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

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Declaration of Interests

Alison M. Schram

- Advisory boards: Mersana, and Merus N.V., Relay Therapeutics
- Consultant: Blueprint Bio, Flagship Pioneering, Redona Therapeutics
- Steering committees: Merus N.V. and Pfizer
- Research funding (institutional): AstraZeneca, ArQule, BeiGene/SpringWorks, Black Diamond Therapeutics, Elevation Oncology, Kura, Lilly, Merus N.V., Northern Biologics, Pfizer, PMV Pharma, Relay Therapeutics, Repare Therapeutics, Revolution Medicines, and Surface Oncology
- Food and beverage: PUMA and Repare Therapeutics
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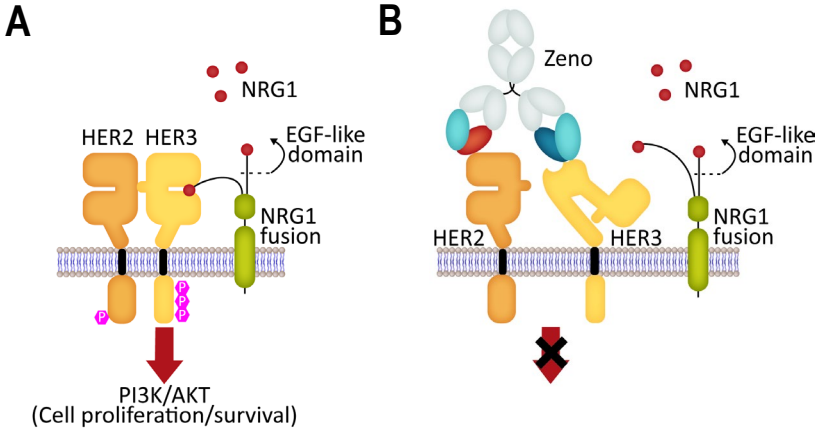
Background

Zenocutuzumab is a Novel Bispecific Antibody Targeting NRG1+ Cancer

- Neuregulin 1 (NRG1) is a ligand that binds to HER3, 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 NSCLC (in <1% of patients)[3,4,5,6]
- *NRG1* fusions may be associated with poor prognosis, including lower response rates to standard therapy, and shorter overall survival in NSCLC[7,8]

***NRG1* Fusion Signaling and Zenocutuzumab Mechanism of Action**



- Zenocutuzumab is a bispecific antibody that binds to the extracellular domains of HER2 and HER3
  - Preclinical data demonstrate anticancer activity is due to blocking NRG1:HER3 binding and HER2:HER3 dimerization, suppressing 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

Figure reprinted from *Cancer Cell*, Vol 33, Geuijen CAW, et al. Unbiased combinatorial screening identifies a bispecific IgG1 that potently inhibits HER3 signaling via HER2-guided ligand blockade, Pages 922-936, Copyright (2018), with permission from Elsevier. ADCC, antibody-dependent cellular cytotoxicity; EGF, epidermal growth factor; HER2/3, human epidermal growth factor receptor 2/3; NRG1, neuregulin 1; NSCLC, non-small cell lung cancer; Zeno, zenocutuzumab.

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4. Schram AM, *et al. J Clin Oncol.* 2019;37(suppl 15):3129. 5. Gupta B, et al. *J Clin Oncol* 2023;41(suppl 26):3132-3132. 6. Benayed R, et al. *Clin Cancer Res.* 2019;25(15):4712-4722.
7. Drilon A, et al. *J Clin Oncol.* 2021; 39:2791-2802. 8. Chang J, et al. *Clin Cancer Res.* 2021;27(14):4066-4076. 9. Schram AM, et al. *Cancer Discov.* 2022;12(5):1233-1247.
10. Geuijen CAW, et al. *Cancer Cell.* 2021;39(8):1163-1164.

Schema

Global, Multicenter Zenocutuzumab NRG1+ Cancer Development Program

Ongoing phase 1/2 global, open-label clinical trial (eNRGy) + Early Access Program (EAP)

NSCLC, PDAC[a], and other solid tumors

Inclusion Criteria

- Locally advanced unresectable or metastatic solid tumor
- NRG1+ cancer
- Previously treated with or unable to receive standard therapy
- ≥ 18 years of age
- ECOG PS ≤ 2

Treatment Plan

- Zenocutuzumab 750 mg IV Q2W until PD
- Tumor assessment Q8W

Follow-up

Survival follow-up: up to 2 years

Endpoints and Population

Primary endpoint

Overall response rate (ORR)[b] using RECIST v1.1 per investigator assessment

Secondary endpoints

Duration of response (DOR)[c], ORR per central review, safety[d]

Primary analysis population

≥ 1 dose of zenocutuzumab, opportunity for ≥ 24 weeks follow-up at the data cutoff date, and met criteria for primary efficacy population

Enrollment and Analysis

Data cutoff date

July 31, 2023

Enrollment

105 patients with NRG1+ NSCLC

NSCLC primary analysis population

79 patients

87 patients with ≥ 24 weeks follow-up[e]; of them, 8 patients were excluded[f]

- 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 anti-cancer medication use
- 1 patient with baseline scan > 5 weeks before first dose

AE, adverse event; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; MedDRA, Medical Dictionary for Regulatory Activities; 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.

