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Phase II Study of iza-bren (BL-B01D1) Combo with Osimertinib in EGFR Mutated Locally Advanced or Metastatic NSCLC Patients

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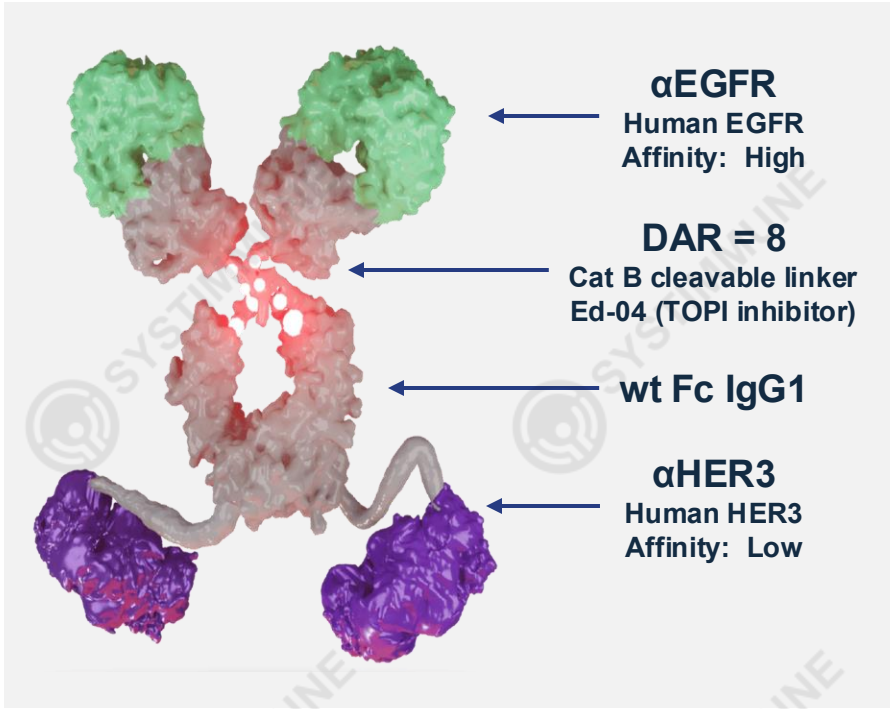
Take-Home Points

- Iza-bren 2.2-2.75 mg/kg D1D8Q3W combined with osimertinib as a first-line treatment showed a tolerable and manageable safety profile in NSCLC with EGFR-sensitizing mutations.
- Iza-bren 2.5 mg/kg D1D8Q3W combined with osimertinib resulted in an ORR of 100%, a cORR of 95.0%, and a 12-mo PFS rate of 92.1% with a median follow up for PFS of 12.5 mo, in first-line treatment of EGFRmt NSCLC.
- Phase III study of iza-bren 2.5 mg/kg D1D8Q3W combined with osimertinib as a first-line treatment for EGFRmt NSCLC is ongoing in China (NCT06838273).

Background

iza-bren (BL-B01D1)



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

- 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.
- This study evaluated iza-bren in combination with osimertinib in first-line locally advanced or metastatic NSCLC patients with EGFR-sensitizing mutations (EGFRmt).
- Safety/efficacy results for this combination therapy are presented.
- Clinical trial information: NCT05880706.

Study Design

Eligibility Criteria

- Locally advanced or metastatic NSCLC
- With EGFR-sensitizing mutations
- ECOG PS 0-1
- Measurable disease per RECIST v1.1
- Treatment-naïve

Treatment (N = 154)

D1D8 Q3W + 80 mg osimertinib QD
- 2.2 mg/kg (N = 41)
- 2.5 mg/kg (N = 40)
- 2.75 mg/kg (N = 42)

