NRG1 as a Target in NSCLC

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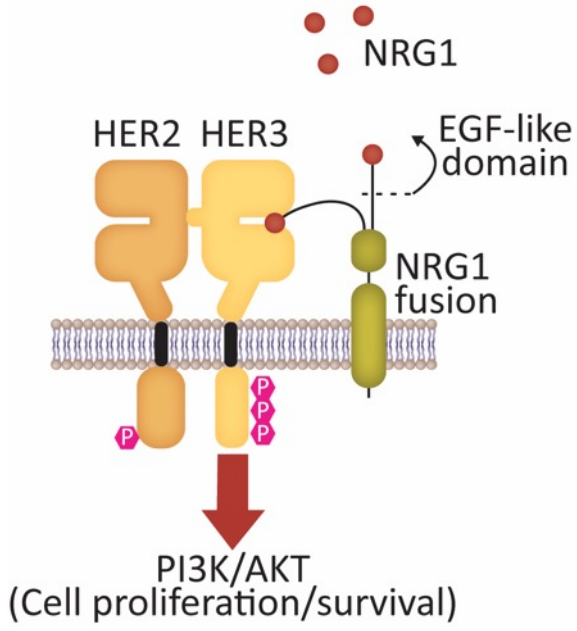
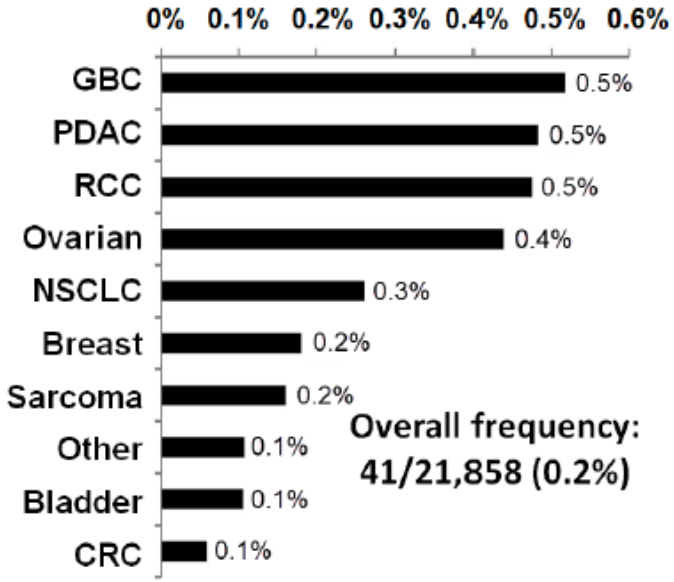
NRG1 (Neuregulin 1) Fusions

- ***NRG1*** is a ***ligand*** that binds HER3 and HER4 receptors, mediated by the EGF-like domain
- This binding promotes ***HER3-HER2 heterodimerization*** with resulting activation of downstream PI3K/AKT/mTOR signaling
- ***NRG1 fusions*** lead to overactivation of **HER3 pathway**



0.26% in NSCLC



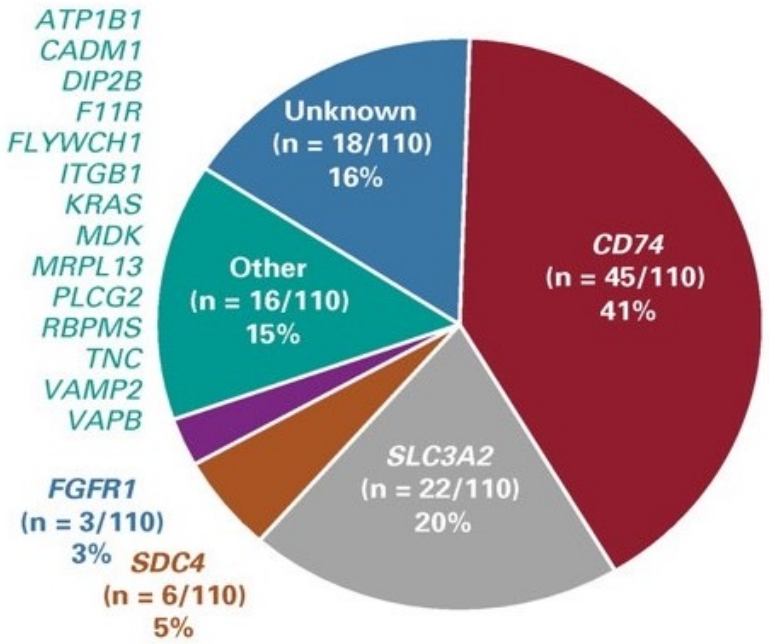
Adapted courtesy of Dr. Shirish Gadgeel

Schram A…Leighl NB et al ESMO 2023, 1315MO.
Jonna S et al., Clin Cancer Res 2019;25:4966-72

NRG1 Fusions in NSCLC

- 0.26% of NSCLC cases, mostly adenocarcinoma
- Emerging biomarker in NSCLC, including in resistance to other targeted therapies
- RNA+DNA-based NGS preferred testing method, as well as fusion panels (e.g. Archer)

