Efficacy and safety of zenocutuzumab, a HER2/HER3 bispecific antibody, in treatment-naïve, advanced *NRG1*+ NSCLC: Updated analysis from the ongoing phase 2 eNRGy trial

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- Has received compensation for a consulting or advisory role from AbbVie, Amgen, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo/UCB Japan, Genentech, Gilead Sciences, GSK, Guardant Health, Janssen Oncology, Jazz Pharmaceuticals, Lilly, Merus, Mirati Therapeutics, MSD Oncology, Natera, Novartis, OSE Immunotherapeutics, Pfizer, RAPT Therapeutics, Regeneron, Revolution Medicines, Takeda, and Yuhan
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The institution of **Antoine Hollebecque** has received speaking honoraria from Amgen, Bristol Myers Squibb, Eisai, Incyte, Seagen, and Servier; advisory board honoraria from Basilea Pharmaceutica, Boehringer Ingelheim, Debiopharm, Merck Sharp & Dohme, QED Therapeutics, Relay Therapeutics, Sanofi, and Taiho Pharmaceutical; and other funding from Pierre Fabre. His institution has received funding from AstraZeneca and Incyte.

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ASCO, American Society of Clinical Oncology; MSD, Merck Sharp & Dohme.

BACKGROUND

- Recent guidelines highlight the benefit of frontline targeted therapy in patients with advanced NSCLC[1]
- *NRG1* gene fusions are rare oncogenic drivers in NSCLC, best identified via RNA-based NGS[2,3]
- NSCLC tumors with *NRG1* fusions (*NRG1*+) are associated with a poor prognosis and demonstrate limited response to standard first-line chemoimmunotherapy[2]

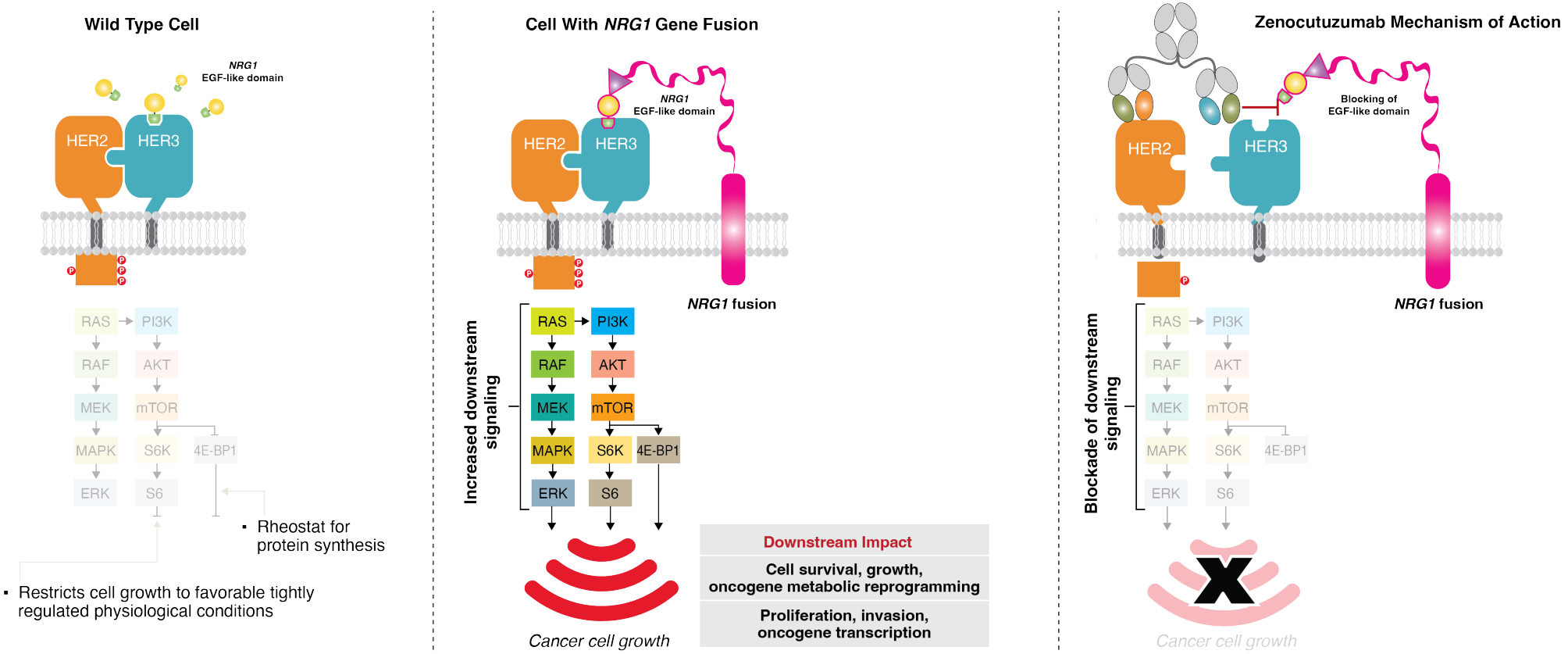
Activity of systemic therapy in *NRG1*+ NSCLC[4]

Data from a retrospective global registry study (N=110)	ORR, %	Median PFS, months (95% CI)
Platinum-doublet-based chemotherapy (n=15)	13	5.8 (2.2–9.8)
Taxane-based chemotherapy (n=7)	14	4.0 (0.8–5.3)
Combination chemotherapy and immunotherapy (n=9)	0	3.3 (1.4–6.3)
Single-agent immunotherapy (n=5)	20	3.6 (0.9–undefined)
Targeted therapy with afatinib (n=20)	25	2.8 (1.9–4.3)

CI, confidence interval; NGS, next-generation sequencing; *NRG1*, neuregulin 1; *NRG1*+, neuregulin 1 gene fusion positive; NSCLC, non-small cell lung cancer; ORR, objective response rate; PFS, progression-free survival.

