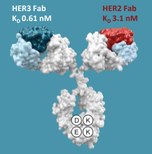
POSTER
595P

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



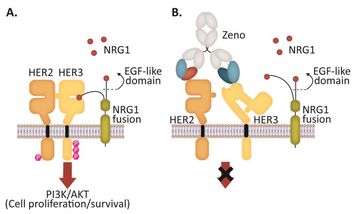
Alison M. Schram,[1] Koichi Goto,[2] Dong-Wan Kim,[3] Antoine Hollebecque,[4] Sun Young Rha,[5] Kazumi Nishino,[6] Michaël Duruisseaux,[7] Kumiko Umemoto,[8] Joon Oh Park,[9] Natasha Leighl,[10] Teresa Macarulla,[11] Stephen V. Liu,[12] Mohammed Najeeb Al Hallak,[13] James Cleary,[14,15] Cindy Neuzillet,[16]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

[1]Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]Department of Thoracic Oncology, National Cancer Center Hospital East, Kashiwa, Japan; [3]Seoul National University Hospital and Seoul National University College of Medicine, Seoul, Republic of Korea; [4]Drug Development (DITEP), GI Oncology, Gustave Roussy Cancer Campus, Villejuif, France; [5]Yonsei Cancer Center, Yonsei University Health System, Seoul, Republic of Korea; [6]Department of Thoracic Oncology, Osaka International Cancer Institute, Osaka, Japan; [7]Department of Respiratory Medicine and Early Phase, Louis Pradel Hospital, Hospices Civils de Lyon Cancer Institute; Cancer Research Centre of Lyon, UMR INSERM 1052 CNRS 5286; Claude Bernard University Lyon 1, University of Lyon, Lyon, France; [8]Department of Clinical Oncology, St. Marianna University School of Medicine, Kawasaki, Japan; [9]Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [10]Princess Margaret Cancer Centre, Toronto, ON, Canada; [11]Vall d'Hebrón University Hospital, Vall d´Hebrón Institute of Oncology (VHIO), Barcelona, Spain; [12]Department of Medicine, Lombardi Comprehensive Cancer Center, Georgetown University, Washington D.C., USA; [13]Barbara Ann Karmanos Cancer Institute, Department of Oncology, Wayne State University School of Medicine, Detroit, MI, USA; [14]Dana-Farber Cancer Institute, Boston, MA, USA; [15]Harvard Medical School, Boston, MA, USA; [16]GI Oncology, Medical Oncology Department, Curie Institute, Versailles-Saint Quentin University, Saint-Cloud, France; [17]Department of Thoracic Oncology, National Cancer Center Hospital, Tokyo, Japan; [18]Merus N.V., Utrecht, The Netherlands; [19]Thoracic Oncology Service, Division of Solid Tumor Oncology, Department of Medicine, Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY, USA.

INTRODUCTION

- Neuregulin 1 (NRG1) is a ligand that binds to human epidermal growth factor receptor (HER) 3, promoting HER2/HER3 heterodimerization and oncogenesis, leading to tumor growth[1,2]
- Chromosomal rearrangements involving *NRG1* are rare oncogenic drivers in a broad range of solid tumors (NRG1+ cancer), including non-small cell lung cancer (NSCLC; in <1% of patients)[3-6]
- *NRG1* fusions may be associated with poor prognosis, including lower response rates to standard therapy, and shorter overall survival in NSCLC[7,8]
- Zenocutuzumab (MCLA-128) is a bispecific antibody that binds to the extracellular domains of HER2 and HER3 (**Figure 1**)[9]
  - Preclinical data demonstrate anticancer activity is due to blocking NRG1:HER3 binding and HER2:HER3 dimerization, which suppresses tumor cell proliferation and survival via the PI3K-AKT-mTOR oncogenic signaling pathway[9,10]
  - *In vitro*, zenocutuzumab also mediates antibody-dependent cellular cytotoxicity (ADCC), eliminating tumor cells[9,10]
- Zenocutuzumab was recently granted Breakthrough Therapy Designations for NRG1+ NSCLC and NRG1+ pancreatic cancer
- Efficacy and safety of zenocutuzumab are being evaluated in patients with advanced NRG1+ cancer in the ongoing, pivotal, phase 2 eNRGy trial and early access program (EAP). Data are presented for patients with NRG1+ NSCLC