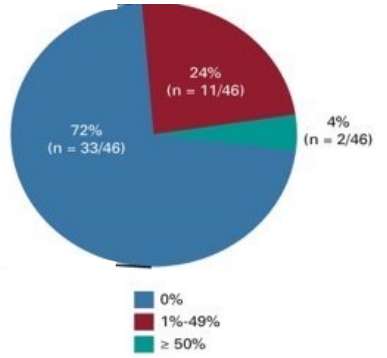
***NRG1* Gene Fusion Partners**

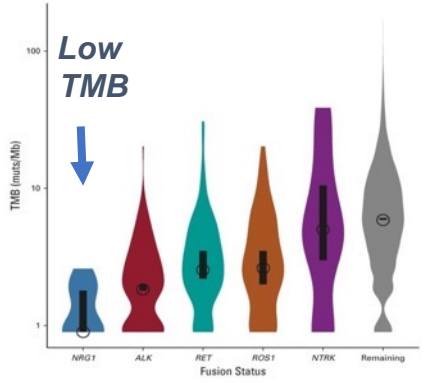


Drilon A, et al, J Clin Oncol, 2021

Sex	
Male	42 (41)
Female	62 (59)
Median age (range), years	64 (29-88)
Ethnicity	
Asian	43 (52)
White	38 (46)
Black	2 (2)
Smoking status	
Never	48 (57)
Former	25 (30)
Current	11 (13)
Median pack-years (range)	37 (1-135)
Histology	
Adenocarcinoma	103 (94)
Invasive mucinous	59 (57)
Invasive nonmucinous	29 (28)
Others or unspecified	15 (15)
Adenosquamous	1 (< 1)
Squamous	4 (4)
Large cell neuroendocrine	1 (< 1)
NSCLC (NOS)	1 (< 1)

72%
PD-L1
Negative





eNRGy1 Global Multicenter Registry
(N=110 tumors), 2021

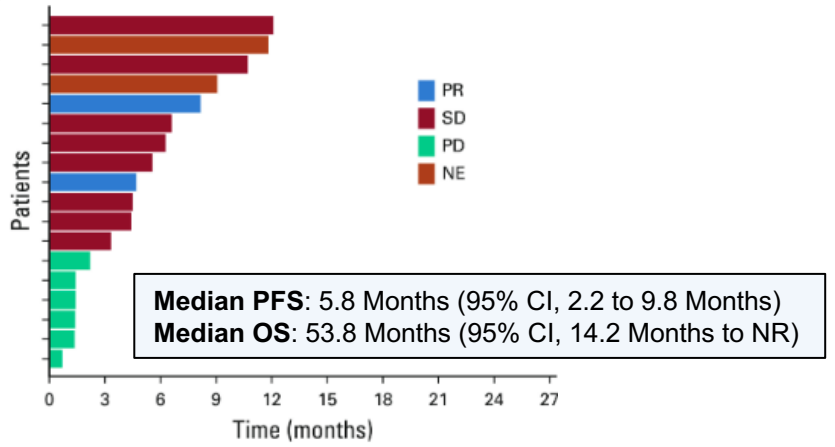
No approved targeted options for NRG1 fusion-positive lung cancer

Response	Platinum-Doublet	Taxane Chemo-therapy	Chemo + Immuno-therapy	Anti-PD(L)1 mono-therapy	Afatinib
Response Rate, % (n/N)	**13** (2/15)	**14** (1/7)	**0**	**20**	**25**
PR+SD, % (n/N)	60 (9/15)	28 (2/7)	44 (4/9)	20 (1/5)	60 (8/20)
Median PFS • (95% CI) • Range	**5.8 Months** (2.2 to 9.8) 0.7-12.1	**4.0 Months** (0.8 to 5.3) 0.8-5.5	**3.3 Months** (1.4 to 6.3) 1.4-15.2	**3.6 Months** (0.9 to NR) 0.9-11.2	**2.8 Months** (1.9 to 4.3) 0.3-25.3)

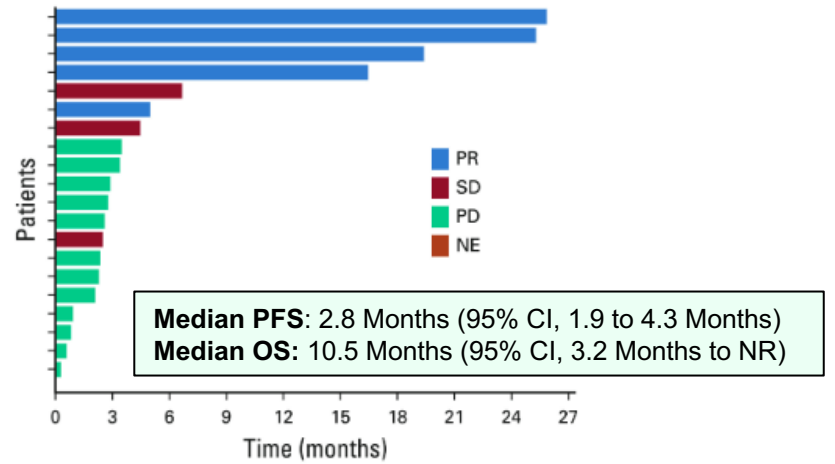
Median Survival	Months	95% CI
Afatinib	**15.9**	**10.1 to 64.5 Months**
No Afatinib	**17.6**	**10.0 t0 21.0 Months**

***No Significant Difference in OS between those that received afatinib versus not**

Platinum-Doublet Chemotherapy (n = 18)



