2025 ASCO ANNUAL MEETING

Phase I study of iza-bren (BL-B01D1), an EGFR x HER3 Bispecific Antibody-drug Conjugate (ADC), in Patients with Locally Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC) with Driver Genomic Alterations (GA) outside of Classic EGFR Mutations (Abstract No: 3001)

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Key Takeaway Points

- The most common adverse events associated with iza-bren are hematologic toxicities which can be well managed. No other new safety signals have been observed.

- iza-bren has encouraging activity in pretreated NSCLC patients with driver genomic alterations outside of classic EGFR mutations, with ORR of 46.2% and median PFS of 7.0 months.

- Promising activity in patients with exon20ins/non-classical EGFR mutations is observed, with ORR of 69.2% (9/13) and median PFS of 10.5 months, which warrants further validation through a larger cohort.

Background

Poor Prognosis Trajectory

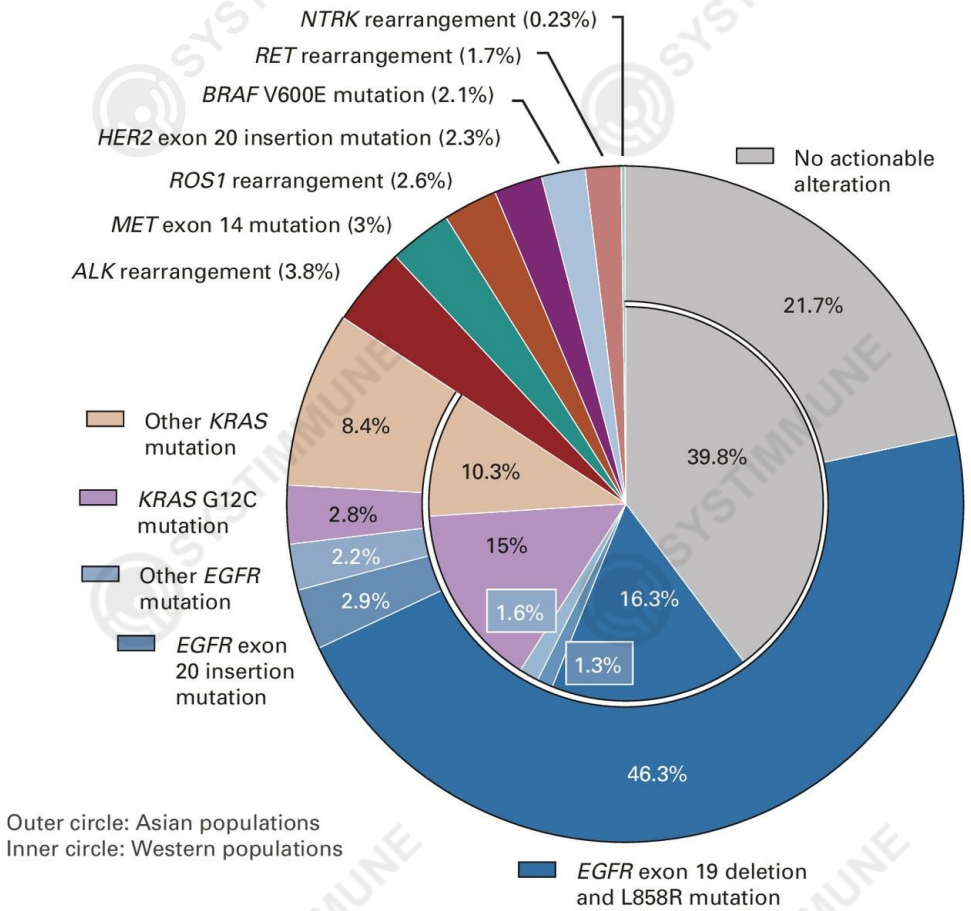
- Lung cancer is the leading cause of cancer-related deaths worldwide.
- Patients with advanced or metastatic NSCLC face declining outcomes with each subsequent line of therapy[1,2].

Unmet Needs

- For patients with actionable genomic alterations, resistance to targeted therapies is inevitable in most cases[3,4].
- For some driver genomic alterations, no targeted therapy is currently available.

Rise of ADCs

- Dato-DXd and SKB264 have encouraging activity in pretreated NSCLC patients with classic EGFR mutations[5,6].
- Treatment options for those with driver genomic alterations beyond classic EGFR mutations are still lacking.

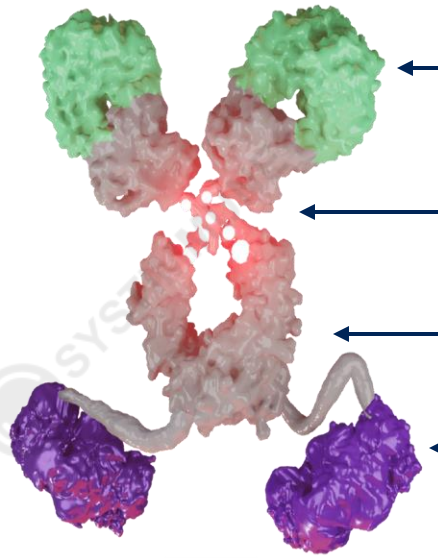


1. Reck M, et al. *J Clin Oncol.* 2021;39:2339-2349. **2.** Paz-Ares L, et al. *J Thorac Oncol.* 2020;15(10):1657-1669. **3.** Shimizu T, et al. *J Cin Oncol.* 2023:41(29):4678-4687. **4.** Mok TSK, et al. *Lancet.* 2019;393(10183):1819-1830. **5.** Sands J, et al. *J Clin Oncol.* 2025;43(10):1254-1265. **6.** Zhao S, et al. *Nat Med.* 2025. **7.** Tan AC, et al. *J Clin Oncol.* 2022;40(6):611-625.

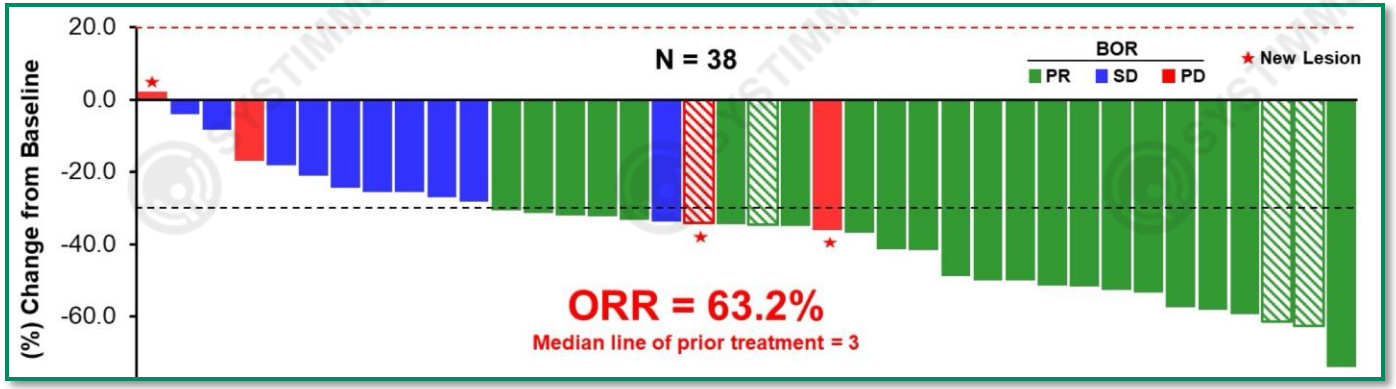
Background

iza-bren (BL-B01D1)

EGFR x HER3 bispecific ADC



- iza-bren (izalontamab brengitecan) 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.
- In the previous phase I trial, iza-bren showed promising anti-tumor activity in **EGFRmut NSCLC patients (63.2% ORR)†.**



The safety and preliminary efficacy of iza-bren in NSCLC patients with **driver genomic alterations outside of classic EGFR mutations** was evaluated in this phase Ib study.