1. Hendricks LE, *et al. Ann Oncol*. 2023;34(4):339–357; 2. Schram AM, *et al. Cancer Discov*. 2022;12(5):1233–1247; 3. Severson E, *et al. J Mol Diagn*. 2023;25(7):454–466; 4. Drilon A, et *al. J Clin Oncol*. 2021;39(25):2791–2802.

MECHANISM OF ACTION OF ZENOCUTUZUMAB, A HER2/HER3 IgG1 BISPECIFIC ANTIBODY[1–4]



Zenocutuzumab (BIZENGRI®) received accelerated US FDA approval (December 2024) for previously treated, advanced *NRG1*+ NSCLC and PDAC[5,6]

4E-BP1, eukaryotic translation initiation factor 4E-binding protein 1; AKT, protein kinase B; EGF, epidermal growth factor; ERK, extracellular signal-regulated kinase; FDA, Food and Drug Administration; HER, human epidermal growth factor receptor; IgG1, immunoglobulin G1; MAPK, mitogen-activated protein kinase; MEK, MAPK kinase; mTOR, mechanistic target of rapamycin; *NRG1*, neuregulin 1; *NRG1*+, neuregulin 1 gene fusion positive; NSCLC, non-small cell lung cancer; P, phosphate; PDAC, pancreatic ductal adenocarcinoma; PI3K, phosphoinositide 3-kinase; RAF, rapidly accelerated fibrosarcoma; RAS, rat sarcoma viral oncogene homolog; S6, ribosomal protein S6; S6K, ribosomal protein S6 kinase.

1. Laskin J, *et al. Ann Oncol*. 2020;31(12):1693–1703; 2. Wee P, Wang Z. *Cancers (Basel)*. 2017;9(5):52; 3. Schram AM, *et al. Cancer Discov*. 2022;12(5):1233–1247; 4. Geuijen C, *et al. Cancer Cell*. 2018;33(5):922–936.e10 [Erratum in: *Cancer Cell*. 2021;39(8):1163–1164]. 5. BIZENGRI® [US Prescribing Information]. Lexington, MA, USA: Partner Therapeutics, Inc.; 2025; 6. US FDA. FDA grants accelerated approval to zenocutuzumab-zbco for non-small cell lung cancer and pancreatic adenocarcinoma. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-zenocutuzumab-zbco-non-small-cell-lung-cancer-and-pancreatic. Accessed November 14, 2025.

eNRGy: PHASE 1/2, GLOBAL, MULTICENTER TRIAL OF ZENOCUTUZUMAB (NCT02912949)[1,2]

eNRGy

NSCLC
PDAC
Other solid tumors

Inclusion criteria

- Age ≥18 years
- Advanced or metastatic solid tumor
- *NRG1* gene fusion*
- Previously treated unless considered unlikely to tolerate or benefit from standard therapy
- ECOG PS ≤2

Treatment plan

- Zenocutuzumab 750 mg, 2-hour† IV infusion Q2W until PD or unacceptable toxicity
- Tumor assessment Q8W

Enrollment and analysis

NSCLC: Treatment-naïve and previously treated patients
Data cutoff date: August 4, 2025

Patients enrolled (SAS):
Treatment naïve: n=21
Previously treated: n=133

Primary efficacy subset:
Treatment naïve: n=20
Previously treated: n=121

Excluded due to another driver mutation
- Treatment naïve: n=1
- Previously treated: n=4

Excluded due to prior anti-HER3 antibody therapy
- Previously treated: n=8‡

Excluded due to nonfunctional *NRG1* fusion
- Previously treated: n=1‡

Endpoints

Primary endpoint
ORR using RECIST v1.1 per investigator assessment

Secondary endpoints
- DOR, CBR, TTR, PFS per investigator assessment
- DOR, ORR, CBR, TTR, PFS per BICR§
- OS
- Safety¶

*_NRG1_ gene fusion status was determined by next-generation sequencing. †To mitigate potential infusion-related reactions, the initial infusion was administered over a period of 4 hours and patients received premedication with antipyretics, antihistamines, and glucocorticoids. ‡One patient was excluded due to prior anti-HER3 antibody therapy and due to nonfunctional *NRG1* fusion. §Not available for this data cut. ¶Adverse events were assessed from the date of the first zenocutuzumab dose up to 30 days after the last dose and graded using CTCAE v4.03.
BICR, blinded independent central review; CBR, clinical benefit rate; CTCAE, Common Terminology Criteria for Adverse Events; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HER3, human epidermal growth factor receptor 3; IV, intravenous; *NRG1*, neuregulin 1; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; PD, progressive disease; PDAC, pancreatic adenocarcinoma; PFS, progression-free survival; Q2W, every 2 weeks; Q8W, every 8 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; SAS, safety analysis set.

1. Schram AM, *et al. N Engl J Med*. 2025;392(6):566–576; 2. ClinicalTrials.gov. NCT02912949. https://clinicaltrials.gov/study/NCT02912949. Accessed November 14, 2025.

