Authors: Liu, Stephen V.;[1] Agarwal, Muskan;[1] Goto, Koichi;[2] Nishino, Kazumi;[3] Tsang, Erica S.;[4] Duruisseaux, Michael;[5] Signorelli, Diego;[6] Kim, Dong-Wan;[7] Rha, Sun Young;[8] Hollebecque, Antoine;[9] Park, Joon O.;[10] Springfeld, Christoph;[11] Furuya, Naoki;[12] Rodon, Jordi;[13] Nagasaka, Misako;[14] Ragsdale, Carolyn E.;[15] Garner, Fiona;[15] Adeyemi, Shola;[16] Jauhari, Shekeab;[16] Schram, Alison M.[17]

Institutions: [1]Georgetown University Department of Medicine, Washington DC, DC, USA; [2]National Cancer Center Hospital East, Kashiwa, Japan; [3]Osaka International Cancer Institute, Osaka, Japan; [4]Princess Margaret Cancer Center, Toronto, ON, Canada; [5]Hospices Civils de Lyon, Centre Hospitalier Universitaire de Lyon, Lyon, France; [6]Niguarda Cancer Centre, Milan, Italy; [7]Seoul National University Hospital, Seoul, South Korea; [8]Severance Hospital - Yonsei Cancer Center, Seoul, South Korea; [9]Gustave Roussy, Villejuif, France; [10]Samsung Medical Center, Seoul, South Korea; [11]Heidelberg University Hospital, Heidelberg, Germany; [12]St. Marianna University Hospital, Kawasaki, Japan; [13]Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [14]University of California Irvine Medical Center, Orange, CA, USA; [15]Partner Therapeutics, Inc., Lexington, MA, USA; [16]Merus N.V., Utrecht, Netherlands; [17]Memorial Sloan Kettering Cancer Center, New York, NY, USA

Presenting author and email: Stephen V. Liu, stephen.v.liu@gunet.georgetown.edu

TITLE (23/75):

Efficacy and Safety of Zenocutuzumab, a HER2/HER3 Bispecific Antibody, in Treatment-Naive, Advanced *NRG1+* NSCLC: Updated Analysis from the Ongoing Phase 2 eNRGy Trial

ABSTRACT (498/500 words [398 text + 100 for table]):

Background

Patients with advanced non-small cell lung cancer (NSCLC) who receive frontline targeted therapy generally have favorable outcomes compared with patients receiving non-targeted therapies. Neuregulin 1 (*NRG1*) gene fusions are rare oncogenic drivers in NSCLC, best identified via tissue-based RNA sequencing. Tumors with *NRG1* fusions are associated with a poor prognosis and demonstrate limited response to standard first-line chemoimmunotherapy. Zenocutuzumab, a HER2/HER3 bispecific antibody, was recently granted accelerated FDA approval for previously treated, advanced *NRG1+* NSCLC and pancreatic adenocarcinoma. By blocking HER3–NRG1 interactions and preventing HER2/HER3 dimerization, zenocutuzumab inhibits key oncogenic pathways. We report a *post hoc* analysis of treatment-naive patients with *NRG1+* NSCLC treated with zenocutuzumab in the ongoing phase 2 eNRGy trial.

Methods

eNRGy (NCT02912949) is an ongoing, open-label, single-arm, phase 2 study of zenocutuzumab in advanced *NRG1+* cancers. Eligible patients are aged ≥18 years, have measurable or evaluable disease per RECIST v1.1, ECOG PS ≤2, and have been previously treated, unless considered unlikely to tolerate or benefit from standard therapy. Zenocutuzumab 750 mg is administered intravenously every 2 weeks until disease progression or unacceptable toxicity. The primary endpoint is investigator-assessed objective response rate per RECIST v1.1. Secondary endpoints include duration of response, time to response, clinical benefit rate (defined as partial/complete response, or stable disease for ≥24 weeks), progression-free survival, and frequency/nature of adverse events.