Clinical trial information: NCT05194982

†: Ma Y, et al. Lancet Oncol. 2024;25(7):901-911.

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

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Study Design

Eligibility Criteria

- Locally advanced or metastatic NSCLC
- Presence of driver genomic alterations outside of classic EGFR mutations (19del and L858R)
- ECOG PS 0-1
- Measurable disease per RECIST v1.1
- Failed standard treatment
- Received no more than one prior line of chemotherapy

Treatment

iza-bren
2.5 mg/kg
D1D8 Q3W

Endpoints

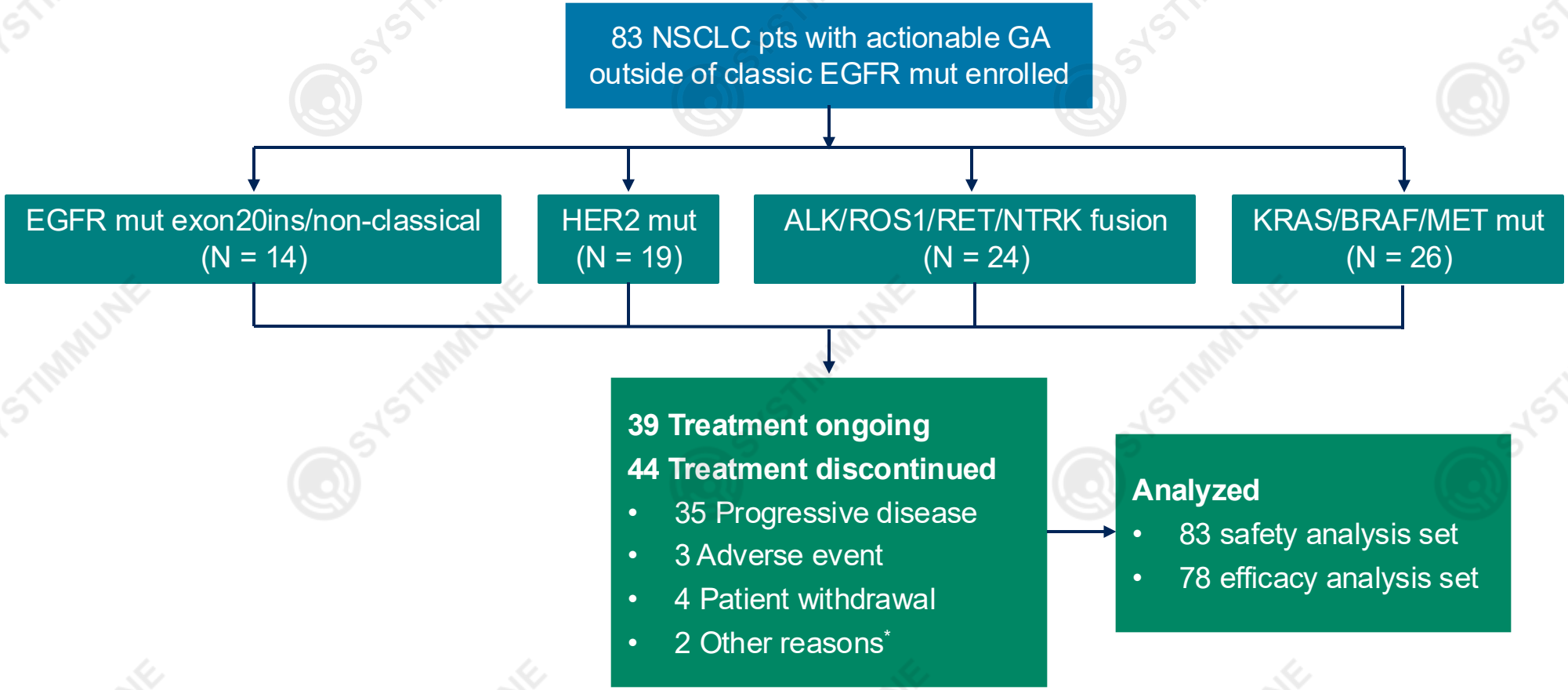
Primary
- Safety

Secondary
- ORR, DCR and DoR

Exploratory
- PFS and OS

ECOG PS: Eastern Cooperative Oncology Group performance status; **RECIST:** Response Evaluation Criteria in Solid Tumors; **ORR:** Overall Response Rate; **DCR:** Disease Control Rate; **DOR:** Duration of Response; **PFS:** Progression Free Survival; **OS:** Overall Survival

Patient Disposition



Data cutoff: Mar 28, 2025

Three patients with non-actionable alteration (SMARCA4-deficient) were not included in the analysis.
*: treatment delay>28 days.

Baseline Characteristics

	Total (N = 83)	EGFR mut exon20ins/non-classical* (N = 14)	HER2 mut (N = 19)	KRAS/BRAF/MET mut† (N = 26)	ALK/ROS1/RET/NTRK fusion (N = 24)
Median (range) age, years	57.0 (28.0, 78.0)	57.0 (28.0, 68.0)	57.0 (44.0, 78.0)	60.5 (36.0, 74.0)	56.0 (31.0, 69.0)
Male, n (%)	49 (59.0)	8 (57.1)	12 (63.2)	19 (73.1)	10 (41.7)
ECOG-PS score, n (%)					
0	6 (7.2)	0	0	2 (7.7)	4 (16.7)
1	77 (92.8)	14 (100)	19 (100)	24 (92.3)	20 (83.3)
Median (range) number of metastasis organs	3 (0, 7)	3 (1, 6)	3 (1, 6)	2 (0, 7)	3 (1, 6)
Baseline brain metastasis, n (%)	7 (8.4)	2 (14.3)	3 (15.8)	1 (3.8)	1 (4.2)
Median (range) LoT	1 (1, 5)	1 (1, 2)	1 (1, 3)	1 (1, 2)	2 (1, 5)
Prior LoT, n (%)					
1L	56 (67.5)	10 (71.4)	15 (78.9)	22 (84.6)	9 (37.5)
2L	15 (18.1)	4 (28.6)	3 (15.8)	4 (15.4)	4 (16.7)
3L and above	12 (14.5)	0	1 (5.3)	0	11 (45.8)
Prior platinum-based chemotherapy, n (%)	62 (74.7)	9 (64.3)	19 (100)	21 (80.8)	13 (54.2)
Prior anti-PD(L)-1, n (%)	42 (50.6)	7 (50.0)	12 (63.2)	19 (73.1)	4 (16.7)
Prior target therapy, n (%)	43 (51.8)	7 (50.0)	6 (31.6)	7 (26.9)	23 (95.8)