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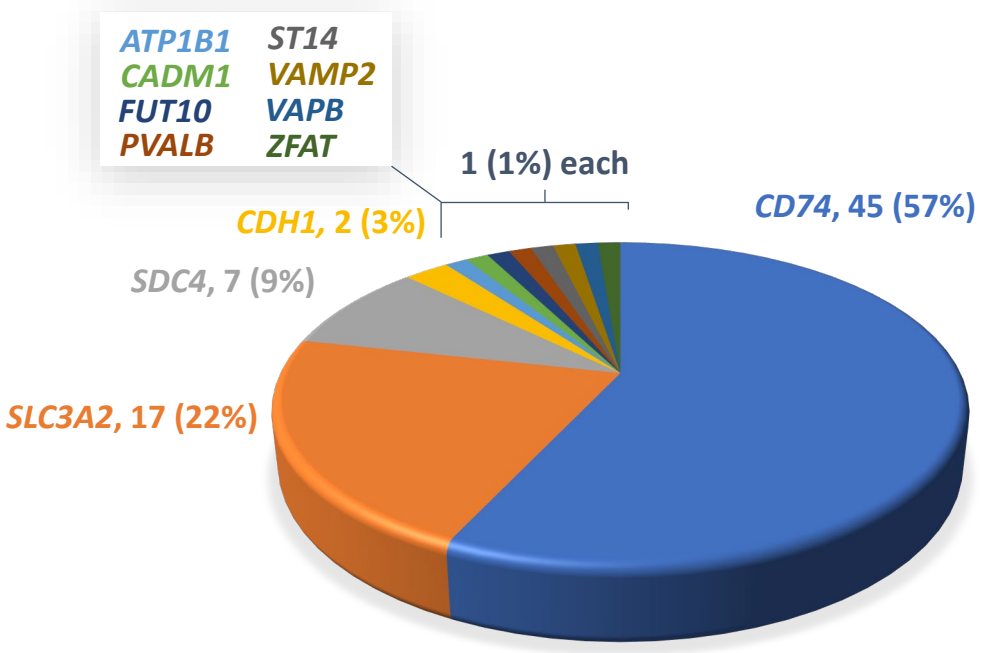
[a] Results from patients with NRG1+ PDAC are presented in **Poster 1618P**. [b] Defined as the proportion of patients with a best confirmed response of CR or PR per RECIST v1.1. [c] Defined as the time from date of first CR or PR to date of first PD or death due to trial indication. [d] AEs were coded using the MedDRA v25.0 and graded using CTCAE v4.03. [e] Patients received the first dose of treatment by 13 February, 2023, allowing for the opportunity of ≥ 24 weeks follow-up at data cut off date 31 July, 2023 [f] Per SAP