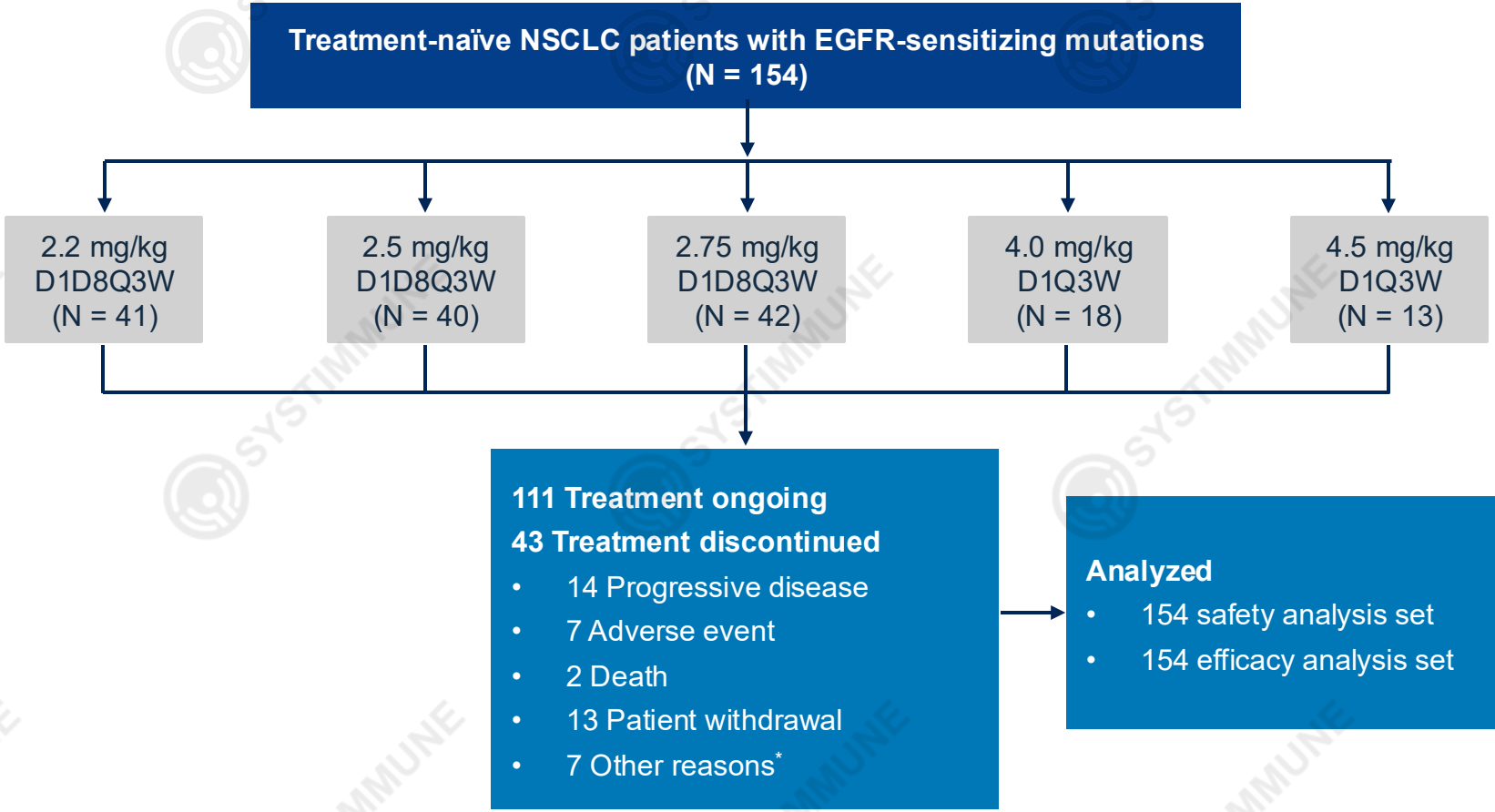
D1 Q3W + 80 mg osimertinib QD
- 4.0 mg/kg (N = 18)
- 4.5 mg/kg (N = 13)

Endpoints

- Primary: RP2D, ORR
- Secondary: PFS, DCR, DOR, Safety
- Exploratory: PK, Nab, DDI, OS, Biomarker

ECOG PS: Eastern Cooperative Oncology Group performance status; **RECIST:** Response Evaluation Criteria in Solid Tumors; **RP2D:** Recommended Phase 2 Dose; **ORR**: Overall Response Rate; **PFS:** Progression Free Survival; **DCR:** Disease Control Rate; **DOR:** Duration of Response; **PK:** pharmacokinetics; **Nab:** Neutralizing antibody; **DDI:** Drug-drug Interaction; **OS:** Overall Survival.