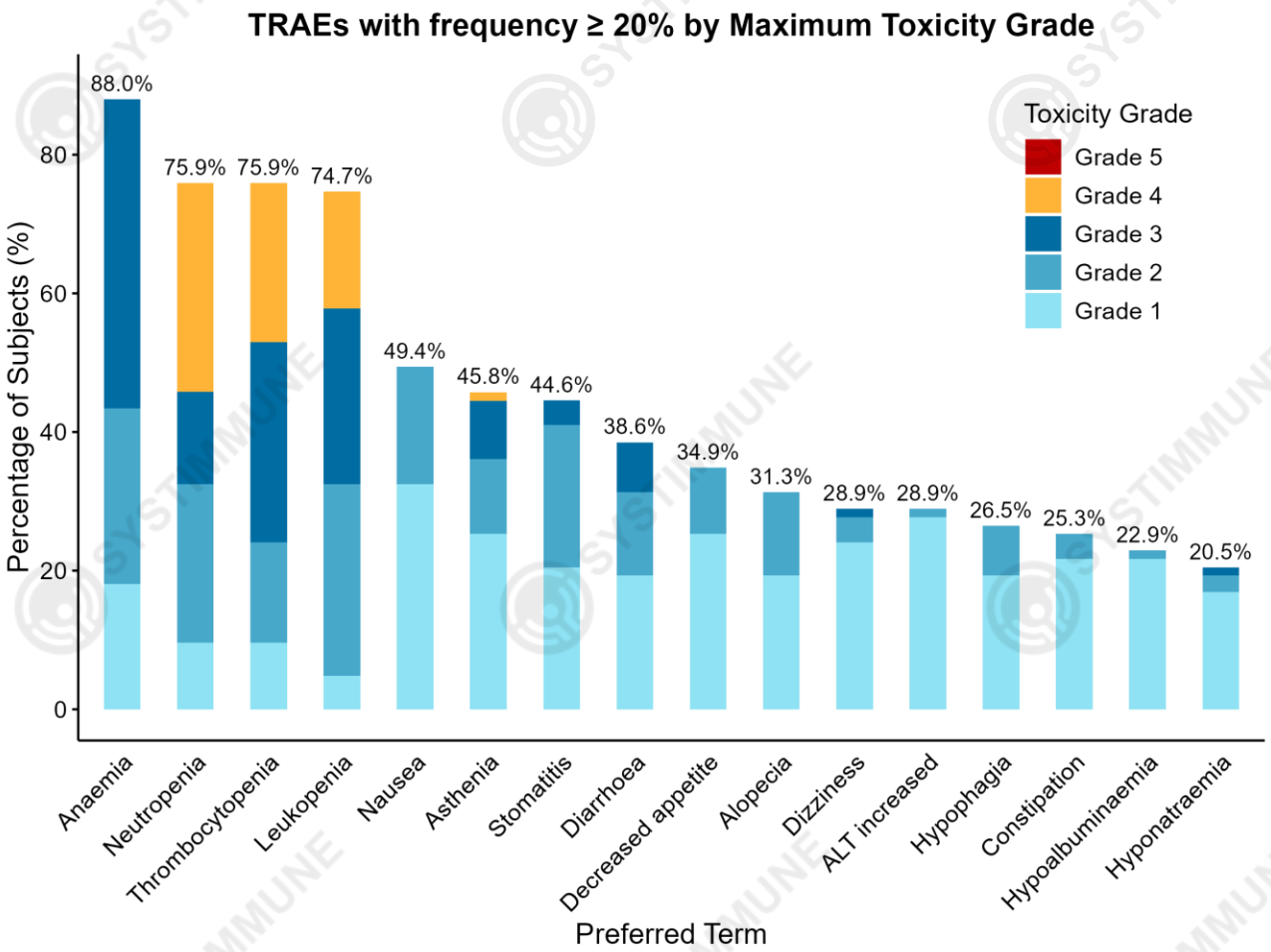
*: Seven subjects with EGFR exon20ins and seven subjects with other EGFR non-classical alterations.
†: KRAS (G12C and others), BRAF (V600E and others), MET (Exon 14)
LoT: Lines of therapy

Overall Safety Summary

	2.5mg/kg D1D8Q3W (N = 83)
TRAEs, n (%)	83 (100)
Treatment-related SAEs, n (%)	30 (36.1)
≥Grade 3 TRAEs, n (%)	66 (79.5)
TRAEs leading to death, n (%)	1 (1.2)
TRAEs leading to discontinuation of study drug, n (%)	2 (2.4)
TRAEs leading to dose reduction, n (%)	46 (55.4)
TRAEs leading to drug delay, n (%)	44 (53.0)

TRAE: treatment related adverse event

TRAEs with Frequency ≥ 20%



Grade 3 and above TRAEs were predominantly hematologic toxicities, which were able to be effectively managed with standard supportive cares including dose reductions.

One death (febrile neutropenia) associated with iza-bren was reported.

One case of G2 ILD was observed.

No new safety signals were identified.

Preliminary Efficacy

	Total (N = 78)	EGFR mut exon20ins/non-classical (N = 13)	HER2 mut (N = 17)	KRAS/BRAF/MET mut (N = 25)	ALK/ROS1/RET fusion (N = 23)
Median (range) LoT	1 (1-5)	1 (1-2)	1 (1-3)	1 (1-2)	2 (1-5)
BOR, n (%)					
PR	36 (46.2)	9 (69.2)	9 (52.9)	10 (40.0)	8 (34.8)
Confirmed PR	31 (39.7)	9 (69.2)	9 (52.9)	7 (28.0)	6 (26.1)
PR pending confirmation[1]	3 (3.8)	0	0	1 (4.0)	2 (8.7)
SD	31 (39.7)	3 (23.1)	8 (47.1)	9 (36.0)	11 (47.8)
PD	8 (10.3)	0	0	5 (20.0)	3 (13.0)
NE[2]	3 (3.8)	1 (7.7)	0	1 (4.0)	1 (4.3)
ORR, % (95%CI)	46.2 (34.8, 57.8)	69.2 (38.6, 90.9)	52.9 (27.8, 77.0)	40.0 (21.1, 61.3)	34.8 (16.4, 57.3)
cORR, % (95%CI)	39.7 (28.8, 51.5)	69.2 (38.6, 90.9)	52.9 (27.8, 77.0)	28.0 (12.1, 49.4)	26.1 (10.2, 48.4)
DCR, % (95%CI)	85.9 (76.2, 92.7)	92.3 (64.0, 99.8)	100 (80.5, 100.0)	76.0 (54.9, 90.6)	82.6 (61.2, 95.0)
Median DoR, mo (95%CI)	NR (5.7, NR)	NR (5.6, NR)	5.7 (4.0, NR)	NR (NR, NR)	4.5 (2.7, NR)
Median PFS, mo (95% CI)	7.0 (5.4, 10.5)	10.5 (6.9, NR)	7.5 (5.4, NR)	7.0 (3.0, NR)	3.8 (2.7, 4.8)
Median OS, mo (95% CI)	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)

Five pts (1 EGFR non-classical, 2 HER2 mut, 1 KRAS other, 1 NTRK fusion) were still on treatment, but were excluded from the analysis due to insufficient follow-up for the first post-baseline scan. The median follow-up time for total subjects is 8.1 months.