DEMOGRAPHICS AND DISEASE BACKGROUND

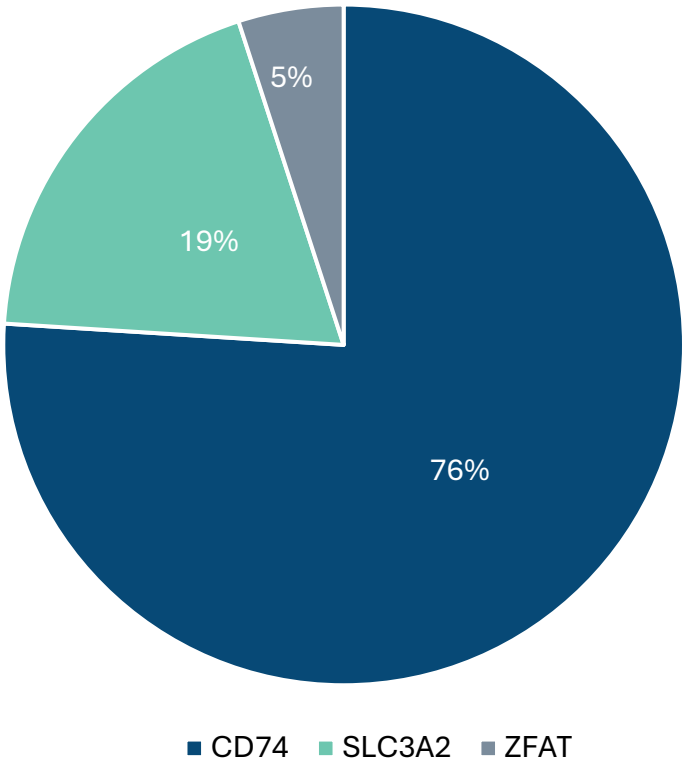
Baseline demographics and patient characteristics	Treatment naïve (n=21)	Previously treated (n=133)
Age, years, median (range)	73 (39–88)	66 (30–87)
Sex, female, n (%)	13 (62)	86 (65)
Race, n (%)		
White	8 (38)	51 (38)
Black	0	3 (2)
Asian	9 (43)	66 (50)
Other	2 (10)	3 (2)
Not provided	2 (10)	10 (8)
ECOG performance status, n (%)		
0	8 (38)	42 (32)
1	11 (52)	83 (62)
2	2 (10)	8 (6)

Disease background	Treatment naïve (n=21)	Previously treated (n=133)
Stage at screening, n (%)		
IIIA	0	1 (1)
IIIB	0	2 (2)
IIIC	0	1 (1)
IV	21 (100)	129 (97)
Histologic diagnosis, n (%)		
Adenocarcinoma	20 (95)	131 (98)
Squamous cell carcinoma	0	2 (2)
Other	1 (5)	0
Brain metastases, n (%)	3 (14)	18 (14)

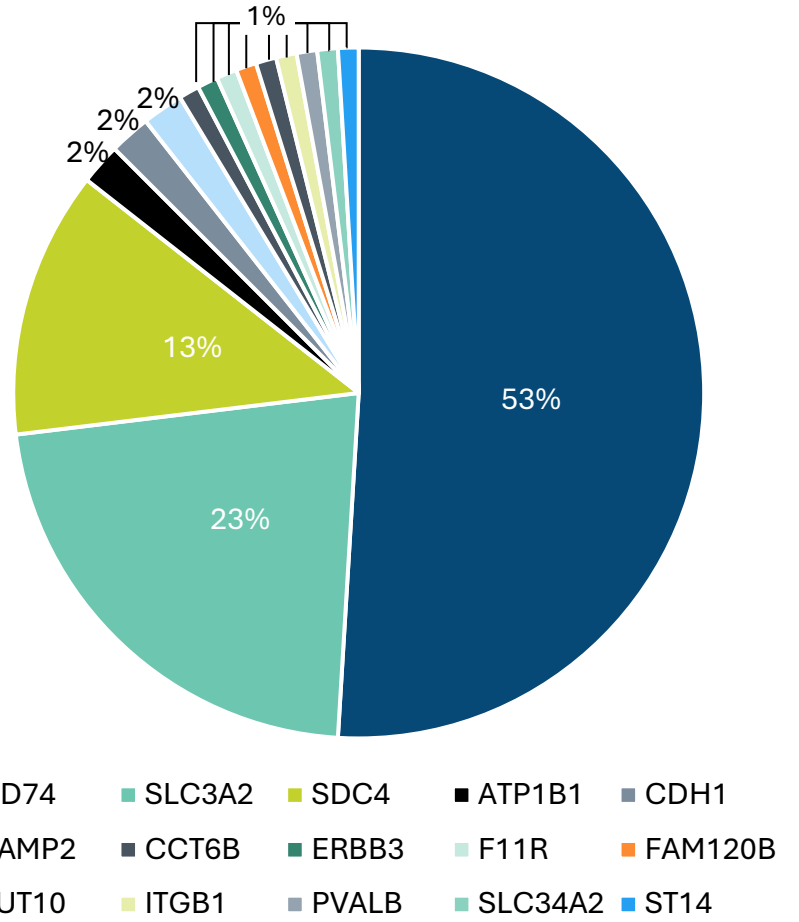
Data cutoff date: August 4, 2025. Safety analysis set.
ECOG, Eastern Cooperative Oncology Group.