Results

As of August 2025, 154 patients with advanced *NRG1+* NSCLC were enrolled, of which 21 were treatment naive and 133 were previously treated. Median age was 67 years, 64% were female, 32%/61%/6% had ECOG PS 0/1/2, 98% had adenocarcinoma, and 14% had brain metastases. Baseline characteristics were comparable between groups. Patients in the previously treated group received a median of one prior line of systemic therapy in the metastatic setting (range 0–4). Outcome data are presented in the Table. Overall response rate and time to response were similar between groups. Notably, median duration of response was longer in the treatment-naive versus previously treated group. All-grade treatment-related adverse events (TRAEs) were similar between groups, and one patient in each group discontinued due to TRAEs.

Conclusion

Zenocutuzumab demonstrated clinically meaningful early and durable responses in *NRG1+* NSCLC. Duration of response was longer in patients who were treatment naive versus previously treated. The safety profile remains favorable and consistent with the overall patient population. These data support the potential role of zenocutuzumab as a first-line therapeutic option in *NRG1+* NSCLC.

Table | Zenocutuzumab efficacy and safety outcomes in patients with *NRG1+* NSCLC

Outcomes (primary efficacy set*)	Treatment naive (n=20)		Previously treated (n=121)	
Overall response rate (CR or PR), n (%)	7 (35)		37 (31)	
95% CI	15.4–59.2		22.5–39.6	
Best overall response, n (%)				
CR	0 (0)		0 (0)	
PR	7 (35)		37 (31)	
SD	8 (40)		55 (46)	
PD	4 (20)		21 (17)	
NE	1 (5)		8 (7)	
Clinical benefit rate,[†] n (%)	13 (65)		70 (58)	
95% CI	40.8–84.6		48.5–66.8	
Time to response (months), median (range)	1.8 (1.7–3.6)		1.9 (1.5–18.3)	
Duration of response (months), median (range)	17.1 (3.7–33.1)		7.4 (1.9–43.1)	
95% CI	3.7–NE		7.4–12.7	
Median PFS (months)	7.5		6.8	
95% CI	3.9–13.2		5.5–7.4	
Outcomes (safety analysis set*)	**Treatment naive (n=21)**		**Previously treated (n=133)**	
	All grades	**Grade 3–4**	**All grades**	**Grade 3–4**
Patients with ≥1 TRAE, n (%)	14 (67)	0 (0)	94 (71)	7 (5)
TRAEs in >10% of patients, n (%)				
Diarrhea	4 (19)	0 (0)	26 (20)	2 (2)
Infusion-related reaction	3 (14)	0 (0)	5 (4)	1 (1)
TRAEs leading to discontinuation, n (%)	1 (5) [pneumonitis]		1[‡] (1) [dyspnea, vomiting, tachycardia]	

*Safety analysis set is defined as all patients who received ≥1 dose of zenocutuzumab. Primary efficacy set excluded patients with other known oncogenic driver mutations or patients treated with other anti-HER3–directed therapies; 1 treatment-naive patient and 12 patients in the prior therapy group were excluded from efficacy analyses.
[†]Defined as the proportion of patients that demonstrated a CR or PR, or who had SD for ≥24 weeks.
[‡]One patient experienced treatment-related dyspnea (Grade 3), and vomiting and tachycardia (both Grade 1) during their first and only infusion, which led to dose interruption and treatment discontinuation.
CI, confidence interval; CR, complete response; HER3, human epidermal growth factor receptor 3; NE, not estimable; *NRG1+*, neuregulin 1 gene fusion positive; NSCLC, non-small cell lung cancer; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; TRAE, treatment-related adverse event.