[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

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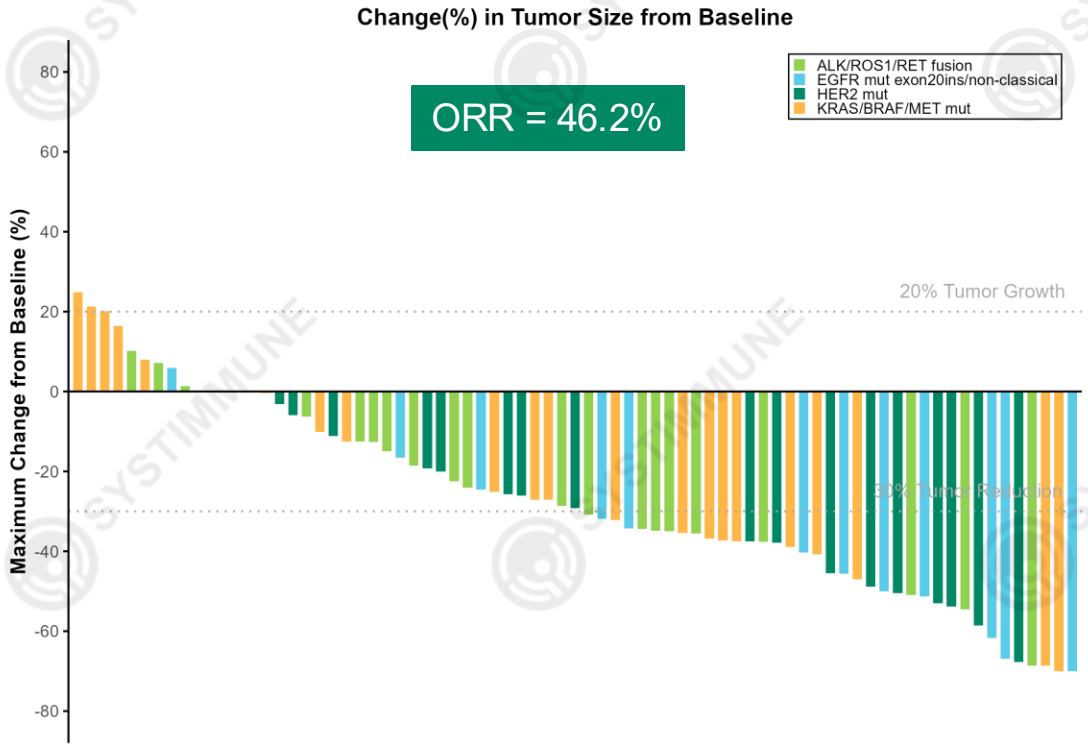
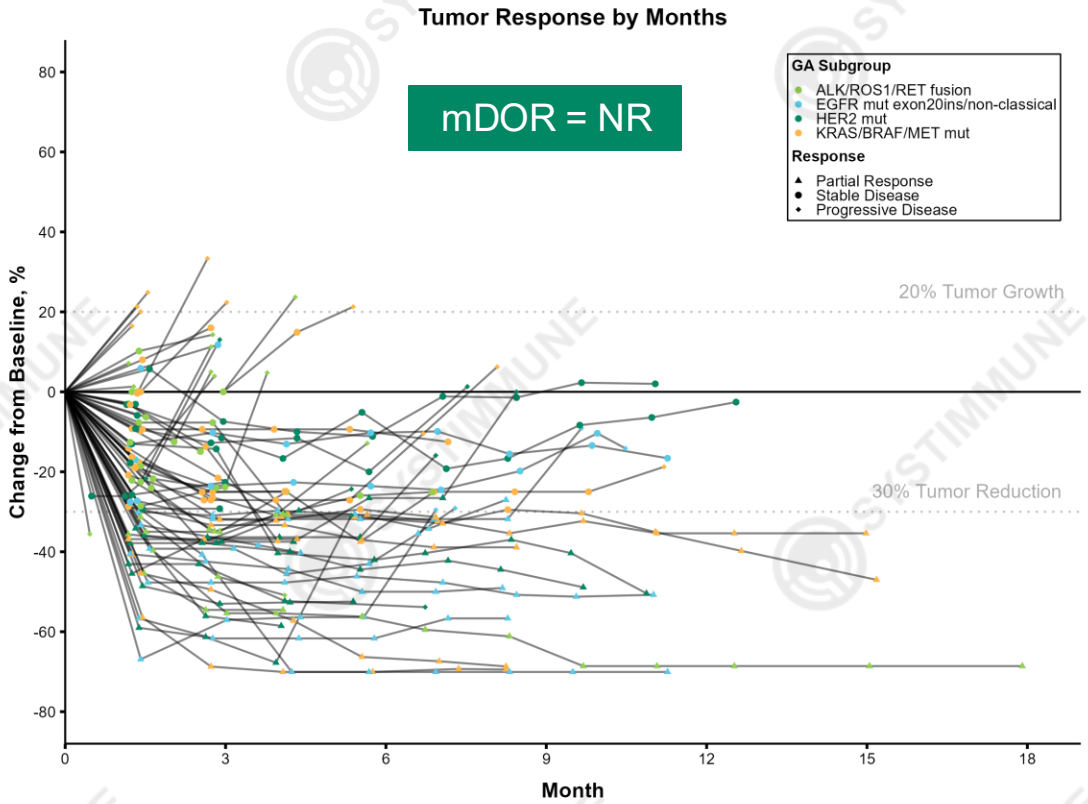
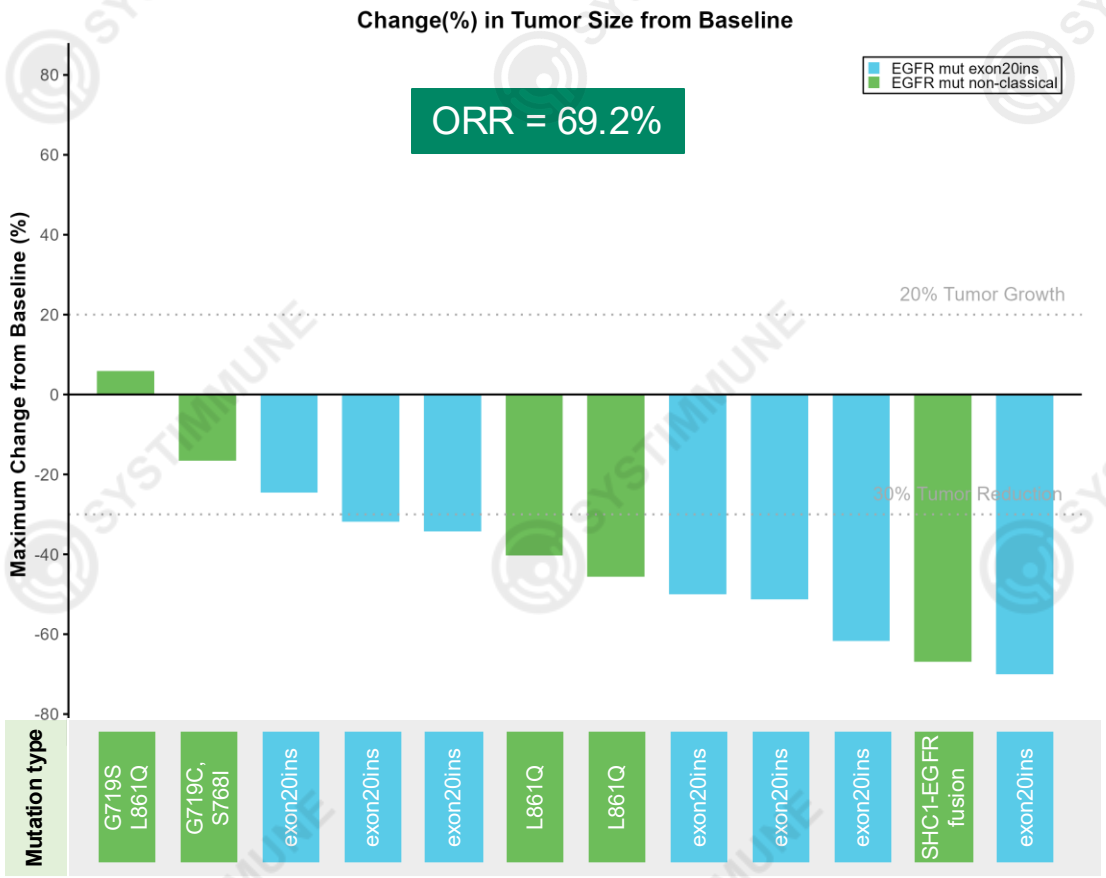
Depth & Duration of Response – Total