HETEROGENEOUS *NRG1* FUSION PARTNERS

Treatment naïve (n=21)

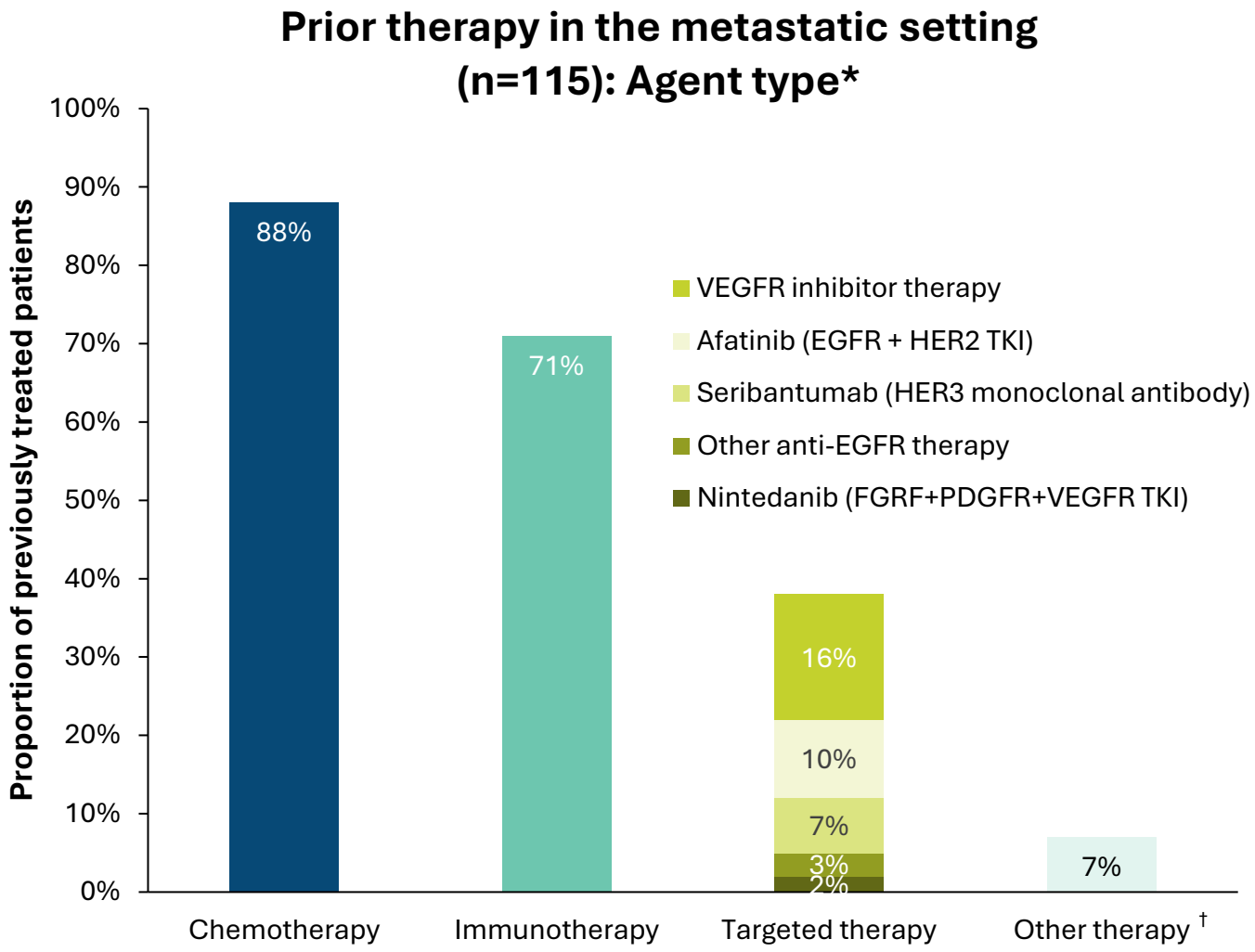


Previously treated* (n=133)



Data cutoff date: August 4, 2025. Safety analysis set.
*Due to rounding, total exceeds 100%.
ATP1B1, ATPase Na^+/K^+ transporting subunit beta 1; CCT6B, chaperonin containing TCP1 subunit 6B; CD74, cluster of differentiation 74; CDH1, cadherin 1; ERBB3, erb-b2 receptor tyrosine kinase 3; F11R, F11 receptor; FAM120B, family with sequence similarity 120B; FUT10, fucosyltransferase 10; ITGB1, integrin subunit beta 1; PVALB, parvalbumin; SDC4, syndecan 4; SLC3A2, solute carrier family 3 member 2; SLC34A2, solute carrier family 34 member 2; ST14, serine protease 14; VAMP2, vesicle-associated membrane protein 2; ZFAT, zinc finger and AT-hook domain containing.