Patient Disposition



*: Including 3 discontinued per investigator decision; 1 lost to follow-up; 1 due to intolerance; 1 non-compliant; 1 received radiotherapy.

Data cutoff: June 30, 2025

Baseline Characteristics

	Total (N = 154)	D1D8Q3W			D1Q3W	
		2.2 mg/kg (N = 41)	2.5 mg/kg (N = 40)	2.75 mg/kg (N = 42)	4.0 mg/kg (N = 18)	4.5 mg/kg (N = 13)
Median (range) age, years	60.0 (33.0, 76.0)	59.0 (33.0, 76.0)	59.0 (39.0, 74.0)	60.0 (38.0, 76.0)	61.5 (35.0, 76.0)	59.0 (46.0, 72.0)
Male, n (%)	67 (43.5)	19 (46.3)	13 (32.5)	23 (54.8)	10 (55.6)	2 (15.4)
Smoking status, n (%)						
Never	93 (60.4)	25 (61.0)	24 (60.0)	25 (59.5)	10 (55.6)	9 (69.2)
Former	39 (25.3)	14 (34.1)	8 (20.0)	9 (21.4)	7 (38.9)	1 (7.7)
Current	6 (3.9)	1 (2.4)	0	4 (9.5)	1 (5.6)	0
Missing	16 (10.4)	1 (2.4)	8 (20.0)	4 (9.5)	0	3 (23.1)
Median (range) BMI, kg/m²	23.0 (16.0, 34.5)	23.8 (17.1, 34.5)	22.4 (16.4, 31.9)	23.3 (16.0, 31.6)	23.1 (17.1, 30.5)	22.7 (18.2, 28.7)
Median (range) baseline SOD, mm	54.0 (15.5, 242.9)	59.0 (17.2, 195.0)	48.7 (23.8, 242.9)	52.0 (18.0, 151.0)	60.3 (15.5, 172.0)	64.5 (25.2, 123.0)
ECOG-PS Score, n (%)						
0	30 (19.5)	8 (19.5)	8 (20.0)	12 (28.6)	1 (5.6)	1 (7.7)
1	124 (80.5)	33 (80.5)	32 (80.0)	30 (71.4)	17 (94.4)	12 (92.3)
Median (range) # of metastatic organs	3 (0, 7)	2 (0, 6)	3 (0, 6)	3 (1, 7)	3 (1, 7)	3 (1, 5)
Baseline brain metastasis, n (%)	42 (27.3)	15 (36.6)	8 (20.0)	12 (28.6)	3 (16.7)	4 (30.8)
EGFR exon19del mutation, n (%)	89 (57.8)	23 (56.1)	26 (65.0)	23 (54.8)	9 (50.0)	8 (61.5)
EGFR L858R mutation, n (%)	65 (42.2)	18 (43.9)	14 (35.0)	19 (45.2)	9 (50.0)	5 (38.5)

SOD: sum of diameters.

