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Title (23/75 maximum):

Continued treatment beyond progression with zenocutuzumab, a HER2/HER3 bispecific antibody, in patients with *NRG1*+ NSCLC: Analysis from the ongoing phase 2 eNRGy trial

Abstract (300+100 for table+100 for figure = 500/500 maximum):

Background

Progressive disease is often considered a surrogate for treatment failure in clinical trials. However, continued treatment beyond progression may offer benefit for patients with oligoprogression, mixed response, or indolent progression who have limited treatment options. Zenocutuzumab, a HER2/HER3 bispecific antibody that blocks HER3-mediated NRG1 signaling and HER2/HER3 dimerization, is the only FDA-approved targeted therapy for previously treated, advanced *NRG1*+ non-small cell lung cancer (NSCLC) and pancreatic adenocarcinoma. We report an analysis of patients with advanced *NRG1*+ NSCLC who continued zenocutuzumab beyond progression.

Methods

eNRGy (NCT02912949) is an ongoing, open-label, single-arm, phase 2 trial of zenocutuzumab in patients with advanced *NRG1*+ cancers. Patients are ≥18 years, previously treated with or ineligible for other therapies, ECOG PS ≤2, and have measurable or evaluable disease (RECIST v1.1). Zenocutuzumab is administered (750 mg IV every 2 weeks) until progression or unacceptable toxicity. Treatment continuation beyond radiographic (RECIST) progression is permitted if ongoing clinical benefit is considered possible by the investigator. This *post hoc* analysis includes patients with *NRG1*+ NSCLC who received ≥3 doses of zenocutuzumab beyond progression.

Results

As of August 2025, 27 patients with advanced *NRG1*+ NSCLC continued zenocutuzumab beyond progression (Table). Treatment remains ongoing in four patients. Median (range) total zenocutuzumab exposure increased to 9.9 (3.3–44.7) from 7.3 (0.5–36.8) months prior to progression (Figure). Eight

patients were treated >6 months post-progression (6–9 months n=4, >9–23 months n=3, and >23 months [ongoing] n=1). Common treatment-related adverse events (≥10%) included diarrhea and paronychia; none were serious. No patient discontinued treatment due to adverse events.

Conclusions

Zenocutuzumab treatment beyond progression was well tolerated and provided meaningful clinical benefit in select patients with *NRG1+* NSCLC. Some patients benefited from local therapy for progressing lesions, permitting continuation of zenocutuzumab. These findings support continued zenocutuzumab treatment beyond progression as a potential viable option.

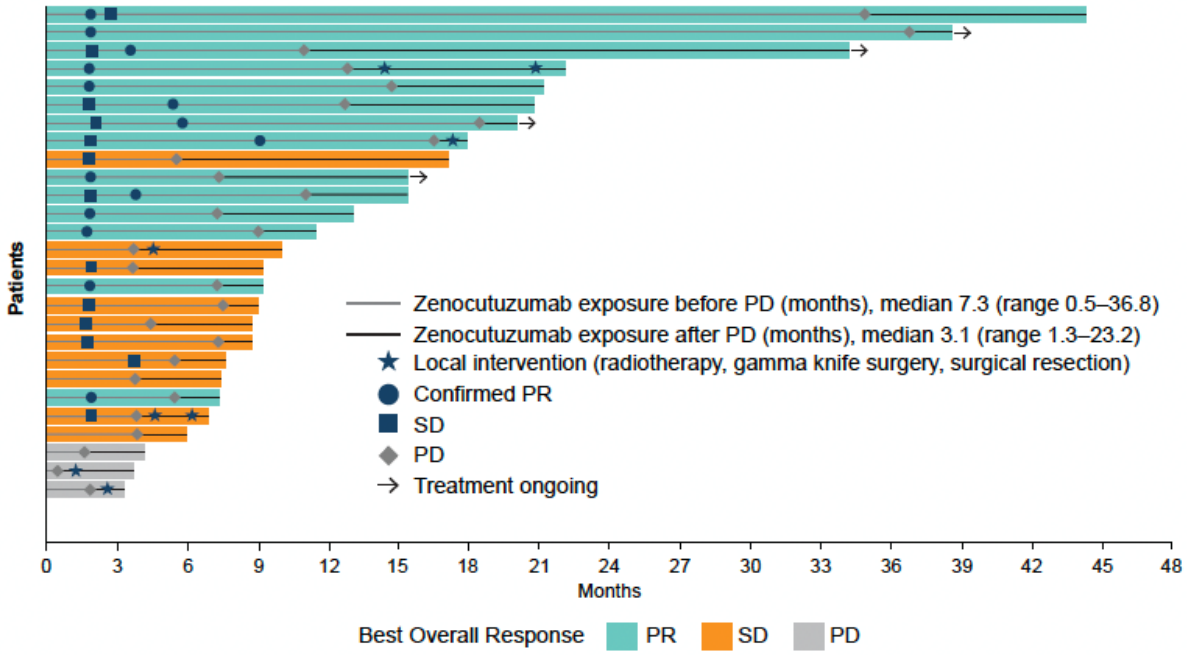
Table | Demographics, initial zenocutuzumab response, and progression details in patients with *NRG1+* NSCLC continuing treatment beyond progression

Characteristic	N=27
Age (years), median (range)	64.0 (39–80)
Sex, female, n (%)	19 (70)
Race, n (%)	
Asian / White / not reported	16 (59) / 7 (26) / 4 (15)
ECOG PS, n (%)	
0 / 1 / 2	11 (41) / 15 (56) / 1 (4)
Histologic diagnosis, n (%)	
Adenocarcinoma	26 (96)
Squamous cell carcinoma	1 (4)
Metastases, n (%)	
Visceral metastases	24 (89)
Non-visceral metastases	2 (7)
Months since metastatic diagnosis at study entry, median (range)	7.5 (1.4–43.3)
Number of prior systemic therapies in metastatic setting, median (range)	1 (0–4)
Overall response rate during initial zenocutuzumab treatment period, n (%) [95% CI]*	14 (52) [32–71]
Time to initial zenocutuzumab response (months), median (range)	1.8 (1.7–9.2)
Duration of initial zenocutuzumab response (months), median (range)	7.4 (3.6–35.1)
Progression pattern during treatment with zenocutuzumab, n (%)	
Oligoprogression†	22 (81)
Diffuse progression‡	5 (19)
Progression including brain metastases, n (%)	5§ (19)
Patients receiving local therapy adjunct to zenocutuzumab, n (%)	6 (22)

*Best overall response per RECIST v1.1 by investigator assessment: 14 PR, 10 SD, 3 PD; 4 had SD ≥24 weeks. †Defined as ≤3 lesions and ≤2 sites. ‡Defined as >3 lesions or >2 sites. §CNS lesions included 4 new lesions (3 oligoprogression and 1 diffuse progression) and 1 target lesion (1 oligoprogression).

CI, confidence interval; CNS, central nervous system; ECOG PS, Eastern Cooperative Group performance status; *NRG1+*, neuregulin 1 gene fusion positive; NSCLC, non-small cell lung cancer; PD, progressive disease; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease.

Figure | Zenocutuzumab exposure in patients with *NRG1+* NSCLC continuing treatment beyond progression



NRG1+, neuregulin 1 fusion positive; NSCLC, non-small cell lung cancer; PD, progressive disease; PR, partial response; SD, stable disease.

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