TREATMENT HISTORY OF PREVIOUSLY TREATED PATIENTS

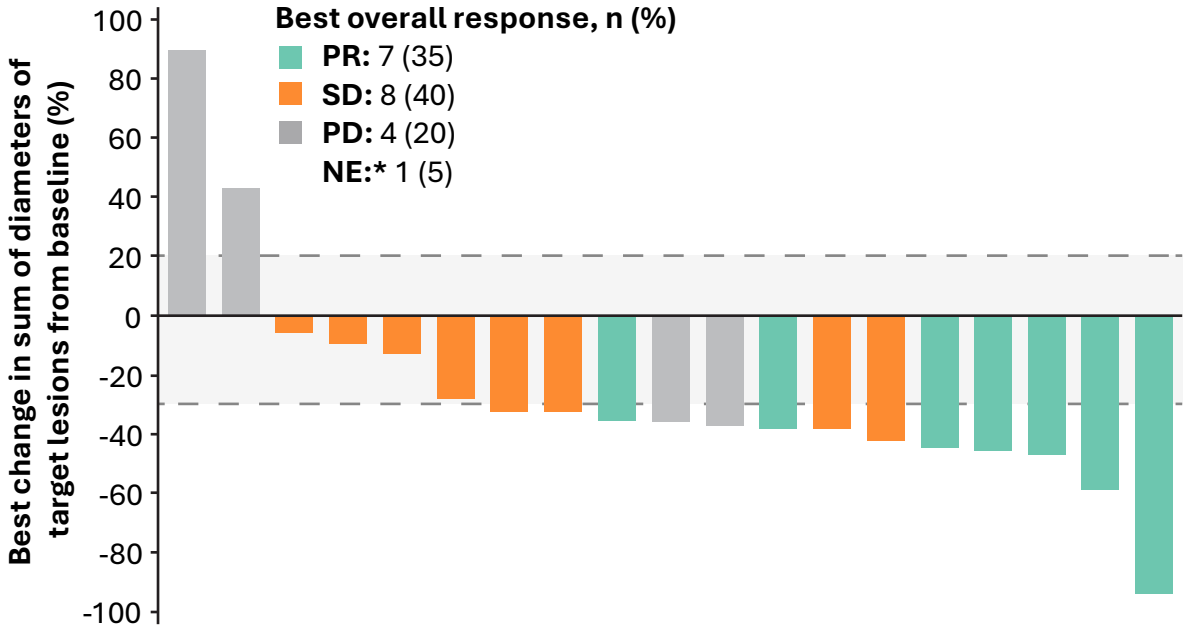


Metastatic treatment history	Previously treated (n=133)
Number of patients receiving systemic therapy in the metastatic setting, n (%)	115 (86)
Number of prior systemic therapy regimens in metastatic setting, median (range)	1 (0–4)

Data cutoff date: August 4, 2025. Safety analysis set, n=133.
*As patients may have received combination therapy, percentages exceed 100%. †Includes 7 patients classified as receiving investigational therapies and 1 classified as other: 'lenvatinib/placebo'.
CAR-T, chimeric antigen receptor T-cell; EGFR, epidermal growth factor receptor; FGFR, fibroblast growth factor receptor; FOLFOX, folinic acid + 5-fluorouracil + oxaliplatin; HER, human epidermal growth factor receptor; PDGFR, platelet-derived growth factor receptor; TKI, tyrosine kinase inhibitor; VEGFR, vascular epidermal growth factor receptor.

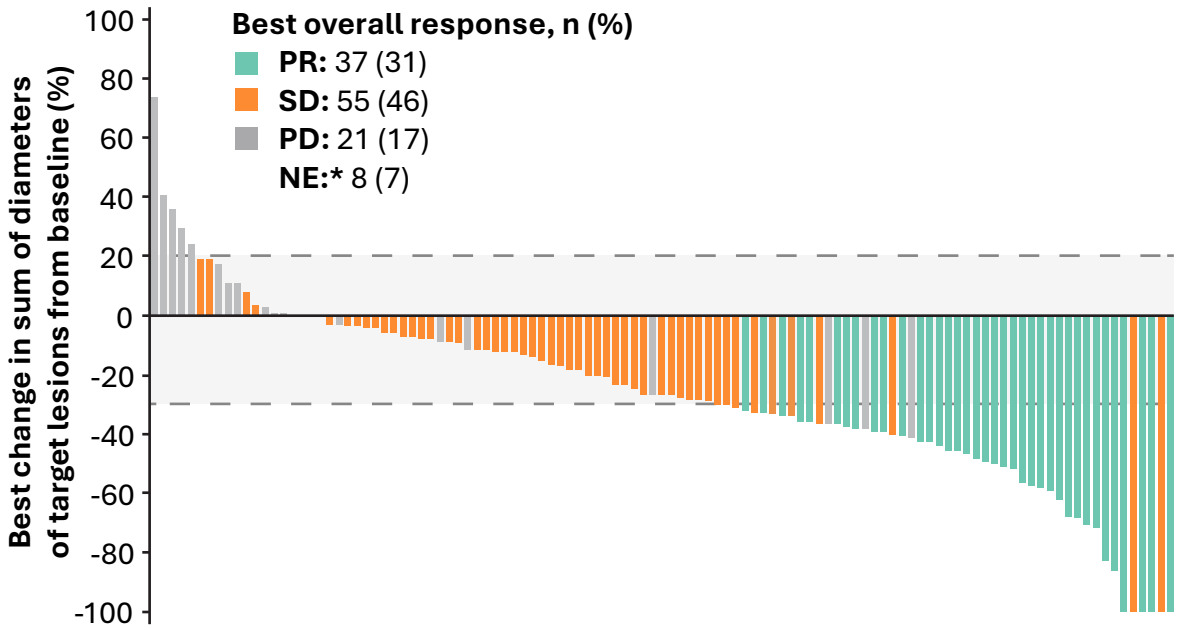
ZENOCUTUZUMAB DEMONSTRATES A CLINICALLY MEANINGFUL RESPONSE RATE IN *NRG1*+ NSCLC

Treatment naïve (n=20)



ORR, n (%) [95% CI]: 7 (35) [15–59]
CBR,† n (%) [95% CI]: 13 (65) [41–85]

Previously treated (n=121)