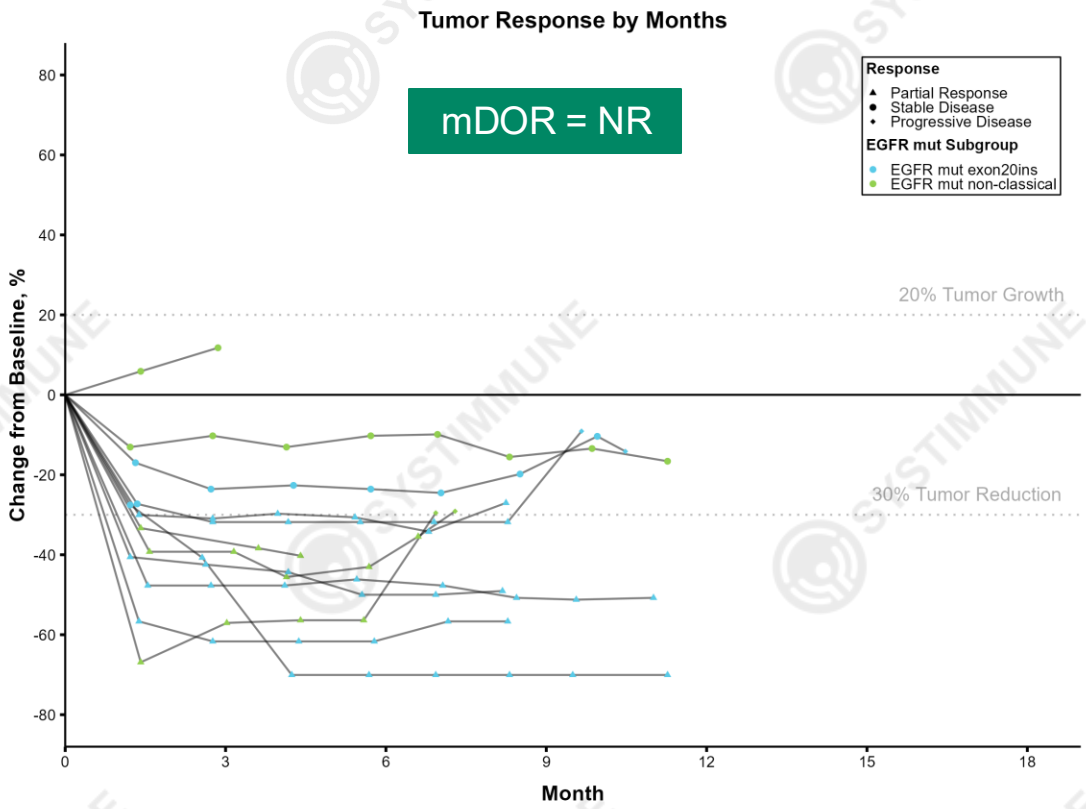




81.3% of patients with tumor shrinkage and the median (range) shrinkage (%) was -29.2 (-70.1, 24.9).