Figure 1 | Zenocutuzumab mechanism of action and *in vitro* activity

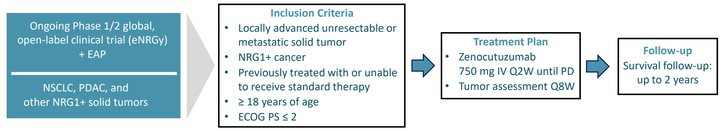


EGF: epidermal growth factor; HER: human epidermal growth factor receptor; NRG1: neuregulin 1; Zeno: zenocutuzumab.
(A) NRG1 fusion proteins function as ligands for HER3 (similar to NRG1) and bind to HER3 with high affinity to promote HER2/HER3 dimerization and downstream signaling.
(B) Zenocutuzumab inhibits the NRG1/HER3 interaction via a "Dock & Block"[9] mechanism, where 1 arm of the antibody binds to the HER2 receptor, optimally positioning the anti-HER3 arm to block the ligand/receptor interaction and prevent HER2/HER3 dimerization.
Figure adapted from Utrecht University Repository, 2017, C. De Nardis. Structural studies of human cell surface receptors: on low-density lipoprotein receptor-related protein 1 and epidermal growth factor receptors 2 and 3. https://dspace.library.uu.nl/handle/1874/354245. Accessed November 1, 2023.

TRIAL DESIGN AND OBJECTIVES

- The eNRGy trial (ClinicalTrials.gov Identifier: NCT02912949) is an ongoing, Phase 1/2, global, open-label, multicenter trial in adult patients with advanced or metastatic NRG1+ solid tumors, including NRG1+ NSCLC (**Figure 2**)
- A concurrent EAP (ClinicalTrials.gov Identifier: NCT04100694) is ongoing and is aligned with the eNRGy trial for eligibility criteria, zenocutuzumab treatment, and efficacy and safety assessment

Figure 2 | Zenocutuzumab NRG1+ cancer development program



Endpoints and Population	Enrollment and Analysis
Primary endpoint ORR[a] using RECIST v1.1 per investigator assessment **Secondary endpoints** DOR,[b] ORR per central review, and safety[c] **Primary analysis population** ≥ 1 dose of zenocutuzumab, opportunity for ≥ 24 weeks of follow-up at the data cutoff date, and met criteria for the primary efficacy population	**Data cutoff date** July 31, 2023 **Enrollment** 105 patients with NRG1+ NSCLC **NSLC primary analysis population** 79 patients 87 patients with ≥ 24 weeks of follow-up[d]; of them, 8 patients were excluded[e] • 2 patients discontinued early for reasons not related to PD • 2 patients with prior anti-HER3 inhibitor • 2 patients with other genetic driver mutation • 1 patient with concomitant anticancer medication use • 1 patient with baseline scan > 5 weeks before the first dose

AE: adverse event; CR: complete response; CTCAE: Common Terminology Criteria for Adverse Events; DOR: duration of response; EAP: early access program; ECOG PS: Eastern Cooperative Oncology Group performance status; HER: human epidermal growth factor receptor; IV: intravenous; MedDRA: *Medical Dictionary for Regulatory Activities*; NRG1: neuregulin 1; NSCLC: non-small cell lung cancer; ORR: overall response rate; PD: progressive disease; PDAC: pancreatic ductal adenocarcinoma; PR: partial response; Q2W: every 2 weeks; Q8W: every 8 weeks; RECIST: Response Evaluation Criteria in Solid Tumors.
[a]Defined as the proportion of patients with a best confirmed response of CR or PR per RECIST v1.1.
[b]Defined as the time from the date of first CR or PR to the date of first PD or death due to trial indication.
[c]AEs were coded using MedDRA v25.0 and graded using CTCAE v4.03.
[d]Patients received the first dose of treatment by February 13, 2023, allowing for the opportunity of ≥ 24 weeks of follow-up at the data cutoff date of July 31, 2023.
[e]Per the statistical analysis plan.

NRG1+ NSCLC PATIENTS

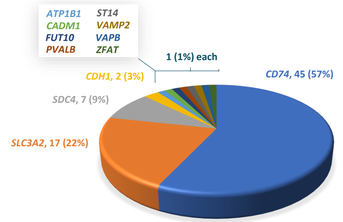
- As of the data cutoff date of July 31, 2023, 79 of the 87 patients treated with zenocutuzumab were included in the primary efficacy population
- Patient demographic and disease characteristics are shown in **Table 1**
- Median age was 64 years (range, 32–88)
- Patients had a median of 1 prior line of systemic therapy (range, 0–6); 72% of patients had received prior platinum-based therapy and 11% had received prior afatinib therapy
- The most frequently detected fusion partner was *CD74* (57%; **Figure 3**)
- Median duration of exposure was 7.4 months (range, 0–36)
- Twenty (25%) patients remained on therapy at the data cutoff date
- Among patients who had discontinued therapy, most (58/79 patients [73%]) had discontinued due to disease progression (radiological or clinical), including 2 patients who died

Table 1 | Demographics and prior therapy (primary efficacy population)

Characteristic	N = 79
Age, years, median (range)	64 (32–88)
Gender, 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 disease 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)

ECOG PS: Eastern Cooperative Oncology Group performance status; PD: progressive disease.
[a]Native Hawaiian or 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.