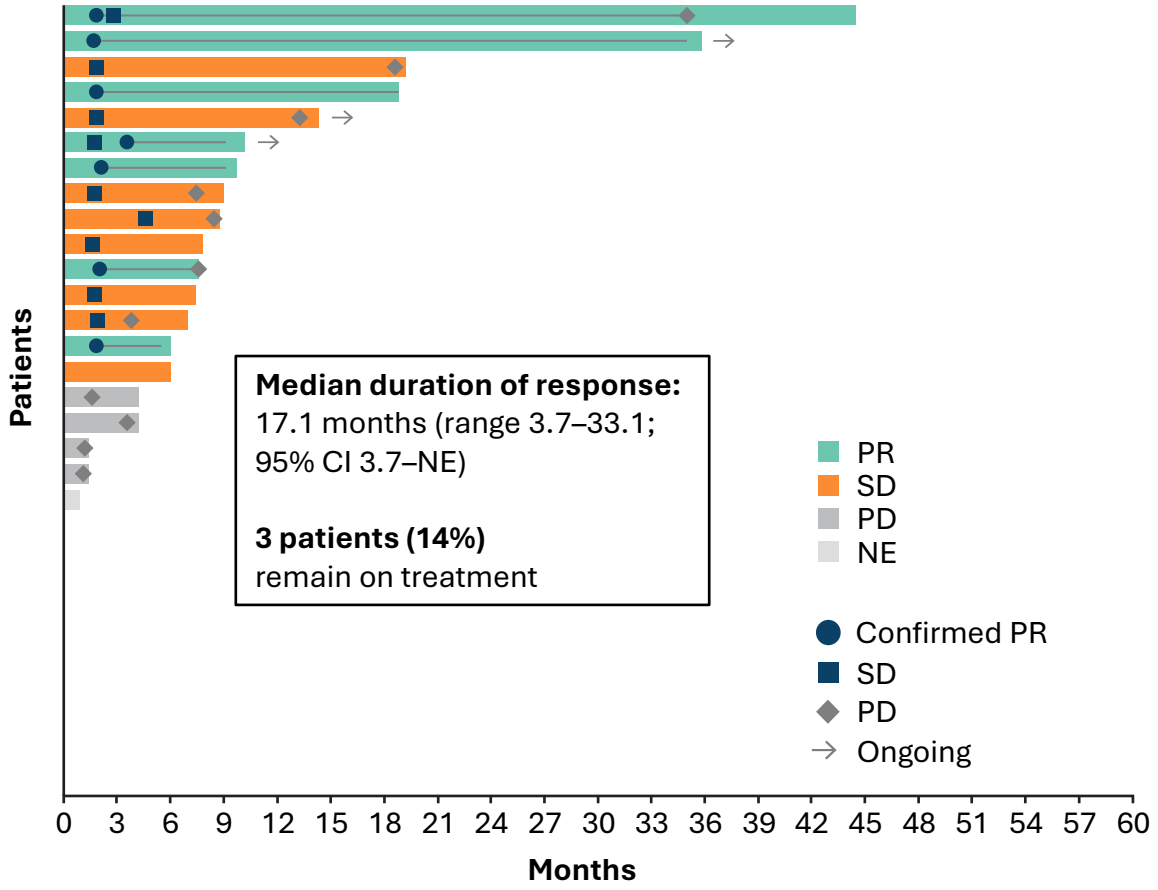


ORR, n (%) [95% CI]: 37 (31) [23–40]
CBR,† n (%) [95% CI]: 70 (58) [49–67]

Data cutoff date: August 4, 2025. Primary efficacy set.
The upper and lower limits of the gray shading indicate 20% growth and 30% shrinkage of target lesions, respectively.
*Data not shown. †Defined as the proportion of patients that demonstrated a CR or PR, or who had SD for ≥24 weeks.
CBR, clinical benefit rate; CI, confidence interval; CR, complete response; NE, not evaluable; *NRG1*+, neuregulin 1 gene fusion positive; NSCLC, non-small cell lung cancer; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

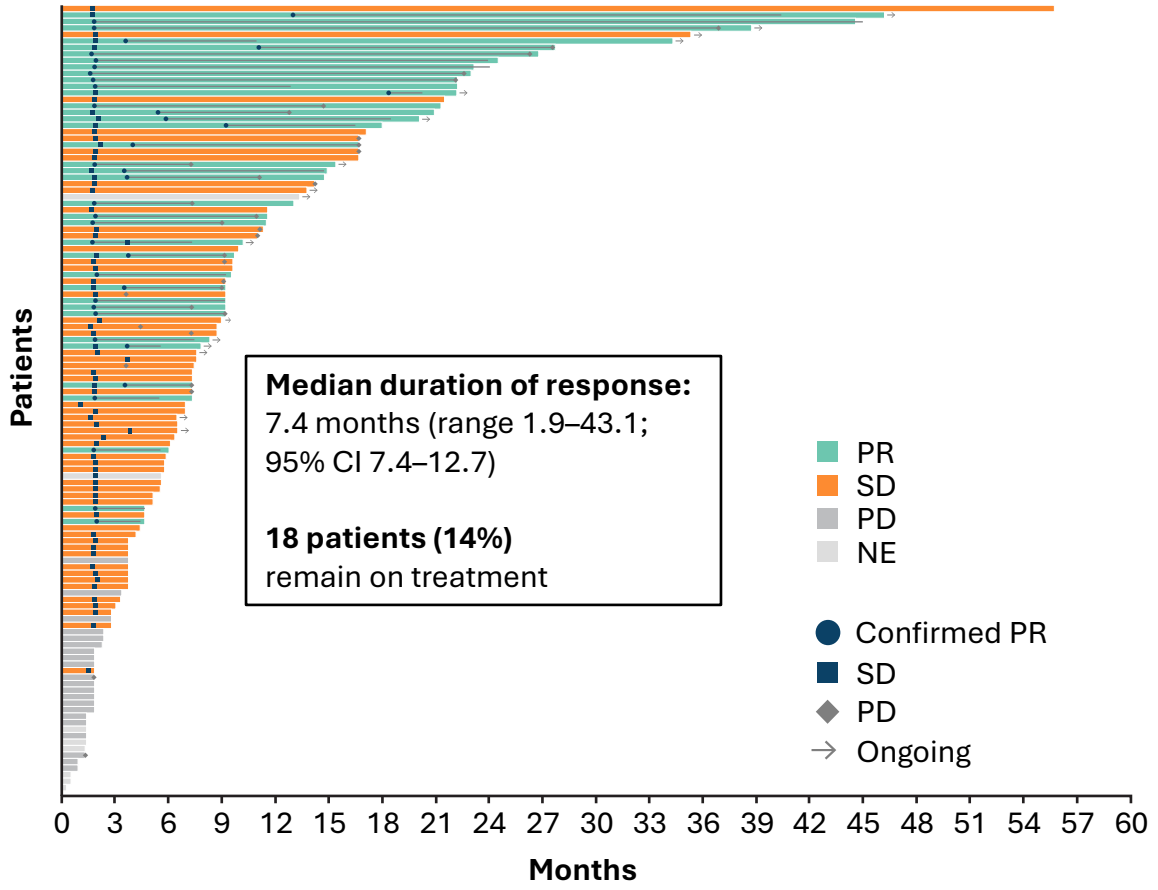
ZENOCUTUZUMAB RESPONSES WERE LONGER IN THE 1L SETTING

Treatment naïve (n=20)