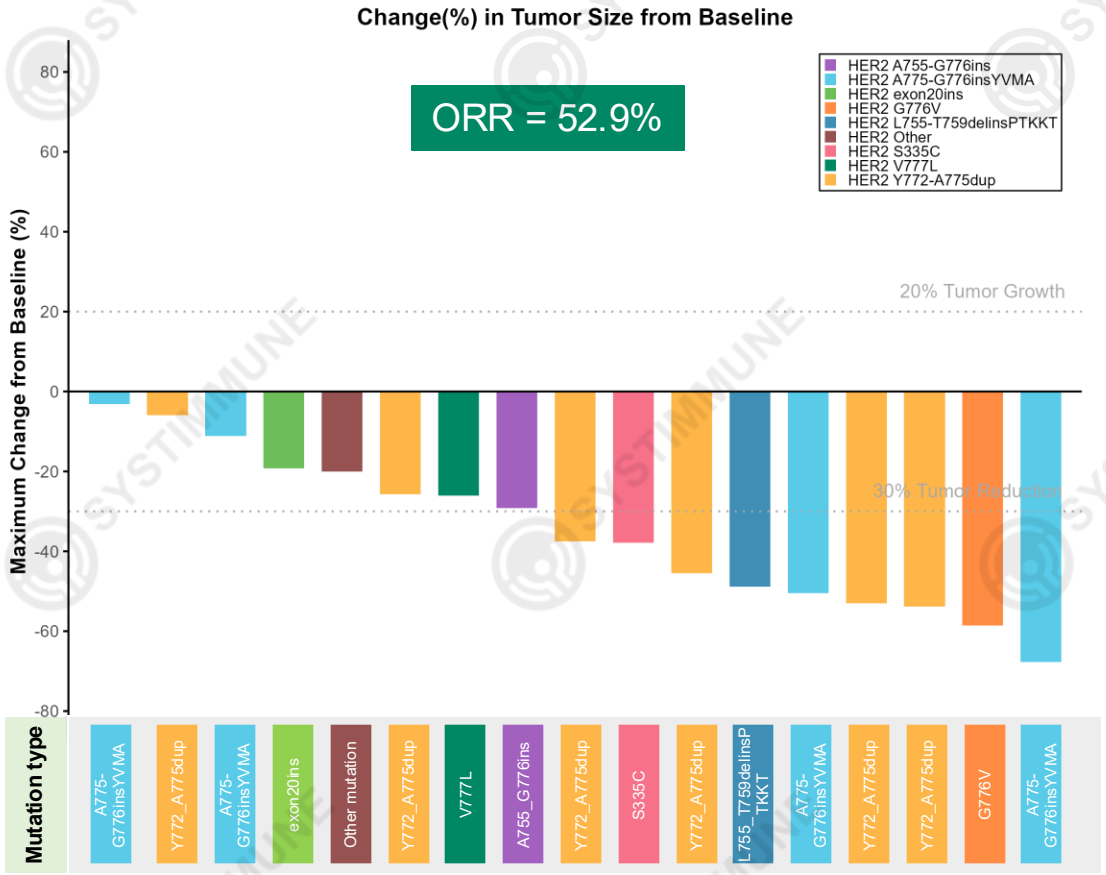
EGFR mut exon20ins/non-classical

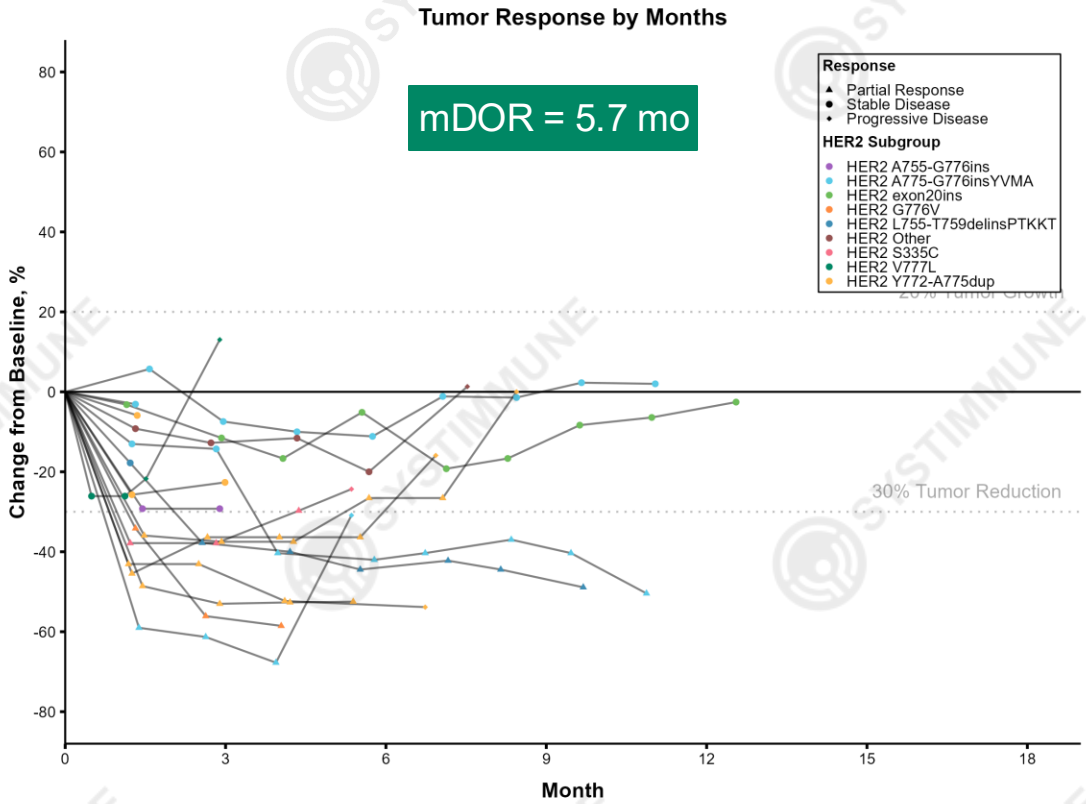




91.7% of patients with tumor shrinkage and the median (range) shrinkage (%) was -42.9 (-70.1, 5.9).

