Zenocutuzumab (BIZENGRI)
National Drug Monograph
June 2025

VA Pharmacy Benefits Management Services and National Formulary Committee

The purpose of VA National Formulary Committee drug monographs is to provide a focused drug review for making formulary decisions. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA APPROVAL INFORMATION

Description / MOA	IgG1 bispecific antibody which binds the extracellular domains of HER2 and HER3, preventing dimerization and neuregulin 1 (NRG1) binding to HER3 thus preventing cell proliferation and signaling via PI3K-AKT-mTOR pathway as well as mediating antibody-dependent cellular cytotoxicity
Indication Under Review[1]	- Adults with advanced, unresectable, or metastatic non-small cell lung cancer (NSCLC) harboring a neuregulin 1 (NRG1) gene fusion with disease progression on or after prior systemic therapy - Adults with advanced, unresectable, or metastatic pancreatic adenocarcinoma harboring a NRG1 gene fusion with disease progression on or after prior systemic therapy *Both FDA approvals under accelerated approval based on overall response rate (ORR)
Dosage Regimen	750 mg IV every 2 weeks until disease progression or unacceptable toxicity
Premedication	First dose requires premedication with a corticosteroid such as dexamethasone 10 mg, an H1 antihistamine equivalent to dexchlorpheniramine 5 mg, and acetaminophen 1000 mg. Corticosteroid may not be indication in subsequent cycles.
Dosage Forms Under Review	375 mg/18.75 mL (20 mg/mL) solution for injection

EFFICACY CONSIDERATIONS

Trial	**Efficacy of Zenocutuzumab in NRG1 Fusion-Positive Cancer (eNRGy Trial)** N Engl J Med 2025; 392:566-576. NCT02912949	
Design	Open label, phase 2 portion of registrational trial (161 patients across 10 tumor types)	
Population	N=161 NGS (DNA- or RNA-based) confirmed NRG1 gene fusion positive tumor, ECOG PS 0-2, measurable disease per RECIST 1.1 or unmeasurable but evaluable disease	
Demographic	female: 60%, 39 different fusion partners in 10 tumor types; received at least 2 prior standard therapies	
	NSCLC: - mean age 65 years old - 58% NSCLC (N=94) - CD74 (in 56%) and SLC3A2 (in 23%) were the most common fusion partners - 52% of previously treated patients received 1 prior therapy and n=12 were treatment naive	**Pancreatic:** - mean age 62 years old - 22% pancreatic carcinoma (N=36) - ATP1B1 (in 44%) was the most common fusion partner - 22% of patients received only 1 prior therapy and 1 patient was treatment naive
Intervention	Zenocutuzumab750 mg IV q2 weeks; median duration of exposure 5.5 mos (0.1-42.3)	
Comparator	None	
Results	**Overall Population** ORR 30% (95% CI 23-37) overall mTTR 1.8 mo mDoR 11.1 mo (95% CI 7.4-12.9)	**NSCLC** ORR 29% (95% CI 20-39), 28% if previously treated mDoR 12.7 mo (95% CI 7.4-20.4) **Pancreatic carcinoma** ORR 42% (95% CI 25-59) mDoR 7.4 mo (95% CI 4.0-11.2) available CA 19-9: 77% had a reduction ≥50%
Notes	• **NCCN guidelines: NSCLC:** Progression after 1-line therapy in NRG1 fusion positive disease **Pancreatic Adenocarcinoma:** Useful in certain circumstances-subsequent therapy for NRG1 gene-fusion positive disease • **VA Oncology Clinical Pathways: O**n Lung Cancer and Pancreatic Cancer clinical pathways	

ORR: overall response rate, mTTR: median time to response, mDOR: median duration of response, NGS: Next-generation Sequencing

