)	69.5 (66.5, 73.5)	63.0 (57.0, 74.0)	62.0 (52.0, 69.0)	48.0 (31.0, 57.0)	67.0 (60.0, 73.0)	58.5 (56.5, 69.5)	57.5 (48.0, 66.0)
Male, n (%)	41 (38.3)	9 (45.0)	12 (57.1)	9 (42.9)	1 (33.3)	6 (30.0)	1 (8.3)	3 (30.0)
ECOG-PS score, n (%)								
0	30 (28.0)	1 (5.0)	4 (19.0)	7 (33.3)	0	9 (45.0)	5 (41.7)	4 (40.0)
1	77 (72.0)	19 (95.0)	17 (81.0)	14 (66.7)	3 (100)	11 (55.0)	7 (58.3)	6 (60.0)
Prior LoT, n (%)								
1L	23 (21.5)	7 (35.0)	4 (19.0)	6 (28.6)	1 (33.3)	2 (10.0)	1 (8.3)	2 (20.0)
2L	20 (18.7)	2 (10.0)	5 (23.8)	5 (23.8)	1 (33.3)	2 (10.0)	3 (25.0)	2 (20.0)
3L and above	62 (57.9)	11 (55.0)	12 (57.1)	9 (42.9)	1 (33.3)	16 (80.0)	7 (58.3)	6 (60.0)
Not Applicable†	2 (1.9)	0	0	1 (4.8)	0	0	1 (8.3)	0
Prior Topo-1 ADC, n (%)	14 (13.1)	4 (20.0)	3 (14.3)	0	1 (33.3)	4 (20.0)	2 (16.7)	0
Prior PD(L)-1, n%	49 (45.8)	11 (55.0)	11 (52.4)	9 (42.9)	1 (33.3)	8 (40.0)	4 (33.3)	5 (50.0)
Tumor Type, n(%)								
Non-Small Cell Lung Cancer	76 (71.0)	13 (65.0)	15 (71.4)	14 (66.7)	1 (33.3)	13 (65.0)	10 (83.3)	10 (100)
EGFR mutated	45 (59.2)	5 (38.5)	7 (46.7)	10 (71.4)	1 (100)	10 (76.9)	7 (70.0)	5 (50.0)
EGFR wild type	31 (40.8)	8 (61.5)	8 (53.3)	4 (28.6)	0	3 (23.1)	3 (30.0)	5 (50.0)
Small Cell Lung Cancer	7 (6.5)	1 (5.0)	1 (4.8)	2 (9.5)	0	3 (15.0)	0	0
Breast Cancer#	17 (15.9)	5 (25.0)	3 (14.3)	3 (14.3)	1 (33.3)	3 (15.0)	2 (16.7)	0
Esophageal Adenocarcinoma	5 (4.7)	1 (5.0)	1 (4.8)	1 (4.8)	1 (33.3)	1 (5.0)	0	0
NPC/HNSCC*	2 (1.8)	0	1 (4.8)	1 (4.8)	0	0	0	0

Pts at 2.3 mg/kg D1D8 Q3W were not included in our analysis due to insufficient follow-up.
†: Prior line of therapy information not applicable due to adjuvant/neo-adjuvant.
#: A total of 9 out of 17 breast cancer pts are TNBC.
*: One NPC pt from 2.0 mg/kg D1D8Q3W and one HNSCC pt from 2.5 mg/kg D1D8Q3W.