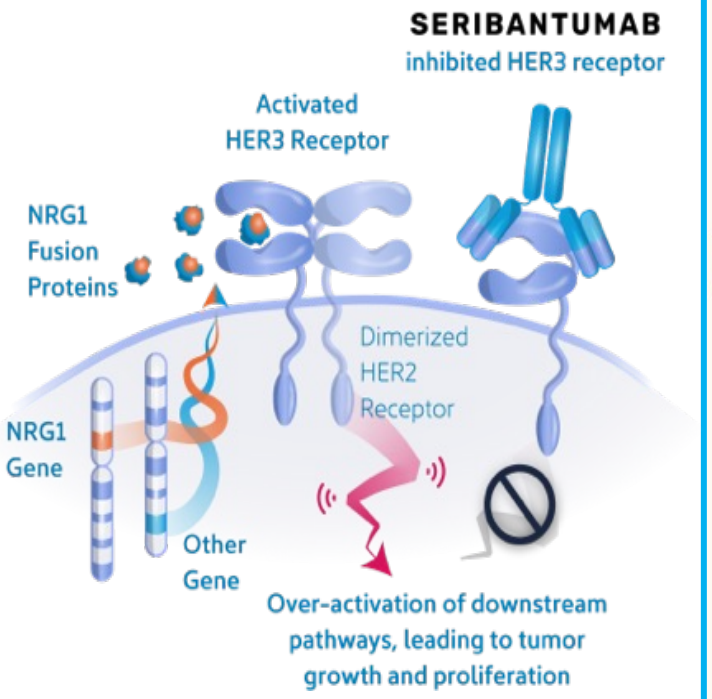
Afatinib Targeted Therapy (n = 20)

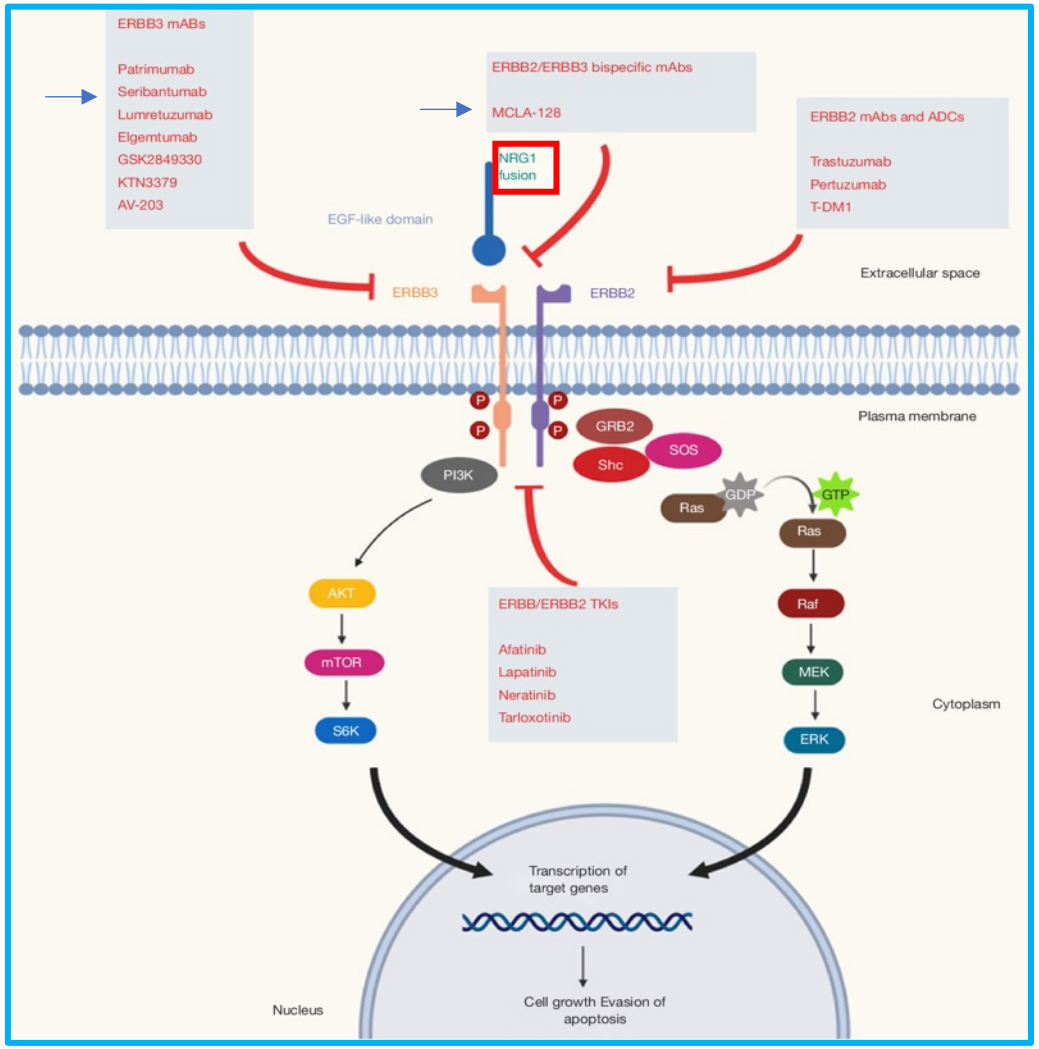


CI, confidence interval;PFS, progression-free survival; PR, partial response; SD, stable disease; NR, not reached