SAFETY CONSIDERATIONS		
	Boxed Warnings	Embryo-fetal toxicity: HER2 antibody use during pregnancy has been reported to result in oligohydramnios with fatal pulmonary hypoplasia, skeletal abnormalities, and neonatal death in literature.
	Contraindications	None
	Other Warnings	Infusion-related reactions/Hypersensitivity/Anaphylaxis: 13% of all patients had an infusion reaction with 91% occurring in the first infusion with median time to onset of 63 min (13-240). All reactions were grade 1 or 2. Monitor for at least 1 hour following first infusion. Premedicate with a corticosteroid such as dexamethasone 10 mg, an H1 antihistamine equivalent to dexchlorpheniramine 5 mg, and acetaminophen 1000 mg prior to the first dose to reduce risk of infusion-related reactions. Corticosteroid premedication may be used as necessary for future doses. Interstitial lung disease/Pneumonitis: 1.1% of patients experienced ILD/pneumonitis, with one grade 2 event (0.6%) resulting in permanent discontinuation. Left Ventricular Dysfunction: Not studied in patients with LVEF < 50% at baseline. 2% of patients experienced a grade 2 LVEF decrease and 1.7% developed cardiac failure without LVEF decrease with 1 fatal event (0.6%). Evaluate baseline LVEF and monitor at regular intervals during treatment as clinically indicated.
	Top 5 AEs	NSCLC: Diarrhea (25%;2%), MSK pain (23%; 1%), Dyspnea (18%; 5%), Fatigue (14%; 2%), Cough (15%;1%) Pancreatic Adenocarcinoma: Diarrhea (36%;5%), MSK pain (28%; 2.6%), Nausea (23%;5%)/Vomiting (23%;2.6%), Abdominal pain (18%;5%), COVID-19 (18%;0%) All: Diarrhea (29%;2%), Fatigue (21%;2%), Nausea (20%;2%), Anemia (17%;5%), Dyspnea (16%;2%)
	Drug Interactions	None

ZENOCUTUZUMAB PLACE IN THERAPY	VANF	CFU	FDA	NCCN Guidelines	VA Clinical Pathway
	TBD	Yes	NRG1 gene fusion positive NSCLC with progression on or after prior systemic therapy	Subsequent therapy after progression NRG1 fusion positive disease	Not yet on pathway
	TBD	Yes	NRG1 gene fusion positive advanced, unresectable, or metastatic pancreatic adenocarcinoma with progression on or after prior systemic therapy	Useful in certain circumstances if NRG1 gene fusion positive with ECOG PS 0-2	Not yet on pathway

This section may be edited prior to final approval of document and posting.

VHA PLACE IN THERAPY		
	Potential Use in VHA	1. NRG1 gene fusions are very rare in both NSCLC and pancreatic adenocarcinoma. 2. Prior therapy for advanced NSCLC included platinum-based plus anti-PD-1/PD-L1, platinum-based, or anti-PD-1/PD-L1. Prior therapy for pancreatic adenocarcinoma included a fluorouracil-irinotecan-oxaliplatin based therapy (FOLFIRINOX) and a gemcitabine/taxane-based therapy. 3. Second or third-line treatment option for patients with NRG1 gene fusion positive NSCLC who have progressed on/after systemic therapy platinum-based chemotherapy and/or targeted therapy if clinically indicated 4. Second- or third-line treatment option for patients with NRG1 gene fusion positive pancreatic adenocarcinoma with progression on/after systemic therapy including fluoropyrimidine- and/or gemcitabine-based chemotherapy. The ORR for 2nd line gemcitabine + nab paclitaxel is approximately 3% with a median Overall Survival of 6.6 months. *Both FDA approvals under accelerated approval based on overall response rate (ORR)

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References

1 Bizengri (zenocutuzumab) formulation [prescribing information online]. Cambridge, MA: Merus NV. 12.2024. Available at: https://www.bizengri.com/pdf/pi.pdf. Accessed 2.6.2025.

2 Schram AM, Goto K, Kim DW, et al; eNRGy Investigators. Efficacy of Zenocutuzumab in NRG1 Fusion-Positive Cancer. N Engl J Med. 2025 Feb 6;392(6):566-576. doi: 10.1056/NEJMoa2405008.