Data cutoff: July 23rd, 2025

Most Frequent TRAEs for All Patients



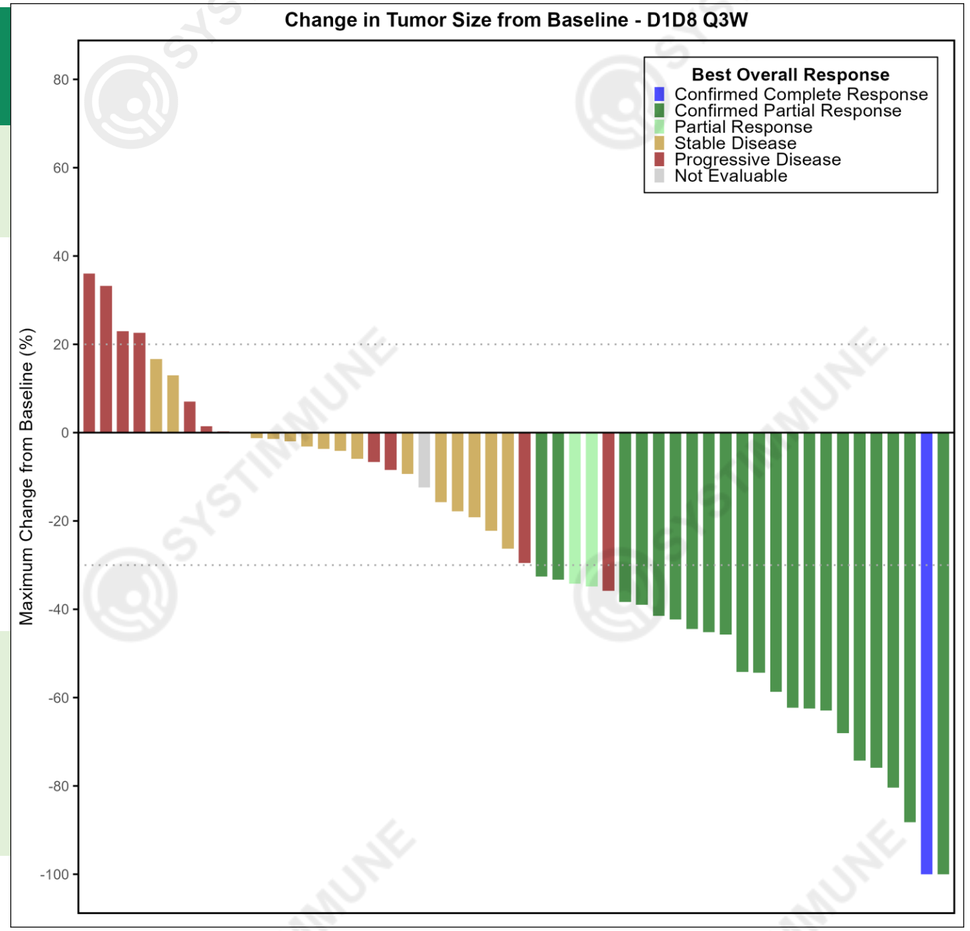
- Hematologic AEs were effectively managed by standard medical measures, as TRAE leading to dose reduction was 27.1% and discontinuation was 1.9%.
- 7.5% of patients had dose reduction and 0 patient had dose discontinuation due to neutropenia. Median time to resolution of Grade 3 or 4 neutropenia was 7 days. Most patients had only one episode.
- Neutropenic fever rate was 5.6%. All grade and grade 3 or higher infection is 7.5% and 1.9%, respectively
- Only 1 (0.9%) patient received primary G-CSF prophylaxis. Primary G-CSF prophylaxis has been implemented in the ongoing dose-expansion phase of the study.
- No interstitial lung disease (ILD) was observed. No new safety signals were observed.
- Only one grade 5 event due to septic shock was reported as possibly related to the drug.

Data cutoff: July 23rd, 2025

TRAE: treatment related adverse event;