Median duration of exposure: 7.7 months (range 0.9–44.7)
Median time to response: 1.8 months (range 1.7–3.6)

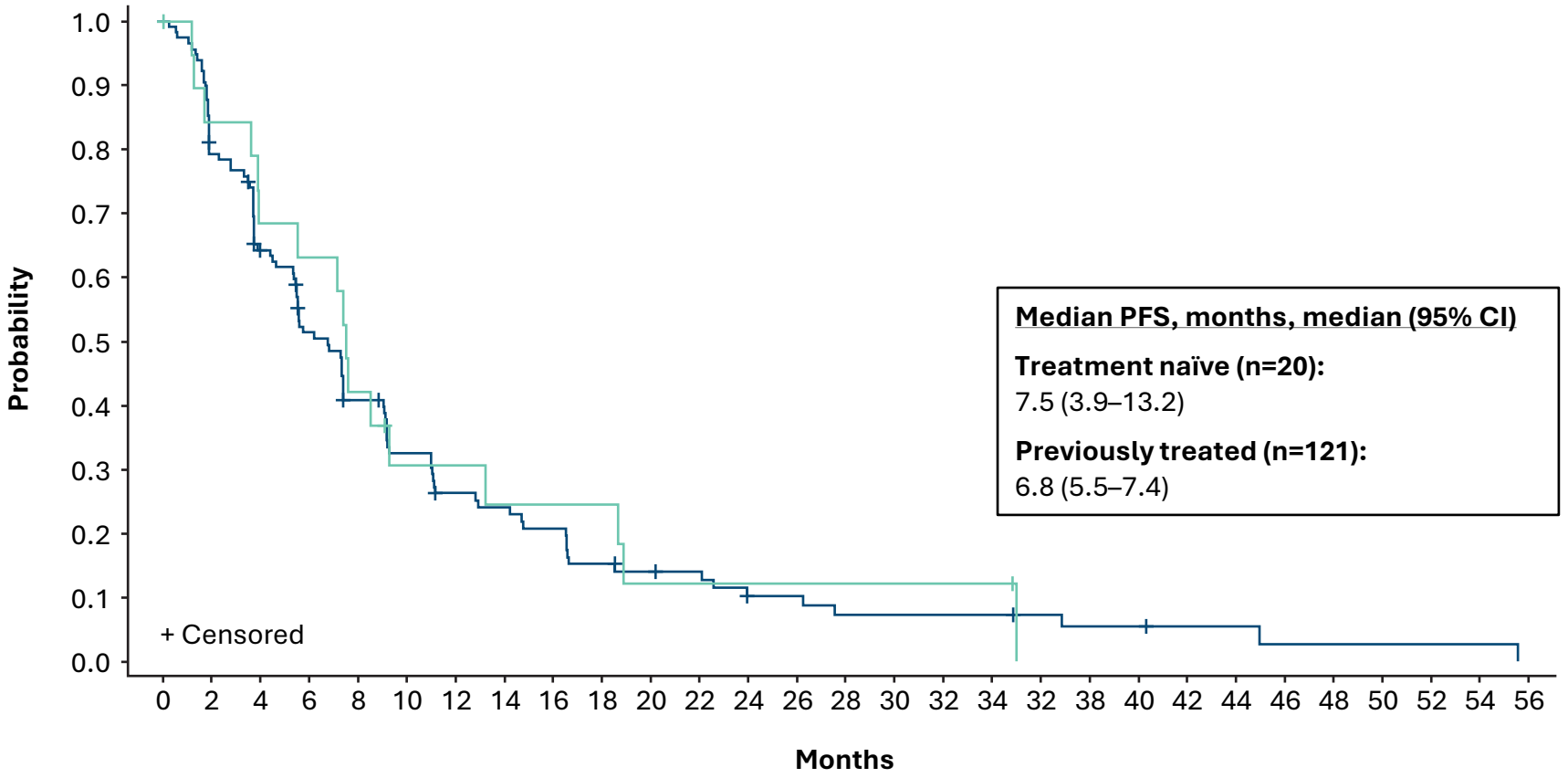
Previously treated (n=121)



Median duration of exposure: 7.3 months (range 0.3–55.6)
Median time to response: 1.9 months (range 1.5–43.1)

Data cutoff date: August 4, 2025. Primary efficacy set.
1L, first-line; CI, confidence interval; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