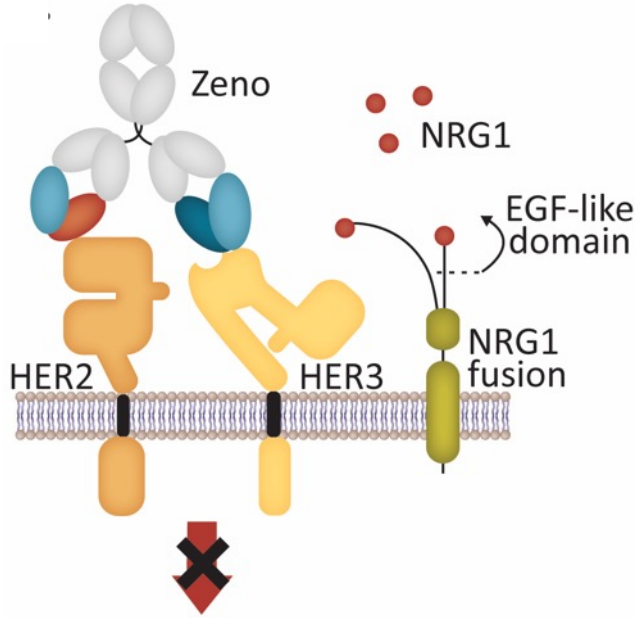
Drilon A, et al. *J Clin Oncol*. 2021;39:2791-2802.

Emerging options for NRG1 fusion-positive lung cancer





Zenocutuzumab
Bispecific HER2XHER3 antibody



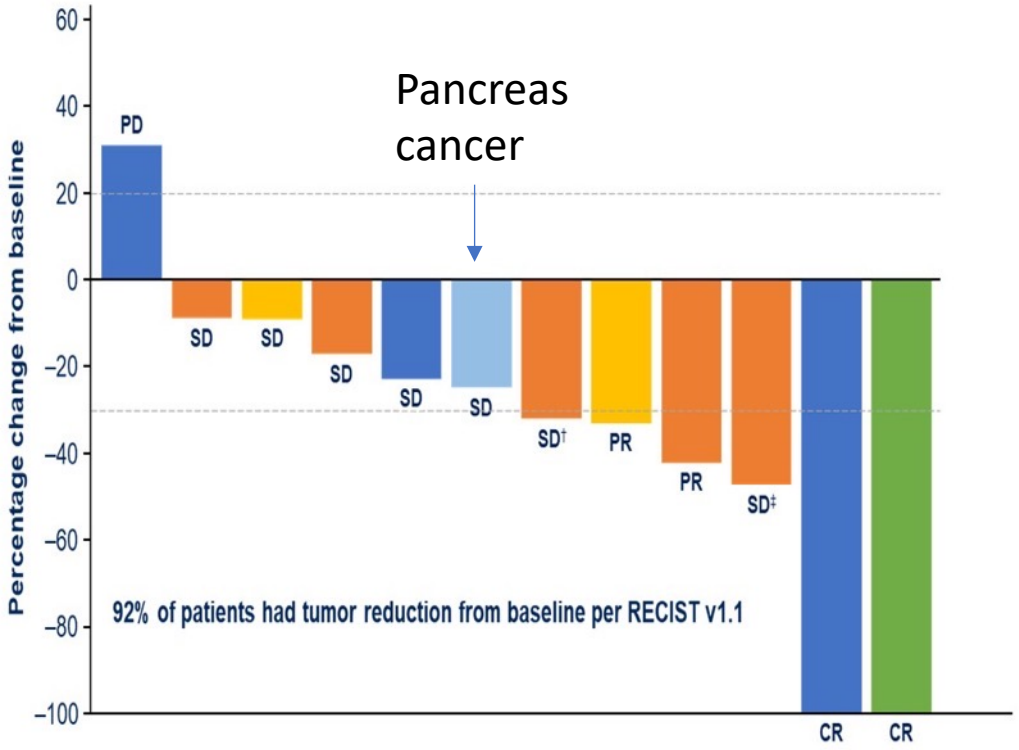
Breakthrough Designation in NRG1 fusion+ NSCLC and pancreatic adenocarcinoma

Russo A, et al. *Precis Cancer Med*. 2020;3:14. http://dx.doi.org/10.21037/pcm.2020.03.02Ru.

Phase II CRESTONE Study of Seribantumab 3 mg IV

Development of Seribantumab
Paused as of 9 Feb 2023

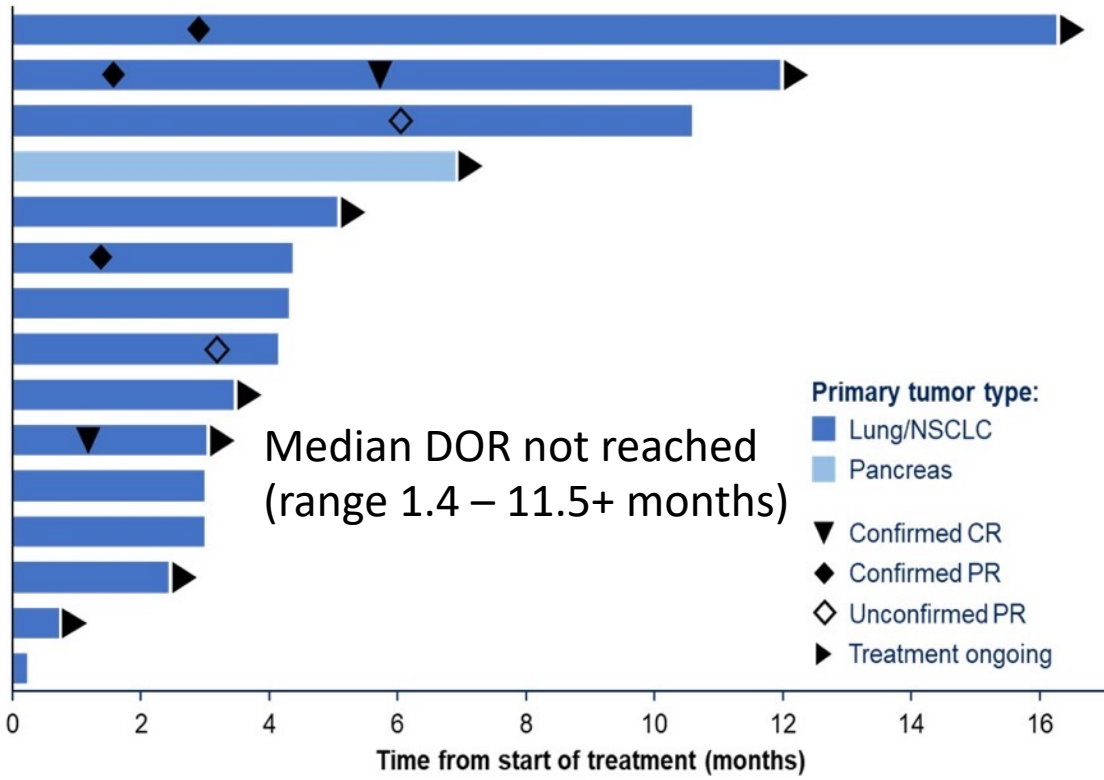
Most responses seen in patients with NSCLC, across a variety of fusion partners



