Zenocutuzumab efficacy and safety in advanced *NRG1+* cholangiocarcinoma: Analysis from the phase 2 eNRGy trial

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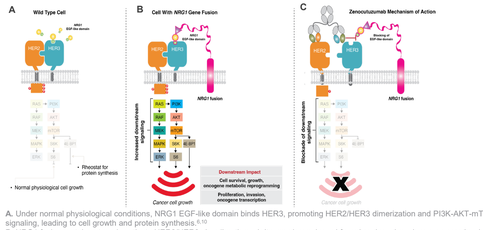
Background

- Cholangiocarcinoma is a rare, aggressive gastrointestinal cancer with a poor prognosis (median survival in advanced disease of ~1 year)[1–4]
- *NRG1* gene fusions are rare oncogenic drivers (prevalence <1% in cholangiocarcinoma) associated with recurrence, metastases, chemoresistance, and poor prognosis in solid tumors[5–7]
- No approved targeted therapies for *NRG1+* cholangiocarcinoma exist; cholangiocarcinoma treatment is limited to palliative systemic therapy for metastatic disease[1]
- BIZENGRI® (zenocutuzumab) received accelerated US FDA approval (December 2024) for previously treated, advanced *NRG1+* non-small cell lung cancer (NSCLC) and pancreatic adenocarcinoma (PDAC)[8] and recently received US FDA breakthrough therapy and orphan drug designation for *NRG1+* cholangiocarcinoma[9]
- Zenocutuzumab is a HER2/HER3 common light chain bispecific antibody that blocks HER3-mediated NRG1 signaling and HER2/HER3 dimerization and mediates antibody-dependent cellular cytotoxicity (Figure 1)

Figure 1 | Zenocutuzumab mechanism of action

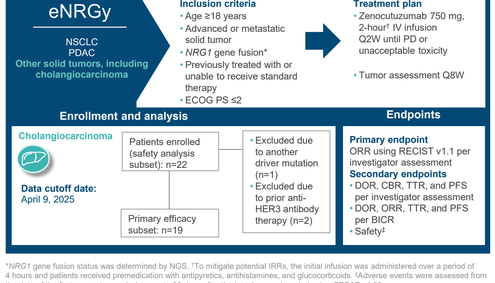


A. Under normal physiological conditions, NRG1 EGF-like domain binds HER3, promoting HER2/HER3 dimerization and PI3K-AKT-mTOR signaling, leading to cell growth and protein synthesis.[6,10]
B. NRG1 fusion proteins strongly activate HER2/HER3 signaling through its membrane-bound form (as shown) or via overexpression (not shown), leading to increased downstream signaling, driving cancer cell growth.[6,10]
C. Zenocutuzumab docks onto HER2, blocking NRG1 binding to HER3 and preventing HER2/HER3 dimerization and downstream signaling, thereby inhibiting cancer cell growth. Zenocutuzumab also mediates ADCC.[11,12]

4E-BP1, eukaryotic translation initiation factor 4E-binding protein 1; ADCC, antibody-dependent cellular cytotoxicity; AKT, protein kinase B; EGF, epidermal growth factor; ERK, extracellular signal-regulated kinase; HER, human epidermal growth factor receptor; MAPK, mitogen-activated protein kinase; MEK, MAPK kinase; mTOR, mechanistic target of rapamycin; NRG1, neuregulin 1; *NRG1+*, neuregulin 1 gene fusion positive; P, phosphate; PI3K, phosphoinositide 3-kinase; RAF, rapidly accelerated fibrosarcoma; RAS, rat sarcoma viral oncogene homolog; S6, ribosomal protein S6; S6K, ribosomal protein S6 kinase.

Methods

Figure 2 | Phase 1/2, global, multicenter zenocutuzumab trial (NCT02912949)[13,14]



NRG1 gene fusion status was determined by NGS. †To mitigate potential IRRs, the initial infusion was administered over a period of 4 hours and patients received premedication with antipyretics, antihistamines, and glucocorticoids. ‡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; HER, human epidermal growth factor receptor; IRR, infusion-related reaction; IV, intravenous; NGS, next-generation sequencing; *NRG1*, neuregulin 1; NSCLC, non-small cell lung cancer; ORR, overall response rate; 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; TTR, time to response.