Figure 3 | *NRG1* fusion partners (primary efficacy population; N = 79)



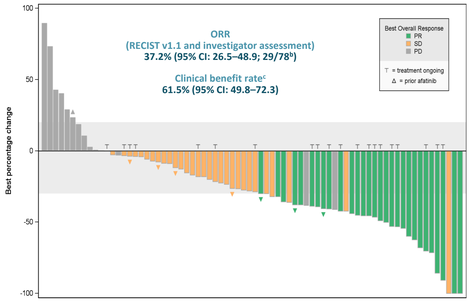
NRG1 identification technology, n (%)	
RNAseq	64 (81)
DNAseq	11 (14)
Nanostring	1 (1)
Missing	3 (4)

DNAseq: DNA sequencing; NRG1: neuregulin 1; RNAseq: RNA sequencing.

ANTITUMOR ACTIVITY IN NRG1+ NSCLC

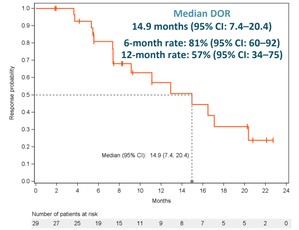
- The confirmed **overall response rate (ORR) was 37.2%** (95% CI: 26.5–48.9) by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 per investigator assessment; all responses were partial responses (**Figure 4**)
- The median duration of response (DOR) was 14.9 months (95% CI: 7.4–20.4) by RECIST v1.1 per investigator assessment (**Figure 5**)
- 20 of 79 patients (25%) were continuing to receive treatment at the data cutoff date (**Figure 6**)
- A case study of a patient with NSCLC adenocarcinoma carrying a *CD74-NRG1* gene fusion is shown in **Figure 7**

Figure 4 | Best percent change in sum of target lesion diameter from baseline[a]



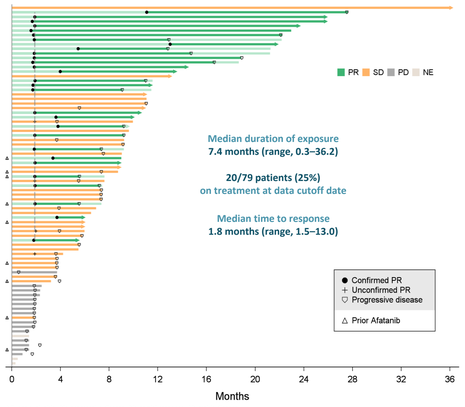
CI: confidence interval; ORR: overall response rate; PD: progressive disease; PR: partial response; RECIST: Response Evaluation Criteria in Solid Tumors; SD: stable disease.
[a]Excludes 4 patients: 3 due to absence of postbaseline tumor assessment and 1 due to incomplete assessment of target lesion at first postbaseline assessment.
[b]1 patient with non-measurable disease was excluded from the analysis.
[c]Clinical benefit rate defined as the proportion of patients in whom a CR, PR, or SD was observed (where SD duration was ≥ 12 weeks).

Figure 5 | Duration of response



CI: confidence interval; DOR: duration of response.

Figure 6 | Time to response and time on therapy[a]



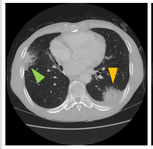
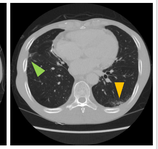
NE: not evaluable; PD: progressive disease; PR: partial response; SD: stable disease.
[a]Time on therapy is defined as treatment duration plus 2 weeks (with possible limitation from data cutoff date or death). Arrows indicate treatment is ongoing at the data cutoff date.

Figure 7 | Patient case study

65-year-old Asian male with NSCLC adenocarcinoma carrying a *CD74-NRG1* gene fusion

Baseline status	ECOG PS 1 Lung and bone metastases
Prior treatment	1. Cisplatin/vinorelbine (adjuvant) 2. Carboplatin/gemcitabine 3. Atezolizumab 4. Docetaxel/dostarlimab
Zenocutuzumab	25 cycles (ongoing at the data cutoff date)
Postbaseline evaluation per RECIST v1.1	BOR: Partial response with **53% reduction** in target lesions (left lower lobe lung mass, right lower lobe lung metastasis)

Clinical results

Baseline	Cycle 11
	

BOR: best overall response; ECOG PS: Eastern Cooperative Oncology Group performance status; NRG1: neuregulin 1; NSCLC: non-small cell lung cancer; RECIST: Response Evaluation Criteria in Solid Tumors. Arrowheads indicate target lesions.