Confirmed INV-ORR	
Overall	33% (4/12)
NSCLC	36% (4/11)

PR+SD = 92%

NRG1 fusion partner:
- SLC3A2
- CD74
- SDC4
- ATP1B1
- ITGB1



75% of responders, 53% of all patients stll on treatment
75% of responses occurred early (6 weeks)

Carrizosa DR et al. ASCO 2022 Annual Meeting. NCT04383210

MADRID 2023 ESMO congress

MADRID SPAIN
20-24 OCTOBER 2023

Durable efficacy of zenocutuzumab, a HER2 x HER3 bispecific antibody, in advanced *NRG1* fusion-positive (NRG1+) non-small cell lung cancer (NSCLC)

Alison M. Schram,[1] Koichi Goto,[2] Dong-Wan Kim,[3] Antoine Hollebecque,[4] Sun Young Rha,[5] Kazumi Nishino,[6] Michaël Duruisseaux,[7] Kumiko Umemoto,[8] Joon Oh Park,[9] Natasha Leighl,[10] Teresa Macarulla,[11] Stephen V. Liu,[12] Mohammed Najeeb Al Hallak,[13] James Cleary,[14,15] Cindy Neuzillet,[16] Yasushi Goto,[17] Andrew K. Joe,[18] Shola Adeyemi,[18] Shekeab Jauhari,[18] Alexander E. Drilon[19]

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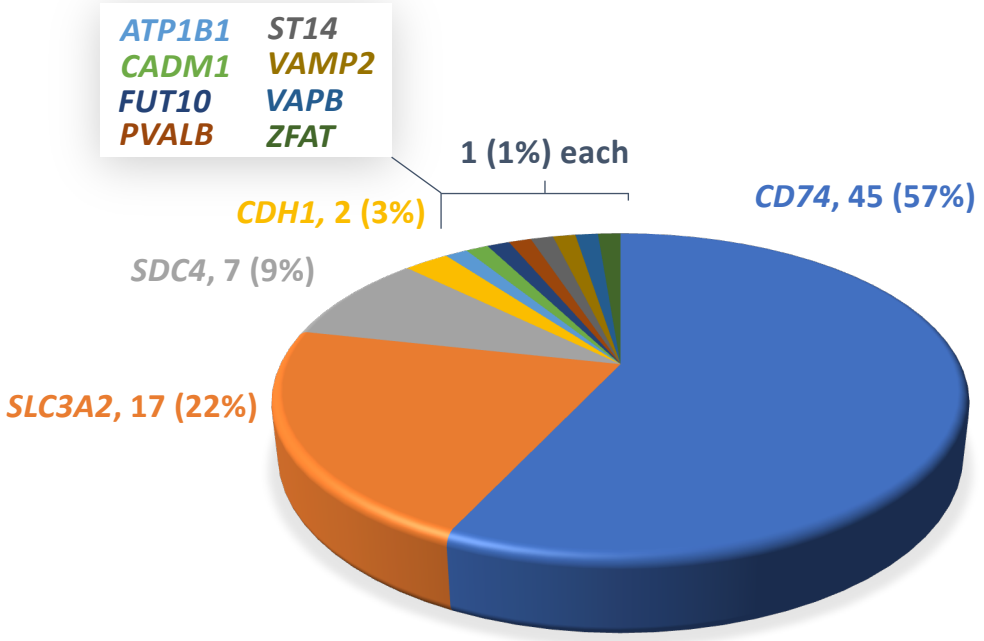
Mini oral presentation number: 1315MO

Phase I/II + EAP: Zenocutuzumab 750 mg IV q2weekly NRG1 Fusion+ NSCLC Primary Efficacy Population

Demographics and Prior Therapy (N = 79)