ZENOCUTUZUMAB DEMONSTRATED CLINICALLY MEANINGFUL MEDIAN PFS IN *NRG1+* NSCLC



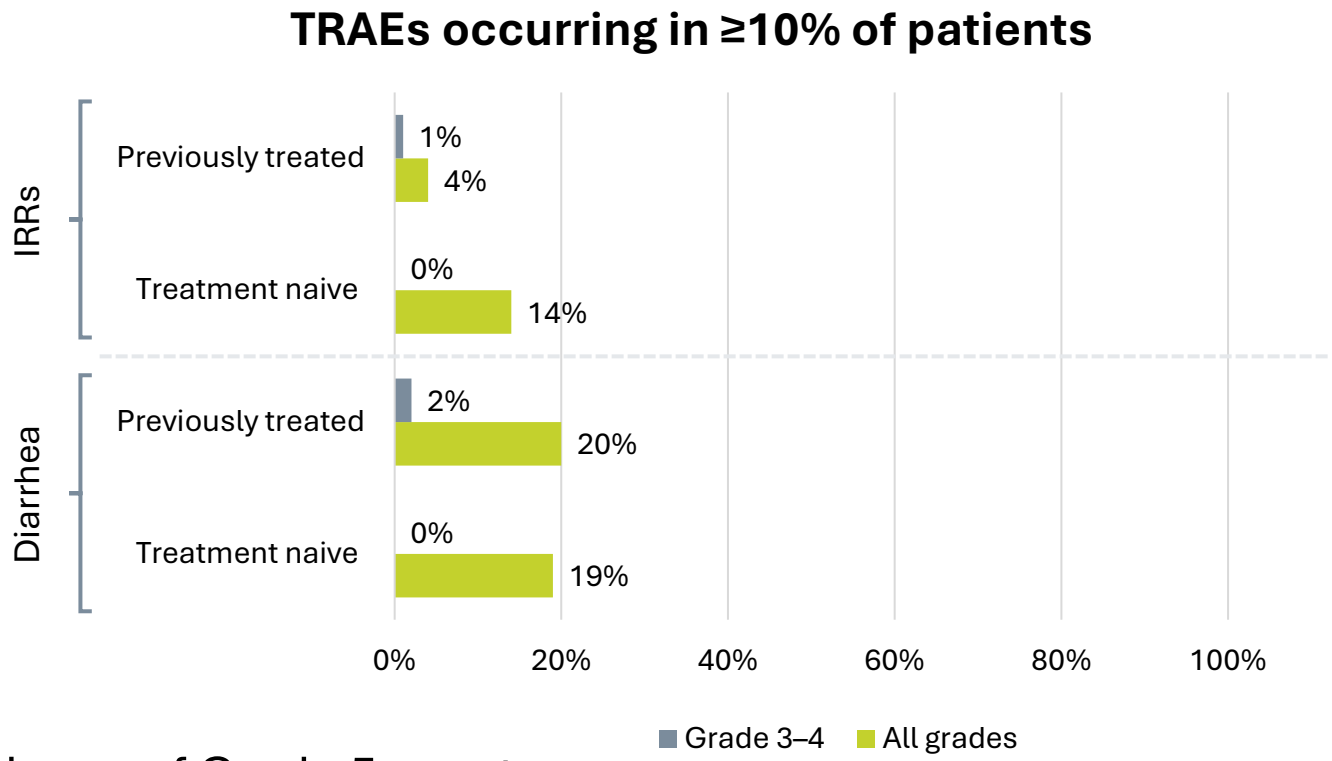
Number of patients at risk

Previously treated	121	91	72	54	41	31	24	22	19	14	12	11	7	7	5	5	5	5	4	3	3	2	2	1	1	1	1	1	0
Treatment naïve	20	16	13	12	8	5	5	4	4	4	2	2	2	2	2	2	2	2	0										

Data cutoff date: August 4, 2025. Primary efficacy set.
CI, confidence interval; *NRG1+*, neuregulin 1 gene fusion positive; NSCLC, non-small cell lung cancer; PFS, progression-free survival.

ZENOCUTUZUMAB DEMONSTRATED A FAVORABLE SAFETY PROFILE

Adverse events, n (%)	Treatment naïve (n=21)		Previously treated (n=133)	
	All grades	Grade 3–4	All grades	Grade 3–4
Patients with ≥1 TRAE	14 (67)	0	94 (71)	7 (5)
Patients with ≥1 serious TRAE	1 (5)	0	3 (2)	1 (1)



- TRAEs were mostly Grade 1 or 2, with no incidence of Grade 5 events
  - Grade 3–4 IRRs were infrequent, with only 1 event occurring in the previously treated group
- In each group, only 1 patient discontinued due to TRAEs*

Data cutoff date: August 4, 2025. Safety analysis set.
*In the treatment-naïve group, 1 patient experienced pneumonitis (Grade 2), which led to treatment discontinuation. In the previously treated group, 1 patient experienced dyspnea (Grade 3), and vomiting and tachycardia (both Grade 1) during their first and only infusion, which led to dose interruption and treatment discontinuation.
IRR, infusion-related reaction; TRAE, treatment-related adverse event.

CONCLUSIONS

- **Zenocutuzumab (BIZENGRI®) received accelerated US FDA approval** for **previously treated, advanced *NRG1*+ NSCLC** and PDAC (December 2024)[1,2]
- **Clinically meaningful early and durable responses** were demonstrated in *NRG1*+ NSCLC in treatment-naïve and previously treated patients, respectively:
  - **ORR:** 35% and 31%
  - **CBR:*** 65% and 58%
  - **Median TTR:** 1.8 and 1.9 months
- **Numerically longer median DOR** in treatment-naïve vs previously treated patients
  - **17.1 months vs 7.4 months**
- **Favorable safety profile** consistent with overall eNRGy trial[3]

Data support the potential role of zenocutuzumab as a 1L therapeutic option in addition to the FDA-approved indication as 2L+ treatment

*Defined as the proportion of patients that demonstrated a CR or PR, or who had SD for ≥24 weeks.
1L, first-line; 2L, second-line; CBR, clinical benefit rate; CR, complete response; DOR, duration of response; FDA, Food and Drug Administration; *NRG1*+, neuregulin 1 gene fusion positive; NSCLC, non-small cell lung cancer; ORR, overall response rate; PDAC, pancreatic adenocarcinoma; PR, partial response; SD, stable disease; TTR, time to response.
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