SAFETY PROFILE

- 189 NRG1+ cancer patients treated with zenocutuzumab 750 mg Q2W monotherapy (**Table 2**)[a]
- Low incidence of grade 3 or 4 treatment-related treatment-emergent adverse events (TEAEs)
- No patient discontinued zenocutuzumab due to treatment-related TEAEs
- No grade 5 treatment-related TEAEs
- Infusion-related reactions[b] occurred in 23 of 189 (12%) patients, with no grade 3 or greater events

Table 2 | Safety profile in NRG1+ cancer patients (N = 189)[a]

	Related TEAEs (≥10% and all grades 3-4) n (%)		TEAEs irrespective of causality (≥10% and all grades 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 (7)	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)

ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyltransferase; NRG1: neuregulin 1; Q2W: every 2 weeks; TEAE: treatment-emergent adverse event.
[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.

CONCLUSIONS

- **Durable responses in previously treated advanced NRG1+ NSCLC**
  - ORR: 37.2% (95% CI: 26.5–48.9; N = 78)
  - Median DOR: 14.9 months (95% CI: 7.4–20.4)
  - Clinical activity in patients with prior afatinib exposure
- **Extremely well tolerated safety profile**
  - Most TEAEs were grade 1 or 2 in severity
  - No treatment-related discontinuations
- **Zenocutuzumab represents potential first and best in class therapy for patients with NRG1+ NSCLC**
  - Significant unmet medical need
  - Currently no approved targeted therapy for NRG1+ cancer

References

1. Werr L, et al. *Mol Cancer Ther*. 2022;21(5):821-830.
2. Fernandez-Cuesta L, et al. *Cancer Discov*. 2014;4(4):415-422.
3. Jonna S, et al. *Clin Cancer Res*. 2019;25(16):4966-4972.
4. Schram AM, et al. *J Clin Oncol*. 2019;37(suppl 15):3129.
5. Gupta R, et al. *J Clin Oncol*. 2023;41(suppl 26):3132.
6. Benayed R, et al. *Clin Cancer Res*. 2019;25(15):4712-4722.
7. Drilon A, et al. *J Clin Oncol*. 2021;39(25):2791-2802.
8. Chang J, et al. *Clin Cancer Res*. 2021;27(14):4066-4076.
9. Geuijen CAW, et al. *Cancer Cell*. 2018;33(5):922-936.
10. Schram AM, et al. *Cancer Discov*. 2022;12(5):1233-1247.

Acknowledgments

We thank the patients who participated in the eNRGy trial or EAP and their families; trial coinvestigators, research nurses, and coordinators at each clinical site; and Viktoriya Stalbovskaya, Jim Ford, and Maria Divinney (Merus N.V.). Medical writing support was provided by Alex Pilote, PhD, of Lumanity Communications Inc., and was funded by Merus N.V.

Funding

The eNRGy trial was sponsored by Merus N.V.

Presenting Author Disclosures

AS received research funding (paid to institution) from Merus N.V., Amgen Inc., Amgen K.K., Amgen Astellas BioPharma K.K., Bayer Yakuhin Ltd., Boehringer Ingelheim Japan Inc., Bristol Myers Squibb K.K., Blueprint Medicines Corporation, Ono Inc., Daiichi Sankyo Co. Ltd., Eisai Co. Ltd., Eli Lilly Japan K.K., Hoihe Biopharma Co. Ltd., Ignyta Inc., Janssen Pharmaceutical K.K., Kissei Pharmaceutical Co. Ltd., Kyowa Kirin Co. Ltd., Life Technologies Japan Ltd., Loxo Oncology Inc., LSI Medicine Corporation, Medical & Biological Laboratories Co. Ltd., Merck Biopharma Co. Ltd., MSD K.K., Novartis Pharma K.K., Ono Pharmaceutical Co. Ltd., Pfizer Japan Inc., Pfizer R&D Japan G.K., Precision Medicine Asia Co. Ltd., Riken Genesis Co. Ltd., Sumitomo Pharma Co. Ltd., Taiho Pharmaceutical Co. Ltd., Takeda Pharmaceutical Co. Ltd., and Yakult Honsha Co. Ltd.; **KG** received research funding (paid to institution) from Amgen Inc., Amgen K.K., Array Biopharma Inc., Astellas Pharma Inc., Bayer Yakuhin Ltd., Boehringer Ingelheim Japan Inc., Daiichi Sankyo Co. Ltd., Eisai Co. Ltd., Eli Lilly Japan K.K., Guardant Health Inc., Hoihe Biopharma Co. Ltd., Janssen Pharmaceutical K.K., Medpace Japan K.K., Merck Biopharma Co. Ltd., Nippon Kayaku Co. Ltd., Novartis Pharma K.K., Ono Pharmaceutical Co. Ltd., Otsuka Pharmaceutical Co. Ltd., Riken Genesis Co. Ltd., Taiho Pharmaceutical Co. Ltd., and Takeda Pharmaceutical Co. Ltd.; and served on a data safety monitoring board or advisory board for Amgen Inc., Amgen K.K., Daiichi Sankyo Co. Ltd., and Eli Lilly Japan K.K.