Age, years, median (range)	**64** (32-88)
Male / **female,** n (%)	30 (38) / 49 **(62)**
ECOG PS 0 / 1 / 2 / Missing, n (%)	24 (30) / 50 (63) / 3 (4) / 2 (3)
Race, Asian / White / Other[a], n (%)	40 (51) / 30 (38) / 9 (11)
Prior lines of systemic therapy, median (range)	1 (0-6)
Platinum pre-treated, n (%)	57 (72)
Prior afatinib, n (%)	**9 (11)**
Treatment naïve, n (%)	12 (15)
Patient disposition, n (%)	
Treatment ongoing	20 (25)
Discontinued due to PD[b] / other reason[c]	58 (73) / 1 (1)
Number of metastatic sites, median (range)[d]	2 (0-8)
Histology, n (%)	
Adenocarcinoma	**66 (84)**
Invasive mucinous adenocarcinoma	11 (14)
Squamous cell carcinoma	1 (1)
Poorly differentiated carcinoma	1 (1)

NRG1 Fusion Partners (N = 79)



NRG1 identification technology, n (%)	
RNAseq	64 (81)
DNAseq	11 (14)
Nanostring	1 (1)
Missing	3 (4)

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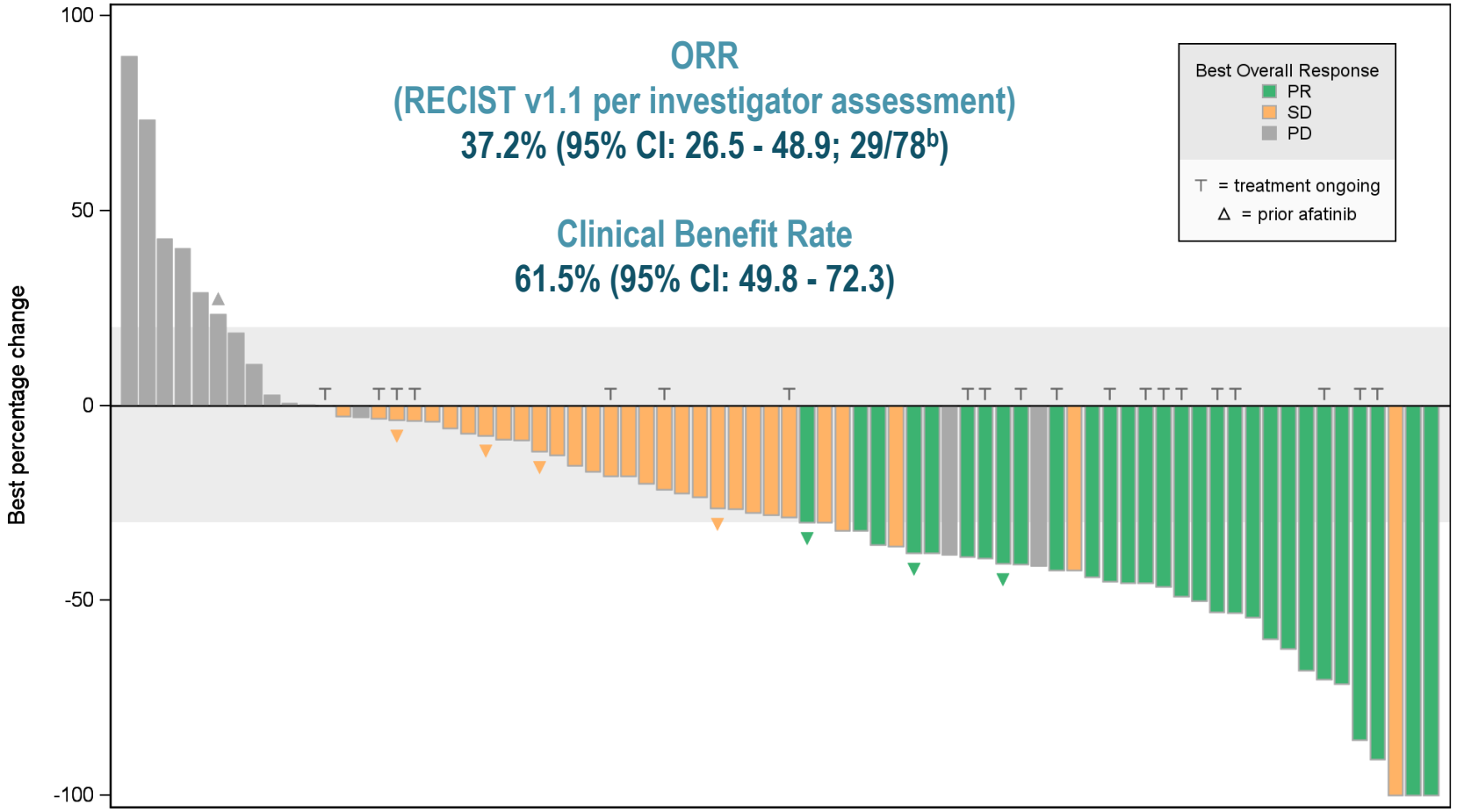
[a] Native Hawaiian or other Pacific islander (n = 1), unknown (n = 2), missing (n = 6); [b] Includes radiological and clinical progression, and 2 fatal cases; [c] Patient withdrew consent; [d] 1 patient had advanced non-metastatic disease; EAP: expanded access program

Zenocutuzumab Activity in NRG1+ NSCLC

Best Percent Change in Target Lesions from Baseline[a]