Data cutoff: June 30, 2025

Preliminary Efficacy

	Total (N = 154)	D1D8Q3W			D1Q3W	
		2.2 mg/kg (N = 41)	2.5 mg/kg (N = 40)	2.75 mg/kg (N = 42)	4.0 mg/kg (N = 18)	4.5 mg/kg (N = 13)
BOR, n (%)						
PR	130 (84.4)	32 (78.0)	40 (100)	33 (78.6)	14 (77.8)	11 (84.6)
Confirmed PR	124 (80.5)	30 (73.2)	38 (95.0)	32 (76.2)	14 (77.8)	10 (76.9)
PR pending confirmation[1]	5 (3.2)	2 (4.9)	2 (5.0)	0	0	1 (7.7)
SD	19 (12.3)	7 (17.1)	0	7 (16.7)	3 (16.7)	2 (15.4)
PD	0	0	0	0	0	0
NE[2]	5 (3.2)	2 (4.9)	0	2 (4.8)	1 (5.6)	0
ORR, % (95%CI)	84.4 (77.7, 89.8)	78.0 (62.4, 89.4)	100 (91.2, 100.0)	78.6 (63.2, 89.7)	77.8 (52.4, 93.6)	84.6 (54.6, 98.1)
cORR, % (95%CI)	80.5 (73.4, 86.5)	73.2 (57.1, 85.8)	95.0 (83.1, 99.4)	76.2 (60.5, 87.9)	77.8 (52.4, 93.6)	76.9 (46.2, 95.0)
Median FU for PFS, mo (95% CI)	12.7 (12.5, 15.0)	15.2 (15.0, 15.2)	12.5 (12.4, 12.5)	15.1 (12.6, 17.9)	15.1 (11.0, 17.9)	13.1 (12.4, 15.2)
12-mo PFS rate, % (95% CI)	86.5 (79.7, 91.2)	86.2 (70.0, 94.0)	92.1 (77.5, 97.4)	81.8 (65.5, 90.9)	80.7 (51.1, 93.4)	92.3 (56.6, 98.9)
Median FU for OS, mo (95% CI)	15.0 (14.2, 15.5)	15.8 (15.4, 17.4)	12.8 (12.5, 13.1)	16.7 (15.3, 18.0)	17.2 (13.2, 17.9)	14.7 (13.1, 15.2)
12-mo OS rate, % (95% CI)	95.9 (91.2, 98.2)	94.9 (81.0, 98.7)	94.8 (80.7, 98.7)	97.6 (84.3, 99.7)	100.0 (100.0, 100.0)	92.3 (56.6, 98.9)

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

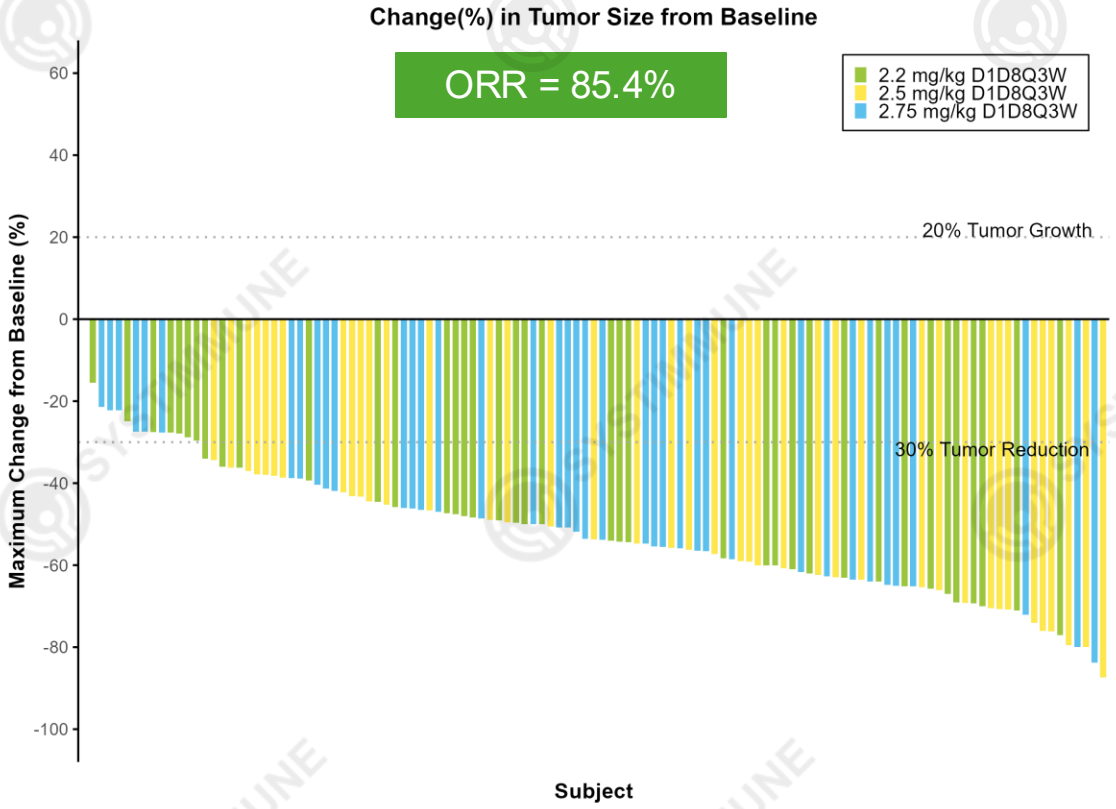
[1] Patients still on study with tumor assessment of PR and not reach to the next time point of tumor assessment.