Promising Efficacy Seen in Heavily Pretreated Patients

D1D8Q3W	Total* (N = 63)	1.5 mg/kg (N = 20)	2.0 mg/kg (N = 20)	2.5 mg/kg (N = 20)	3.0 mg/kg (N = 3)
Median (range) LoT	3 (1-10)	3 (1-10)	3 (1-6)	**2 (1-9)**	2 (1-3)
BOR, n					
CR	1	0	1	**0**	0
Confirmed CR	1	0	1	**0**	0
PR	23	4	6	**11**	2
Confirmed PR	21	4	4	**11**	2
SD	15	6	5	**4**	0
PD	15	6	5	**3**	1
NE*	9	4	3	**2**	0
ORR, % (95%CI)	38.1 (26.1, 51.2)	20.0 (5.7, 43.7)	35.0 (15.4, 59.2)	**55.0 (31.5, 76.9)**	66.7 (9.4, 99.2)
cORR, % (95%CI)	34.9 (23.3, 48.0)	20.0 (5.7, 43.7)	25.0 (8.7, 49.1)	**55.0 (31.5, 76.9)**	66.7 (9.4, 99.2)
mPFS, mo (95%CI)	4.5 (3.4, 5.6)	3.4 (1.4, 5.4)	6.7 (1.2, 8.1)	**5.4 (3.8, 11.1)**	5.4 (1.4, NR)
Median FU for OS	8.3 (7.2, 9.1)	8.8 (4.3, 11.3)	7.7 (5.4, 9.6)	**8.5 (5.8, 9.3)**	10.2 (NR, NR)



All pts on D1D8 Q3W dosing regimen from ITT population

*: Non-evaluable includes pts who discontinued or died 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 time.

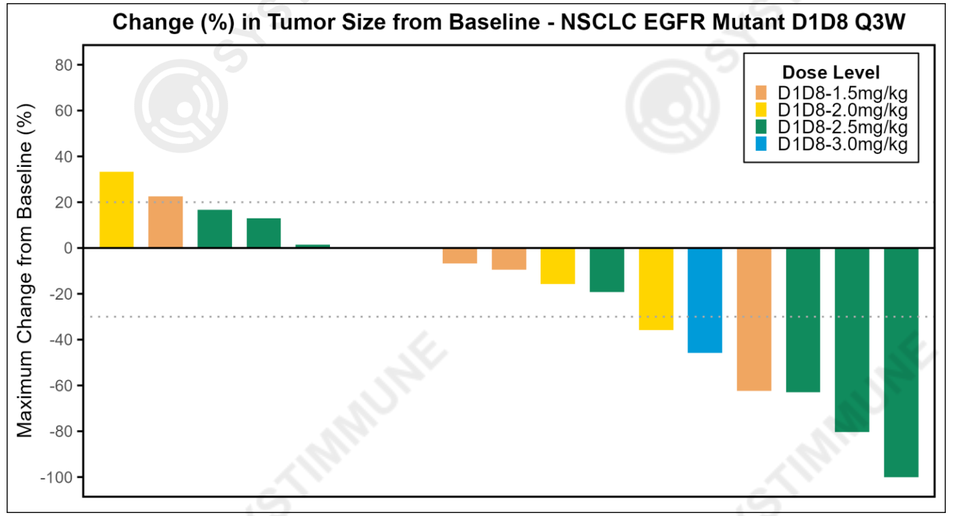
Data cutoff: July 23rd, 2025

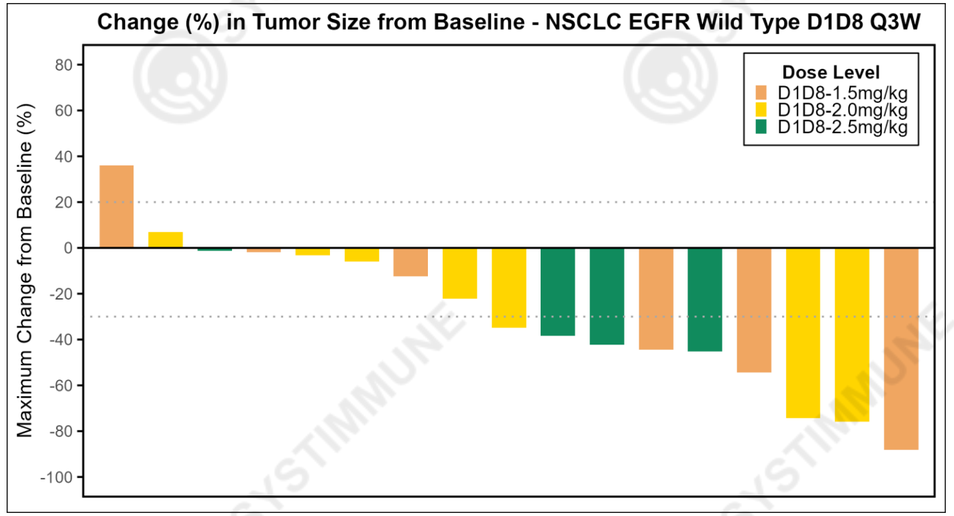
Promising Efficacy in EGFR mutant and wildtype NSCLC