Results

Table 1 | Demographics

Characteristic	Safety analysis set (N=22)
Age, years, median (range)	57.5 (23–82)
Male, n (%)	10 (45)
ECOG PS, n (%)	
0 / 1 / 2	14 (63) / 7 (32) / 1(5)
Anatomical location, n (%)	
Intrahepatic / Unknown	18 (82) / 4 (18)
Stage at screening, n (%)	
IIIB / IV	1 (5) / 21 (95)

ECOG PS, Eastern Cooperative Oncology Group performance status.

Table 2 | Treatment history

Diagnosis and prior therapy	Primary efficacy set (N=19)
Time since metastatic diagnosis, months, median (range)	9.3 (1.6–34.2)
Patients receiving prior systemic therapy, n (%)	17 (89)
Prior systemic therapy regimens*, n, median (range)	1 (0–4)
Type of prior therapy, n (%)	
Chemotherapy / Immunotherapy	16 (84) / 3 (16)
Anti-VEGF therapy / Transarterial chemoembolization	1 (5) / 1 (5)

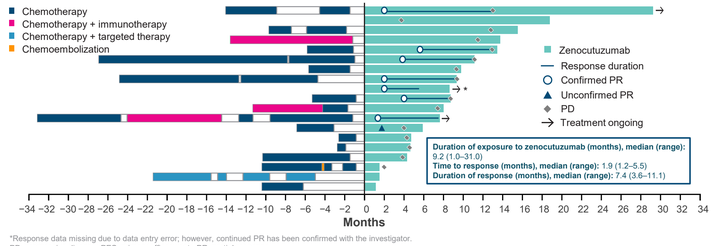
*Number of prior systemic therapy regimens were 0 (n=2), 1 (n=9), 2 (n=5), 3 (n=1), and 4 (n=2).
VEGF, vascular endothelial growth factor.

Table 3 | Safety summary

Adverse events	Safety analysis set, n (%) (N=22)	
Patients with ≥1 TRAE*	13 (59)	
Patients with Grade ≥3 TRAE	1 (5)†	
TRAE leading to discontinuation	0 (0)	
Patients with ≥1 TEAE	21 (95)	
TEAEs occurring in ≥20% patients	All grades	Grade 3-4
Anemia	10 (45)	3 (14)
Diarrhea	9 (41)	0 (0)
Hypomagnesemia	6 (27)	2 (9)
Abdominal pain	6 (27)	1 (5)
Cough	6 (27)	0 (0)
Fatigue	6 (27)	0 (0)
Nausea	6 (27)	0 (0)
ALT increased	5 (23)	1 (5)
GGT increased	2 (9)‡	2 (9)
Grade 5 TEAEs	0 (0)	

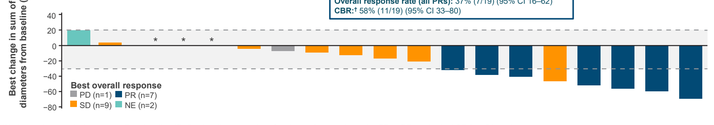
*Most AEs were Grade 1 or 2; †One patient experienced Grade 3 anemia; ‡Occurred in <20% of patients; however, included as both events were Grade ≥3. Neither event was treatment-related.
GGT, gamma-glutamyltransferase; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

Figure 3 | Prior treatment exposure (left) and study treatment exposure and response (right)



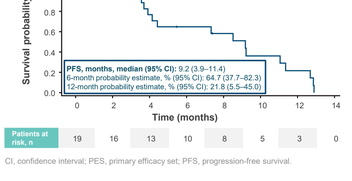
*Response data missing due to data entry error; however, continued PR has been confirmed with the investigator.
PD, progressive disease; PES, primary efficacy set; PR, partial response.

Figure 4 | Best overall response



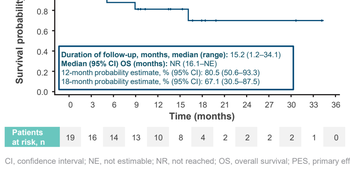
‡% change in target lesion too small to visualize; †Defined as the proportion of patients who experienced a CR or PR or who had SD for ≥24 weeks.
CBR, clinical benefit rate; CI, confidence interval; CR, complete response; NE, not evaluable; PD, progressive disease; PES, primary efficacy set; PR, partial response; SD, stable disease.