Authorship disclosures

- **Stephen V. Liu** 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 N.V., Mirati Therapeutics, MSD Oncology, Natera, Novartis, OSE Immunotherapeutics, Pfizer, RAPT Therapeutics, Regeneron, Revolution Medicines, Takeda, and Yuhan. His institution received research funding from AbbVie, Alkermes, AstraZeneca, Bristol Myers Squibb Foundation, Cogent Biosciences, Duality Biologics, Elevation Oncology, Ellipses Pharma, Genentech/Roche, Gilead Sciences, Merck, Merus N.V., Nuvalent, Inc., Nuvation, OSE Immunotherapeutics, Partner Therapeutics, Inc., Puma Biotechnology, RAPT Therapeutics, and SystImmune; and he had uncompensated relationships with Roche/Genentech.
- **Muskan Agarwal** has no relationships to disclose.
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- **Diego Signorelli** has received honoraria from Amgen, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi, Johnson & Johnson, MSD, Novartis, Pfizer, Pierre Fabre, Roche, Sanofi, Takeda
- **Dong-Wan Kim**'s institution received research funding from Alpha Biopharma, Amgen, AstraZeneca/MedImmune, Boehringer Ingelheim, BridgeBio Pharma, Chong Kun Dang Pharmaceutical, Daiichi Sankyo, GSK, Hanmi, IMBdx, inno.N, Janssen, Merck, Merus N.V., Mirati Therapeutics, MSD, Novartis, Ono Pharmaceutical, Partner Therapeutics, Inc., Pfizer, Roche/Genentech, Takeda, TP Therapeutics, Xcovery, Yuhan, and Zymeworks.
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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.
- **Joon O. Park** has received grants or contracts from ABL Bio, Bristol Myers Squibb (Celgene), Eutilex, MedPacto, and Servier; consulting fees from AstraZeneca, Immunoncia, Intocell, and Merck Sereno; and support for attending meetings and/or travel from Minneamrita Therapeutics and advisory boards with Adicet Bio, Arcus Biosciences, and MediRma. His institution has received research funding from Merus N.V. and Partner Therapeutics, Inc.
- **Christoph Springfeld** has received payment/honoraria for lectures from Roche; support for travel from Servier; and has received payment for advisory board participation from AstraZeneca, Bayer, Bristol Myers Squibb, Incyte, Merck Sharp & Dohme, Revolution Medicines, and Taiho. His institution has received research funding from Merus N.V. and Partner Therapeutics, Inc.
- **Naoki Furuya** has no relationships to disclose.
- **Jordi Rodon** has received consulting or advisory board compensation from AADi, Amgen, BridgeBio Pharma, Ellipses Pharma, iOnctura, Mekanistic Therapeutics, Merus N.V., Monte Rosa Therapeutics, and Sardona Therapeutics; travel, accommodations, or expense payments from 280 Bio, American Society of Clinical Oncology (ASCO), Dava Oncology, European Society for Medical Oncology, Loxo, National Taiwan University Cancer Center, and STOP Cancer; and whose institution received research funding from Partner Therapeutics, Inc. Other relationships include Boxer Capital, Chinese University of Hong Kong, Guidepoint Pharmacy, Sequenom, Tang Advisors, and Vall d'Hebron Institute of Oncology/Ministerio de Empleo y Seguridad Social.
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- **Carolyn E. Ragsdale** and **Fiona Garner** are employees of and have stock options for Partner Therapeutics, Inc.
- **Shola Adeyemi** and **Shekeab Jauhari** are employees and have stock options for Merus N.V.
- **Alison M. Schram** has received advisory board compensation from Day One Biopharmaceuticals, Endeavor Biotherapeutics, Mersana Therapeutics, Merus N.V., PMV Pharmaceuticals, Relay Therapeutics, Repare Therapeutics, Revolution Medicines, and Schrödinger.; has consulted for Blueprint Bio, Flagship Pioneering, Pro-Clin Solutions LLC, and Redona Therapeutics; and has research funding paid to her institution from AstraZeneca, ArQule, BeiGene/SpringWorks Therapeutics, Black Diamond Therapeutics, Boehringer Ingelheim, Elevation Oncology, Eli Lilly and Company, Kura Oncology, Merus N.V., Northern Biologics, Partner Therapeutics, Inc., Pfizer, PMV Pharmaceuticals, Relay Therapeutics, Repare Therapeutics, Revolution Medicines, and Surface Oncology. She would like to acknowledge support from the ASCO Conquer Cancer Foundation Career Development Award (CDA), National Cancer Institute (NCI) P30CA008748 Cancer Clinical Investigator Team Leadership Award (CCITLA), Cycle for Survival, and Memorial Sloan Kettering Cancer Center Support Grant (P30 CA008748).

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