NSCLC EGFRmt D1D8Q3W	Total (N = 22)	1.5 mg/kg (N = 5)	2.0 mg/kg (N = 6)	2.5 mg/kg (N = 10)	3.0 mg/kg (N = 1)
Median (range) LoT	3 (1-9)	2 (1-4)	3 (1-5)	**3 (1-9)**	1 (1-1)
Prior Ami *, n (%)	9 (40.9)	2 (40.0)	3 (50.0)	4 (40.0)	0
Baseline CNS mets, n (%)	5 (22.7)	1 (20.0)	1 (16.7)	3 (30.0)	0
BOR, n (%)					
PR	5	1	0	**3**	1
Confirmed PR	5	1	0	**3**	1
SD	5	1	1	**3**	0
ORR, % (95%CI)	22.7 (7.8, 45.4)	20.0 (0.5, 71.6)	0 (0.0, 45.9)	**30.0 (6.7, 65.2)**	100 (2.5, 100.0)
cORR, % (95%CI)	22.7 (7.8, 45.4)	20.0 (0.5, 71.6)	0 (0.0, 45.9)	**30.0 (6.7, 65.2)**	100 (2.5, 100.0)
mPFS, mo (95%CI)	3.2 (1.2, 8.1)	1.3 (1.2, NR)	1.3 (1.2, NR)	**5.4 (0.5, NR)**	NR (NR, NR)

NSCLC EGFRwt D1D8Q3W	Total (N = 20)	1.5 mg/kg (N = 8)	2.0 mg/kg (N = 8)	2.5 mg/kg (N = 4)
Median (range) LoT	2 (1-9)	3 (1-9)	2 (1-5)	**2 (1-3)**
Squamous, n (%)	6 (30.0)	4 (50.0)	1 (12.5)	**1 (25.0)**
BOR, n (%)				
PR	9	3	3	**3**
Confirmed PR	8	3	2	**3**
SD	5	1	3	**1**
ORR, % (95%CI)	45.0 (23.1, 68.5)	37.5 (8.5, 75.5)	37.5 (8.5, 75.5)	**75.0 (19.4, 99.4)**
cORR, % (95%CI)	40.0 (19.1, 63.9)	37.5 (8.5, 75.5)	25.0 (3.2, 65.1)	**75.0 (19.4, 99.4)**
mPFS, mo (95%CI)	6.9 (2.8, 10.0)	5.4 (1.5, NR)	6.9 (0.4, NR)	**NR (4.5, NR)**

***:** Patients with prior Amivantamab, Amivantamab+PBC, Amivantamab+Lazertinib, or Amivantamab with any other combinations.





Data cutoff: July 23rd, 2025

Conclusion

- Iza-bren has demonstrated encouraging efficacy with a manageable safety profile in heavily pre-treated patients across multiple tumor types, including NSCLC, in this first report of a global population, generally consistent with the strong efficacy previously reported in Chinese patients. Primary G-CSF prophylaxis has been implemented in the dose-expansion phase of the US-Lung-101 study and global registrational studies.
- Global registrational studies of first line metastatic TNBC (NCT06926868), second line metastatic EGFRmt NSCLC post TKI (NCT05983432) and second line metastatic UC post a checkpoint inhibitor (NCT07106762) are ongoing, with studies in other indications planned.

Acknowledgements

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- Systimmune has entered a joint global co-development collaboration of iza-bren with BMS in December 2023.