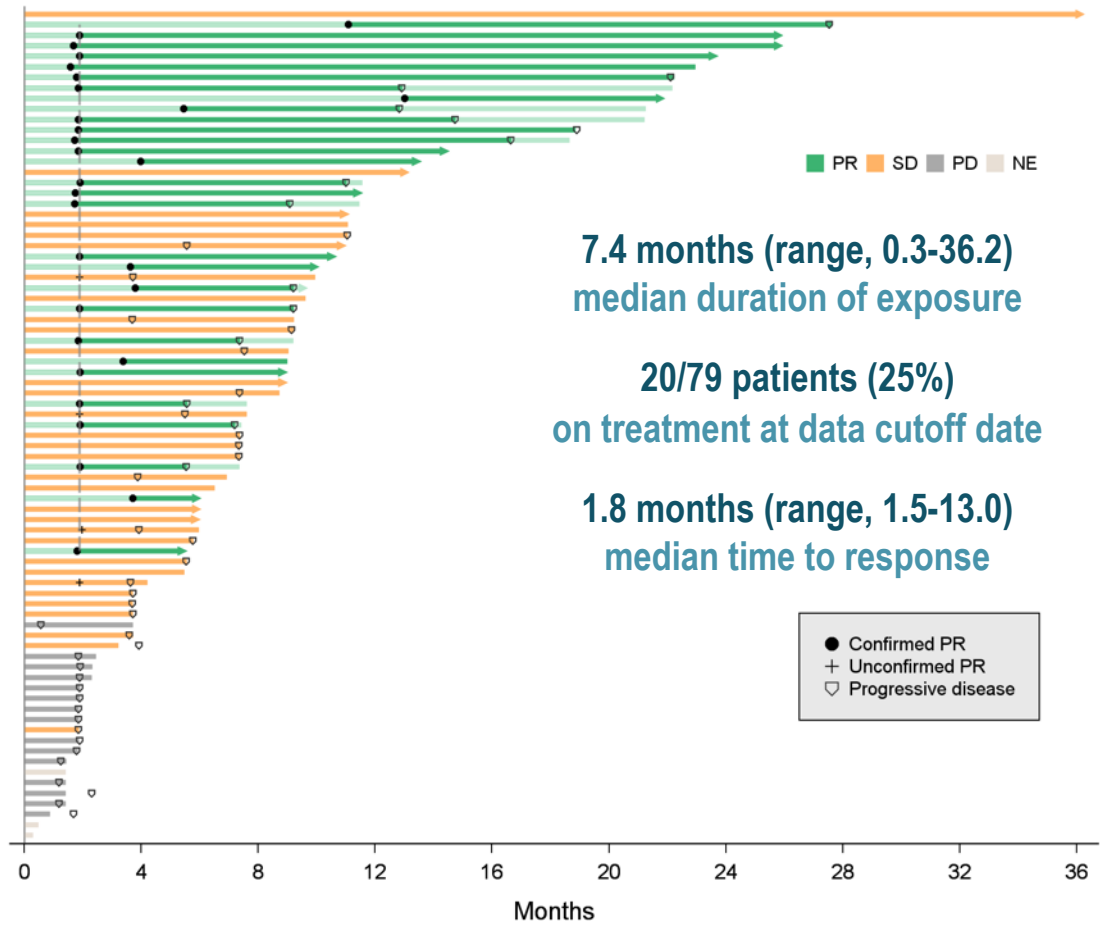


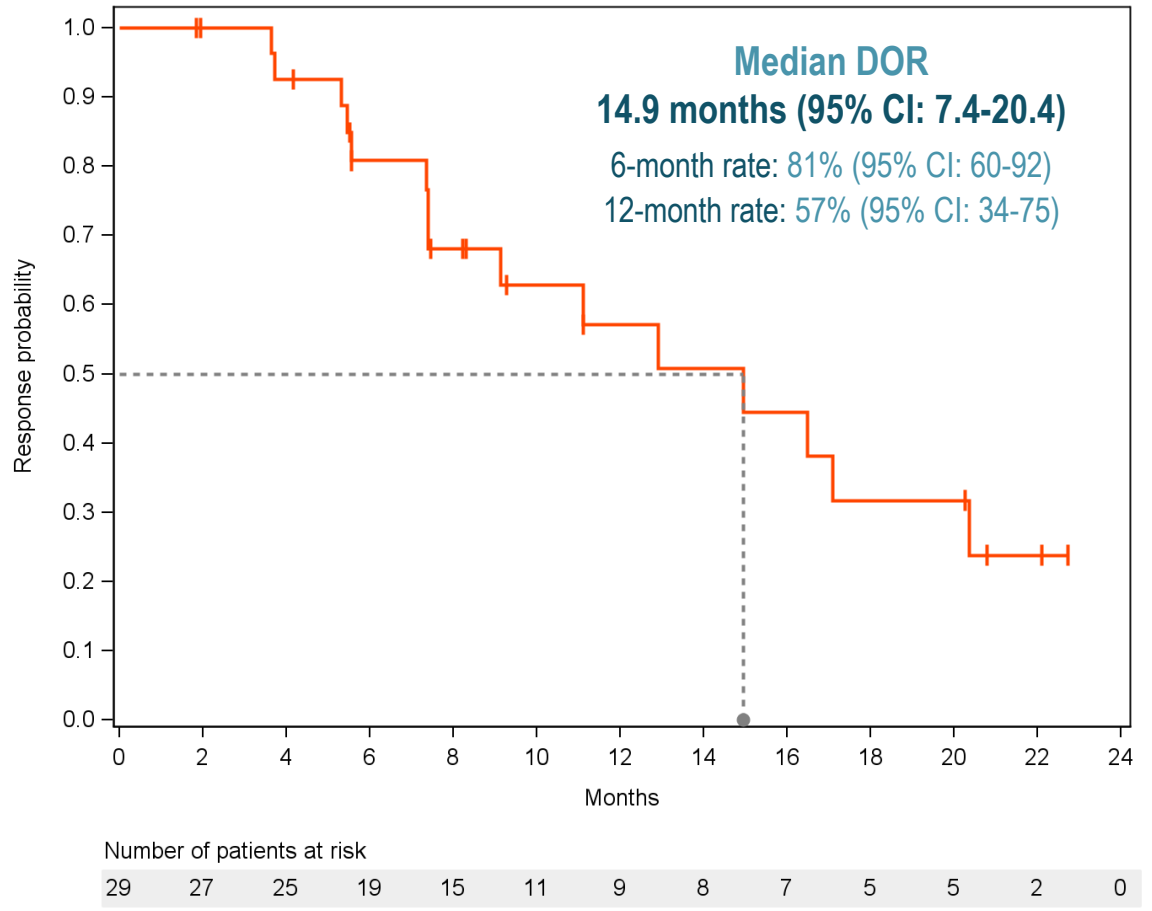
CI, confidence interval; SD, stable disease.