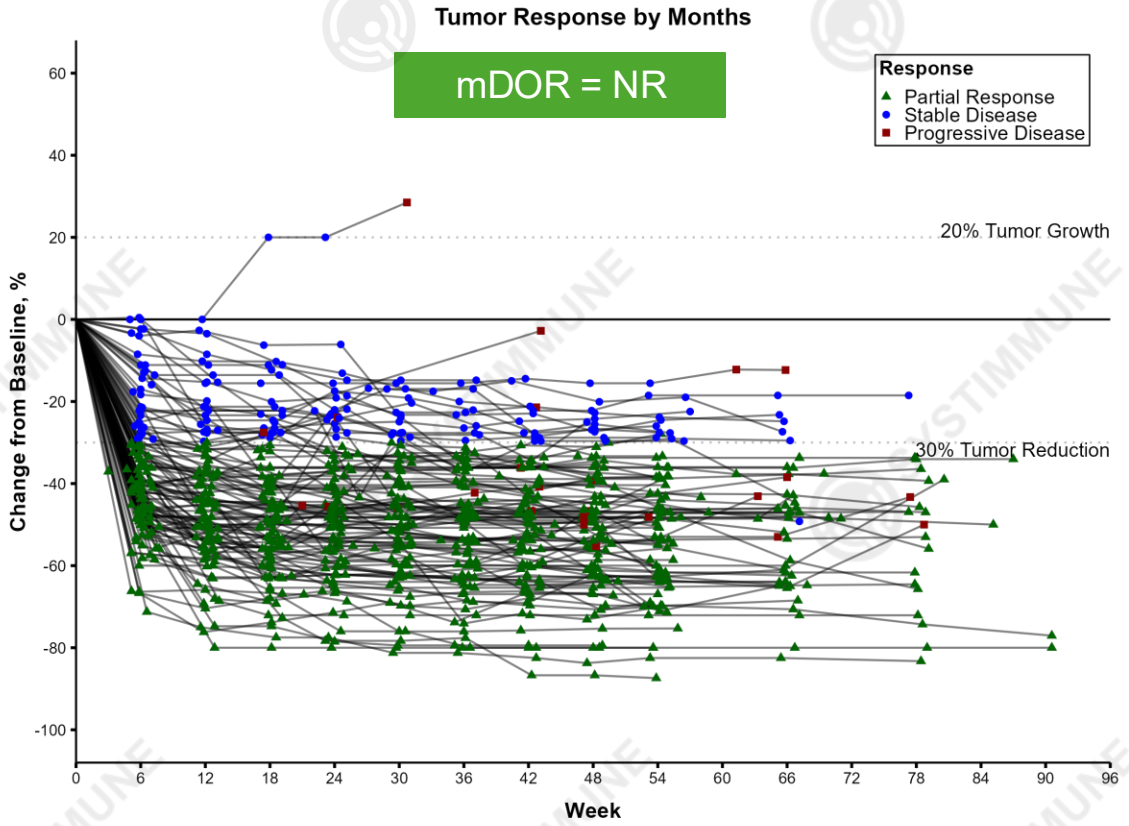
[2] Including patients without post-baseline tumor assessment.