NRG1+ 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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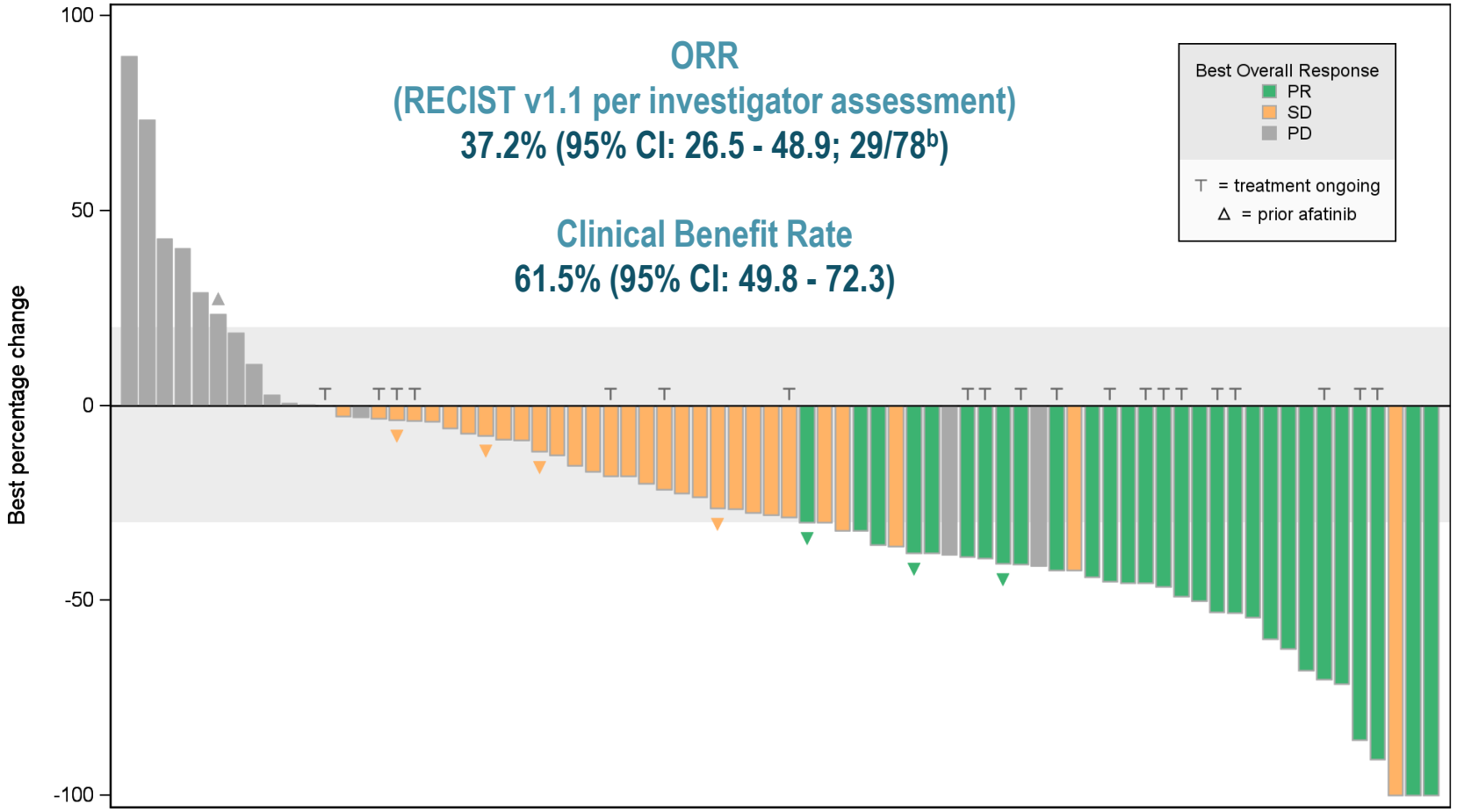
[a] Native Hawaiian or other Pacific islander (n = 1), unknown (n = 2), missing (n = 6); [b] Includes radiological and clinical progression, and 2 fatal cases; [c] Patient withdrew consent; [d] 1 patient had advanced non-metastatic disease

Zenocutuzumab Activity in NRG1+ NSCLC

Best Percent Change in Target Lesions from Baseline[a]