[a] Excludes 4 patients, 3 due to absence of post baseline assessment and 1 due to incomplete assessment of target lesion at first post baseline assessment.
[b] 1 patient with non-measurable disease was excluded from analysis.

Zenocutuzumab Activity in NRG1+ NSCLC

Time on Therapy[a] and Duration of Response





NE, not evaluable.

[a] Time on therapy defined as treatment duration plus 2 weeks (with possible limitation from data cutoff date or death). Arrows indicate treatment is ongoing at the data cutoff date.

Zenocutuzumab Safety Profile

Safety Profile in NRG1+ Cancer

- 189 NRG1+ cancer patients treated with zenocutuzumab 750 mg Q2W monotherapy[a]
- Low incidence of grade 3 or 4 treatment-related TEAEs
- No patient discontinued treatment due to treatment-related TEAEs
- No grade 5 treatment-related TEAEs
- Infusion-related reactions[b] in 23 of 189 (12%) patients, with no grade 3 or greater events

[a] 189 patients enrolled in the eNRGy trial or EAP, including 105 patients with NSCLC.
[b] Composite term covering preferred terms considered by the investigator to be infusion-related reactions occurring within 24 hours of infusion start.

	Related TEAEs (≥10% patients and all Grade 3-4) n (%)		TEAEs Irrespective of Causality (≥10% patients and all Grade 3-4) n (%)	
	All grades	Grades 3-4	All grades	Grades 3-4
≥1 TEAE	115 (61)	11 (6)	166 (88)	66 (35)
Diarrhea	**33 (17)**	**3 (2)**	53 (28)	4 (2)
Infusion-related reactions[b]	**23 (12)**	**0**	23 (12)	0
Fatigue	**18 (10)**	**0**	30 (16)	4 (2)
Nausea	16 (8)	2 (1)	30 (16)	3 (2)
Vomiting	11 (6)	1 (1)	21 (11)	1 (1)
Anemia	7 (4)	1 (1)	29 (15)	7 (4)
Constipation	5 (3)	0	24 (13)	0
ALT increased	5 (3)	1 (1)	18 (10)	5 (3)
AST increased	5 (3)	2 (1)	14 (7)	5 (3)
Decreased appetite	5 (3)	1 (1)	16 (8)	2 (1)
Abdominal pain	3 (2)	1 (1)	21 (11)	4 (2)
Dyspnea	2 (1)	0	24 (13)	6 (3)
GGT increased	2 (1)	1 (1)	13 (6)	6 (3)
Platelet count decreased	2 (1)	1 (1)	4 (2)	1 (1)
Hyperuricemia	2 (1)	1 (1)	3 (2)	1 (1)
Bacteremia	1 (1)	1 (1)	2 (1)	2 (1)
Hypertransaminasemia	1 (1)	1 (1)	1 (1)	1 (1)

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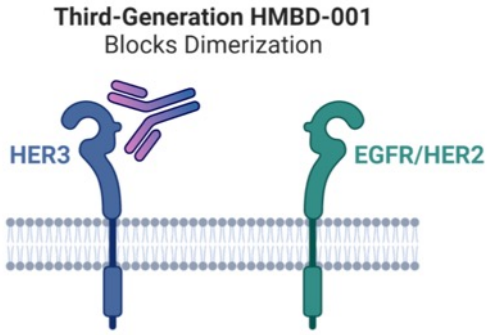
Moving forward

- Resistance to HER2/3-directed treatment includes emergence of *MET* amplification, alterations in *MEK* pathway

- Ongoing trials
  - Zenocutuzumab + afatinib in NSCLC (MCLA128-CL03, NCT)
  - Zenocutuzumab monotherapy (NCT 02912949)
  - Zenocutuzumab early access program (NCT04100694)
  - Zenocutuzumab in CNS metastasis (investigator initiated trial, pending)

  - HMBD-001 +/- Chemotherapy in NRG1 fusion+ tumors (NCT05919537)



Potential for HER3-targeting ADCs?

Key Take Aways

- NRG1 fusions are an important driver of NSCLC and other cancers
  - Emerging biomarker with no standard targeted treatment → important unmet need
  - Consider further RNA testing in patients with no other driver
  - More common in women, never smokers, mucinous adenocarcinoma

- Emerging treatment options focus on HER3, HER2
  - Seribantumab — ORR 36%, median duration of response not reached
  - Zenocutuzumab — ORR 37%, median duration of response 14.9 months
  - Afatinib — ORR 25%, median PFS 2.8 months
  - HMBD-001 — No data yet in NRG1 fusion+

  - Enroll your patient on trials!

Thank you!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