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

Data cutoff: June 30, 2025

Depth & Duration of Response – D1D8Q3W (N = 123)

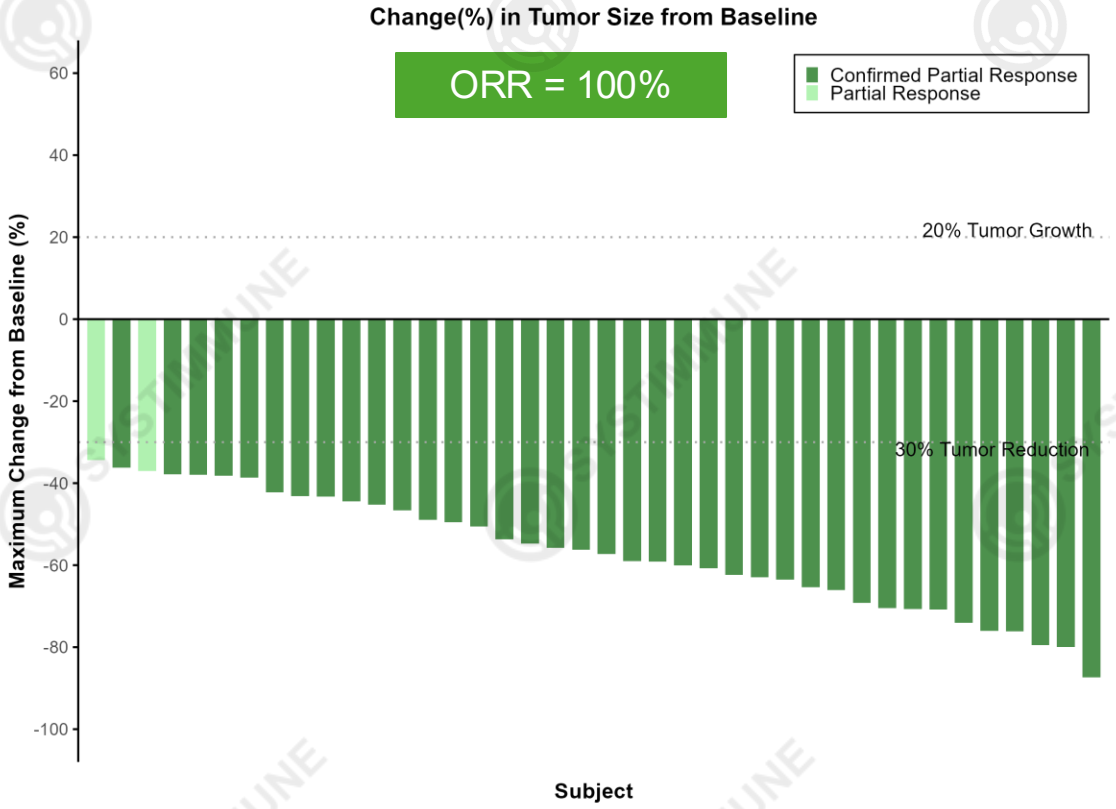