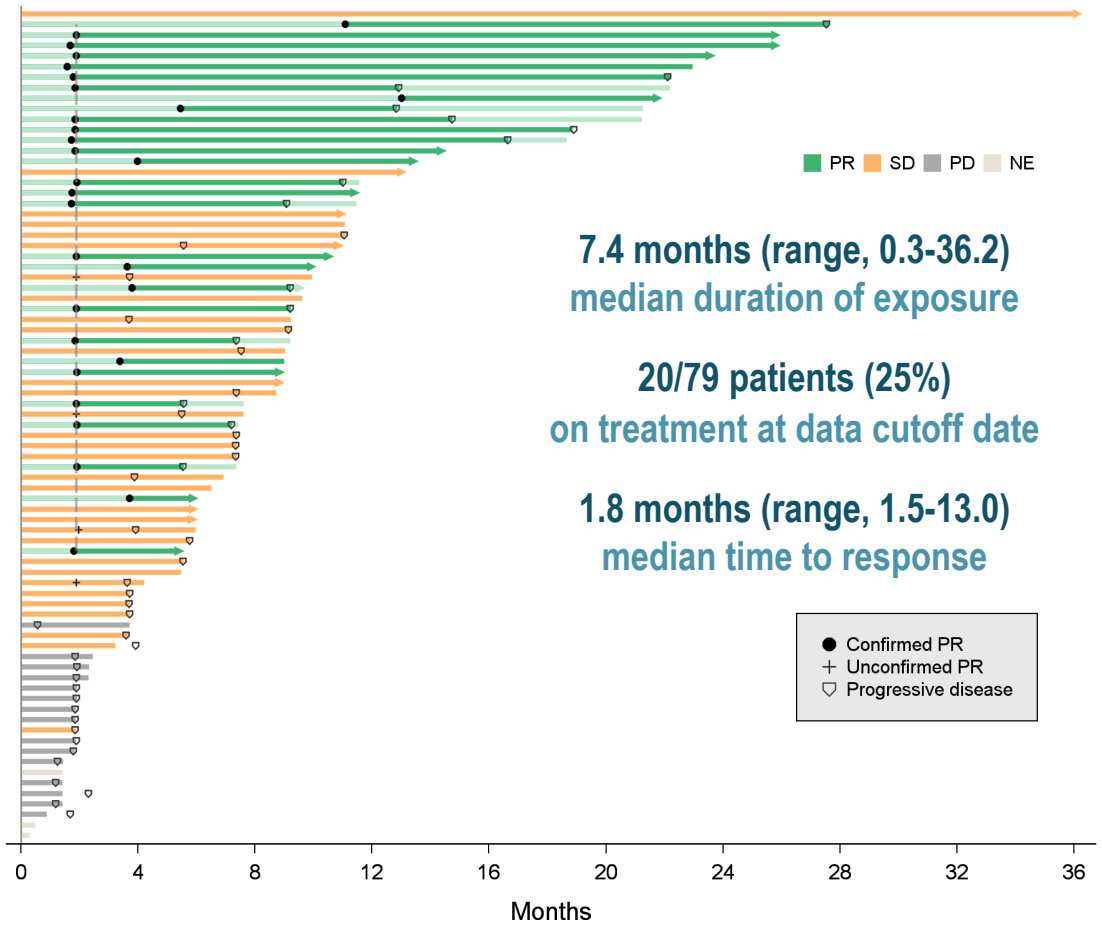


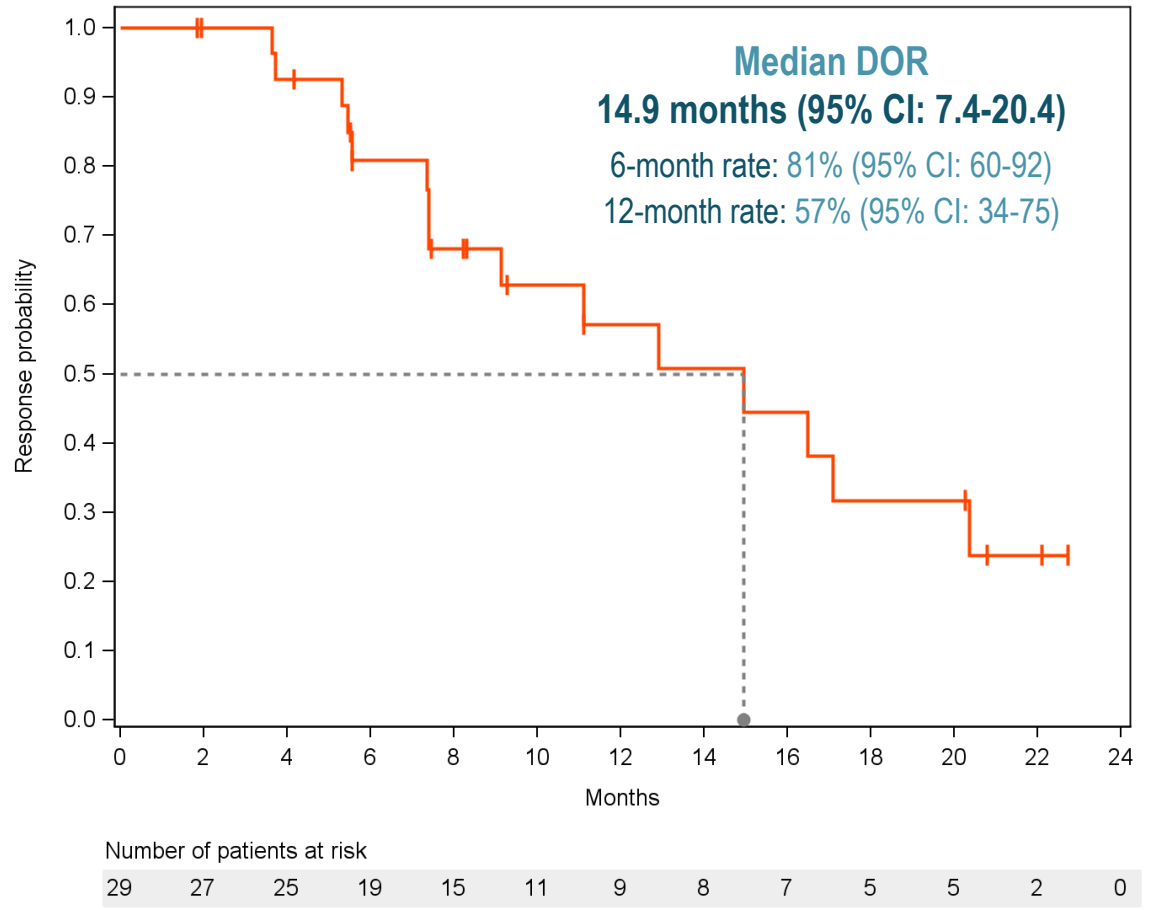
CI, confidence interval; SD, stable disease.

[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.

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[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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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