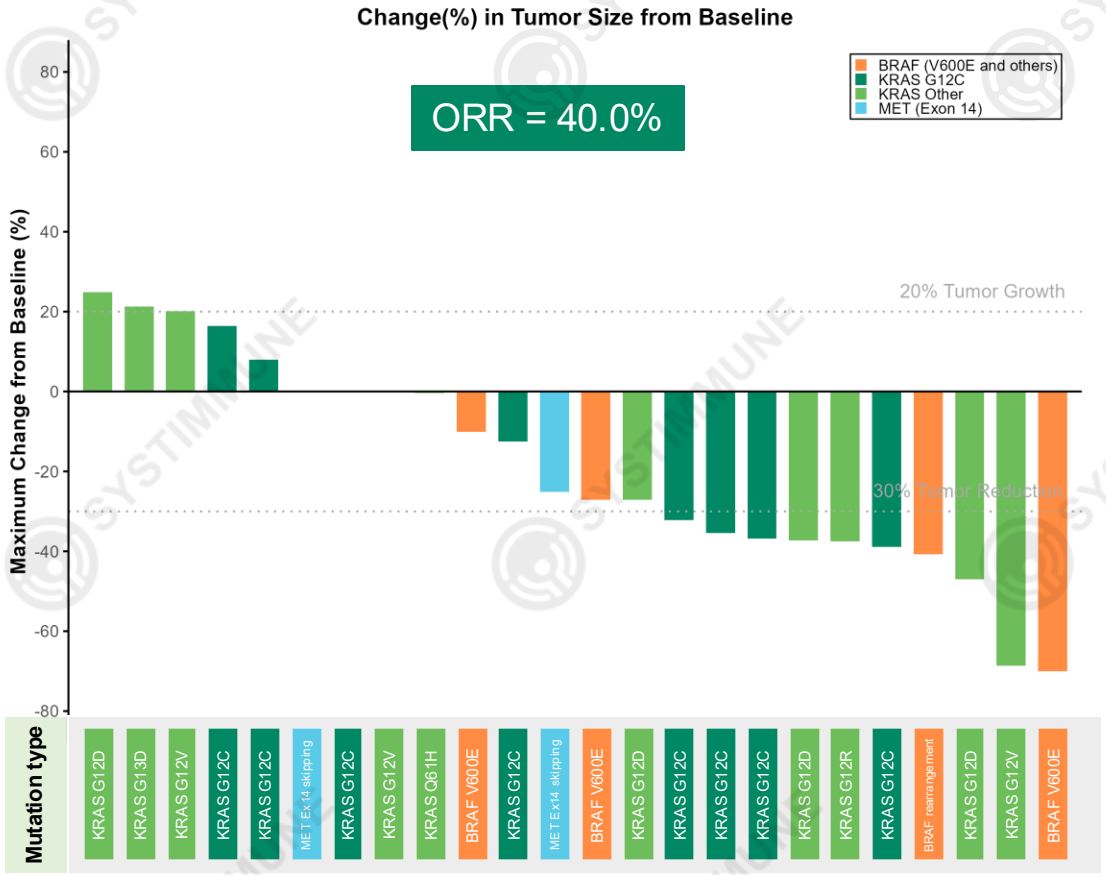
HER2 mut

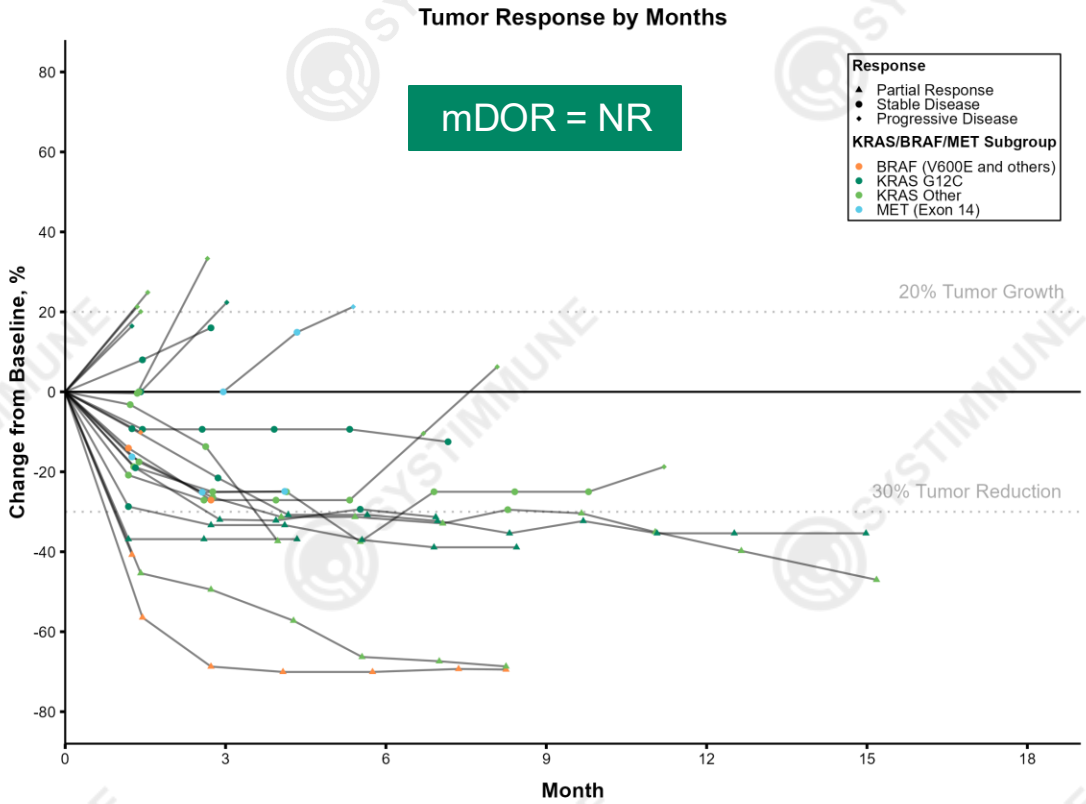




100% of patients with tumor shrinkage and the median (range) shrinkage (%) was -37.5 (-67.7, -3.1).

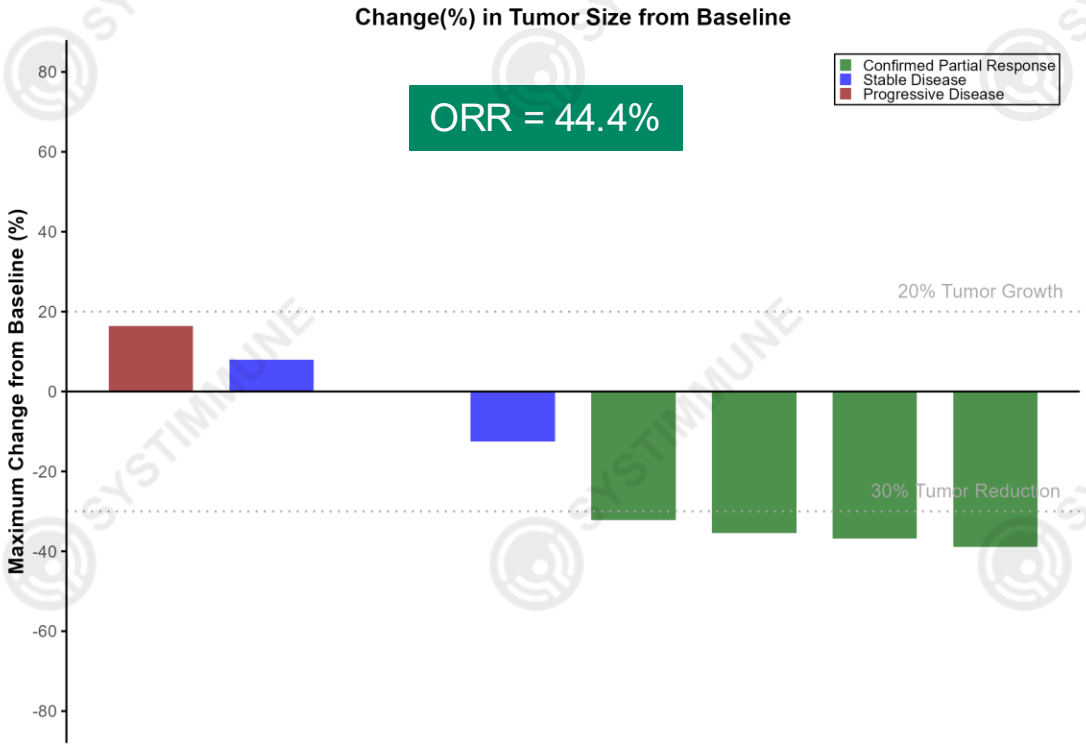
KRAS/BRAF/MET mut

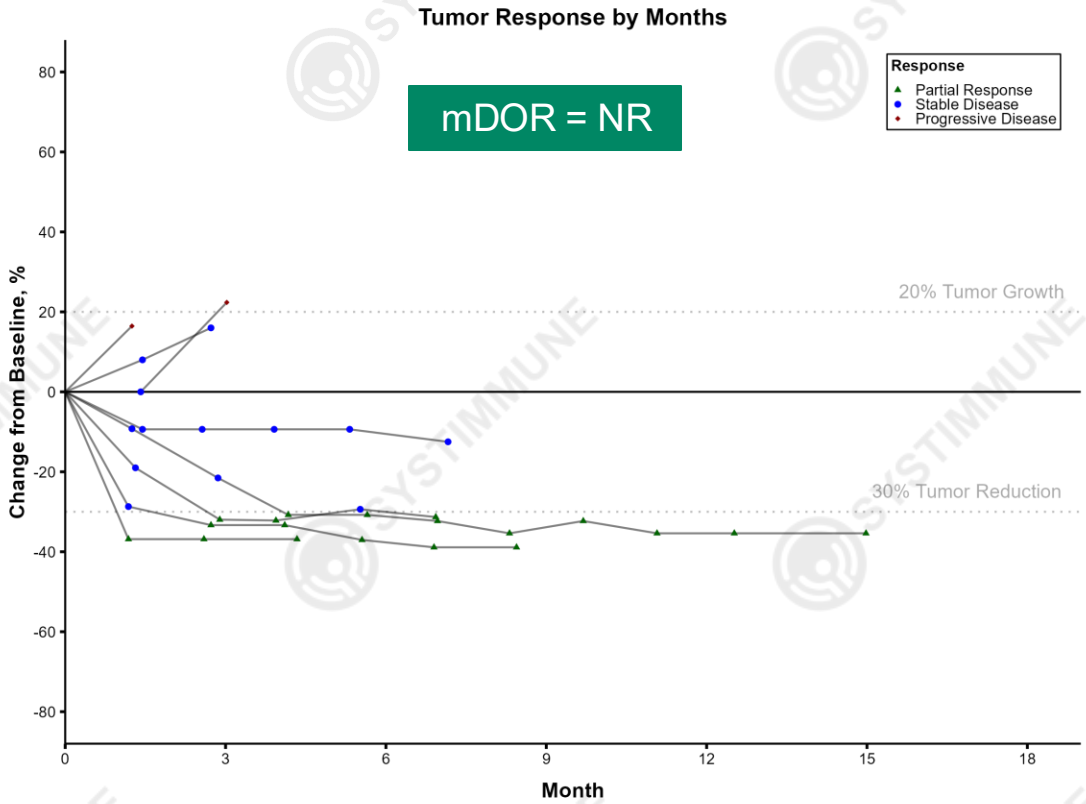




66.7% of patients with tumor shrinkage and the median (range) shrinkage (%) was -26.1 (-70.1, 24.9).