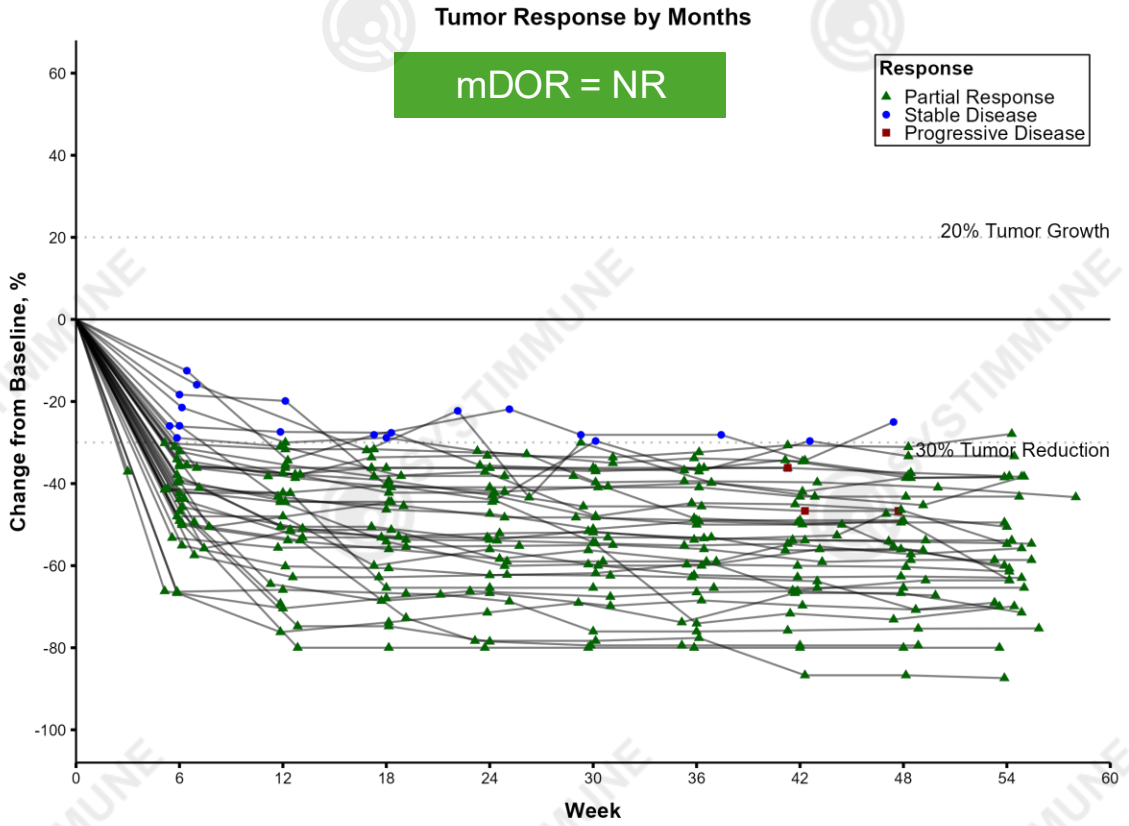


95.9% of patients with tumor shrinkage and the median (range) shrinkage (%) was -53.8 (-87.4, -15.6).