Figure 5 | Kaplan–Meier of PFS (PES, n=19)



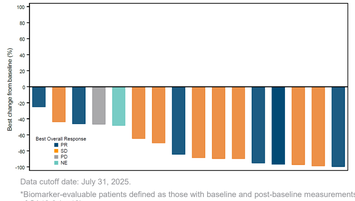
CI, confidence interval; PES, primary efficacy set; PFS, progression-free survival.

Figure 6 | Kaplan–Meier of OS (PES, n=19)



CI, confidence interval; NE, not estimable; NR, not reached; OS, overall survival; PES, primary efficacy set.

Figure 7 | Best percent change from baseline in CA19-9 over time*



Data cutoff date: July 31, 2025.
*Biomarker-evaluable patients defined as those with baseline and post-baseline measurements of CA19-9 (n=16).
CA19-9, carbohydrate antigen 19-9; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

- CA19-9 declined in 100% of CA19-9–evaluable patients (16/16) including >50% reduction in 69% (11/16)

Conclusions

- **Zenocutuzumab demonstrated meaningful clinical activity in patients with *NRG1+* cholangiocarcinoma**
  - Overall response rate of 37%; clinical benefit rate of 58%
  - Median time to response of 1.9 months; median duration of response of 7.4 months
  - Median progression-free survival was 9.2 months; median overall survival has not been reached
  - CA19-9 declined in 100% of CA19-9–evaluable patients (16/16) including >50% reduction in 69% (11/16)
  - All patients with available subtype data (18/18) had intrahepatic cholangiocarcinoma
- **A manageable safety profile was observed with zenocutuzumab in this cohort**
  - Most AEs were Grade 1 or 2
- **Results are consistent with those observed with zenocutuzumab in patients with other *NRG1+* solid tumors, including NSCLC and PDAC[13]**
- **Based on the results of this study, zenocutuzumab is now included in the NCCN guidelines for cholangiocarcinoma[14]**

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Disclosures
Study sponsored by Merus B.V. and Partner Therapeutics, Inc. Full author disclosures are available via the Quick Response (QR) code. Copies of this poster obtained through QR code are for personal use only and may not be reproduced without permission from the author of this poster.

Acknowledgments
With gratitude, we thank participating patients and their families for their willingness to take part in this important research, study teams and research staff for conducting the trial, and Partner Therapeutics, Inc. and Merus B.V. colleagues.

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ORIGINAL CONGRESS INFORMATION: AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics; Boston, MA, USA; October 22–26, 2025

CONGRESSINFORMATION: Cholangiocarcinoma Foundation 13th Annual Conference; Salt Lake City, UT, USA; May 1–3, 2026

Patient Friendly Lay Summary

Background

- Cholangiocarcinoma is a type of gastrointestinal cancer that forms in the bile ducts.
- Some patients with cholangiocarcinoma can have a change in their tumor called an *NRG1* gene fusion that can help the cancer grow.
- Zenocutuzumab is a medicine designed to target tumors with this gene change (*NRG1+* cancer).

Objective

This study tested how well zenocutuzumab works for the treatment of *NRG1+* cholangiocarcinoma.

Methods

- **Participants: P**atients with *NRG1+* cholangiocarcinoma
- **Treatment:** Zenocutuzumab 750 mg was given as an IV infusion every 2 weeks

Results

As of April 2025, 22 patients with *NRG1+* cholangiocarcinoma received zenocutuzumab.

- About 4 in 10 patients (37%) had their tumors shrink.
- About 6 in 10 patients (58%) had their tumors either shrink or stay stable for 6 months.
- On average, it took about 2 months to see improvement after starting zenocutuzumab.
- When patients responded, the benefit typically lasted for about 7.4 months.
- A blood test called CA19-9, which can help monitor some cancers, went down in all patients who could be evaluated, suggesting the treatment was helping.
- Zenocutuzumab was well tolerated. No patients had to stop zenocutuzumab due to side effects.
- These results were similar to what was seen in patients with *NRG1+* lung cancer and pancreatic cancer who received zenocutuzumab.

Conclusion

Many patients with *NRG1+* cholangiocarcinoma experienced meaningful improvement with zenocutuzumab with few side effects.