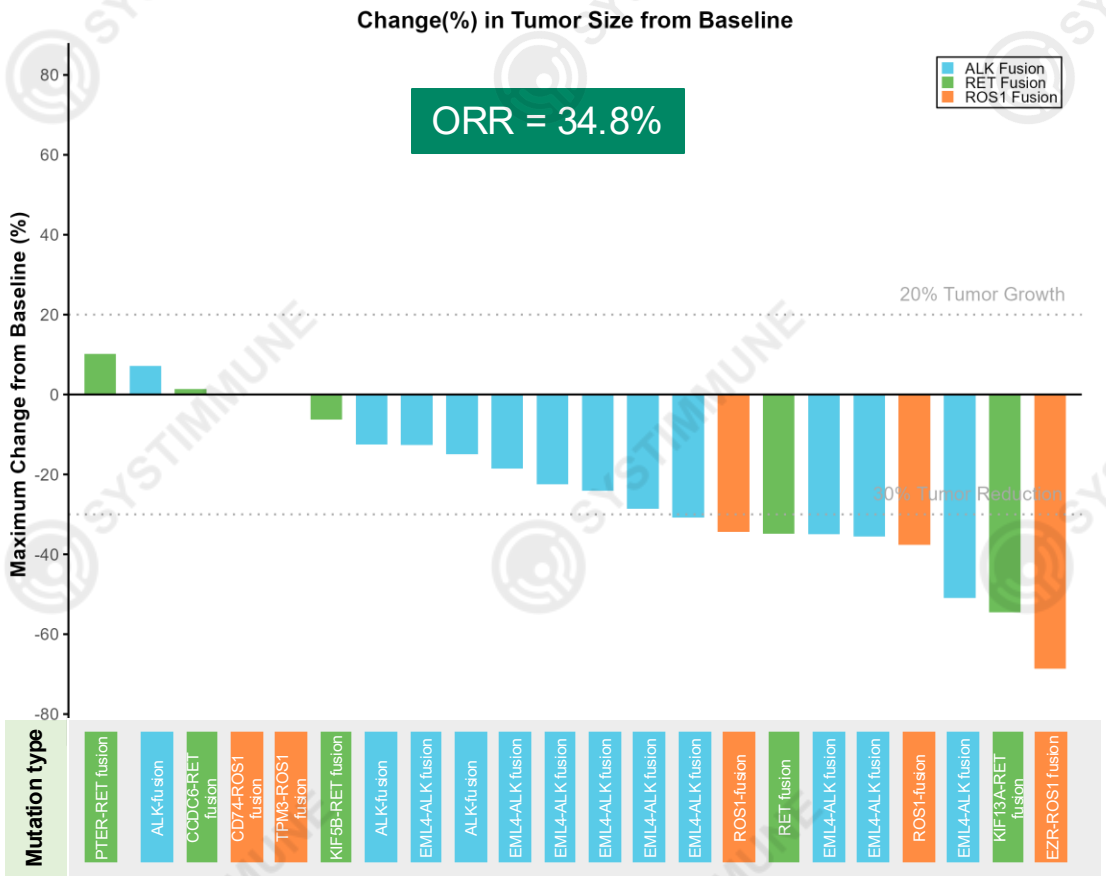
KRAS G12C

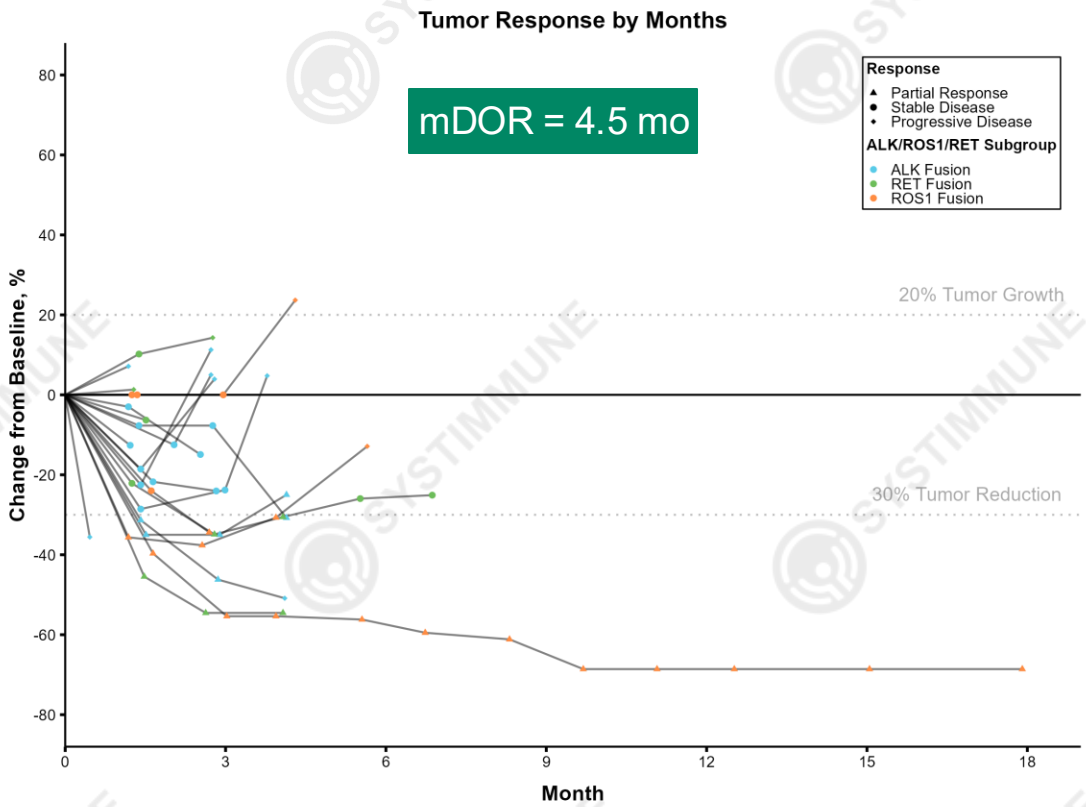




62.5% of patients with tumor shrinkage and the median (range) shrinkage (%) was –22.3 (-38.9, 16.4).

ALK/ROS1/RET fusion





77.3% of patients with tumor shrinkage and the median (range) shrinkage (%) was -23.3 (-68.6, 10.2).

Conclusions

- The most common adverse events associated with iza-bren are hematologic toxicities which can be well managed. No other new safety signals have been observed.

- iza-bren has encouraging activity in pretreated NSCLC patients with driver genomic alterations outside of classic EGFR mutations, with months. ORR of 46.2% and median PFS of 7.0

- Promising activity in patients with exon20ins/non-classical EGFR mutations is observed, with ORR of 69.2% (9/13) and median PFS of 10.5 months, which warrants further validation through a larger cohort.

Acknowledgments

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