Data cutoff: June 30, 2025

Depth & Duration of Response – 2.5 mg/kg D1D8Q3W

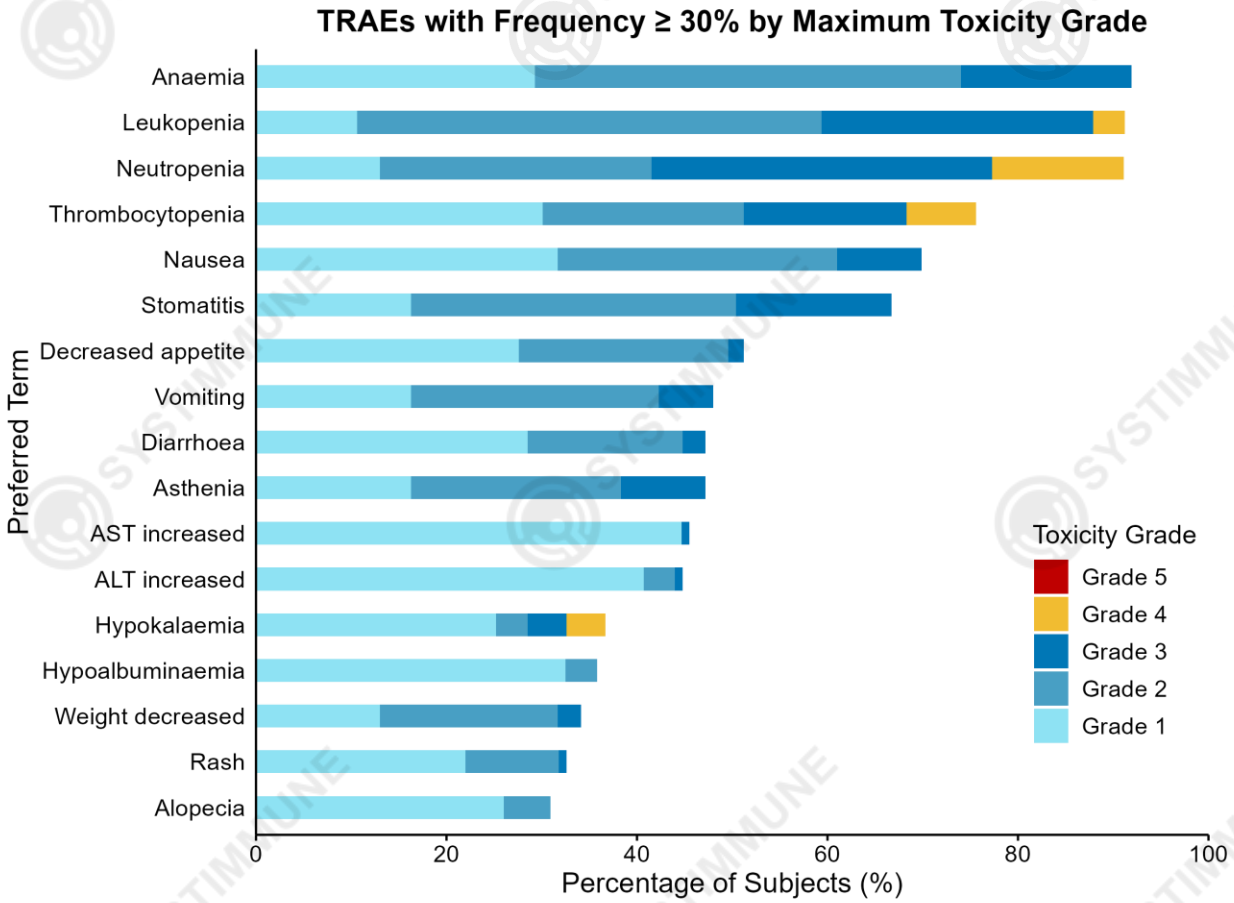




100% of patients with tumor shrinkage and the median (range) shrinkage (%) was -56.7 (-87.4, -34.4).

Data cutoff: June 30, 2025

TRAEs in ≥ 30% of patients in D1D8Q3W



- Most common AEs were hematologic toxicities*, which were effectively managed with standard supportive care.
- Most common Grade 3 and above AE was neutropenia:
  - Neutropenia leading to dose reduction was 11.4%, and leading to discontinuation was 0.8%.
  - The median time to resolution of Grade 3 or 4 neutropenia was 6-7 days. Most only had one or two episodes.
  - Febrile neutropenia was not observed.
  - 2.4% patients received primary G-CSF prophylaxis.
- Two cases of ILD were reported (1.6%; one Grade 2, one Grade 3). No new safety signals were identified.

* Patients were frequently monitored with weekly CBC.

Data cutoff: June 30, 2025

Conclusions

- Iza-bren at 2.2-2.75 mg/kg D1D8Q3W combined with osimertinib as a first-line treatment showed a tolerable and manageable safety profile in patients with EGFRmt NSCLC.
  - Common TRAEs were hematologic toxicities.
  - Low incidence of TRAEs leading to treatment discontinuation.
- Preliminary antitumor activity of iza-bren combined with osimertinib was encouraging.
  - In the cohort of iza-bren **2.5 mg/kg D1D8Q3W**, ORR: **100%**, cORR: **95.0%**; 12-mo PFS rate: **92.1%**; median follow up for PFS: 12.5 mo; 12-mo OS rate: 94.8%.
- Phase III study of iza-bren 2.5 mg/kg D1D8Q3W combined with osimertinib as a first-line treatment for EGFRmt NSCLC is ongoing in China (NCT06838273).

Acknowledgements

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