

Zenocutuzumab

Category:

Best Product for Orphan/Rare Diseases

Company Name:

Merus N.V.

Product/Solution Name:

Zenocutuzumab

Compound/Tech Name:

MCLA-128

Trade Name:

BIZENGRI

Corporate Name:

Merus N.V.

Date of Approval:

2024-12-04

Indications:

- advanced, unresectable, or metastatic non-small cell lung cancer (NSCLC) harboring a neuregulin 1 gene fusion with disease progression on or after prior systemic therapy, or
- advanced, unresectable, or metastatic pancreatic adenocarcinoma (PDAC) harboring a neuregulin 1 gene fusion with disease progression on or after prior systemic therapy

Therapeutic Areas:

Non-small cell lung cancer and pancreatic adenocarcinoma with neuregulin 1 gene fusion

General Information File Document upload:

Background information and need for drug / device:

PDAC: Cytotoxic chemotherapy combinations have remained the mainstay treatment for locally advanced and metastatic PDAC in the first-line setting over the last decade, after significant benefit over gemcitabine was demonstrated in several Phase 3 studies. Standard-of-care options after failure of first-line therapy are limited and treatment is based on the patient's general status and prior treatment. Liposomal irinotecan in combination with 5-FU/leucovorin is the first and only agent to be Food and Drug Administration (FDA)-approved for patients with metastatic PDAC that has progressed following gemcitabine-based therapy, which was approved based on the pivotal Ph3 NAPOLI study demonstrating a 7.7% CR rate, mPFS of 3.1 months, mOS of 6.1 months, with high frequencies of Gr3-4 AEs. No specific therapies have been approved for NRG1+ PDAC, and patients are treated according to the current treatment guidelines for PDAC generally.

NRG1 fusions have been identified across many tumor types and generally occur in the absence of other driver mutations.

Studies observed that NRG1+ tumors possess aggressive histological features associated with increased tumor growth, invasiveness, recurrence, resistance to therapy, metastasis, and worse prognosis in lung cancer. As with other advanced/metastatic solid tumors, patients with unresectable advanced or metastatic NRG1+ PDAC that have progressed after standard therapy have a poor prognosis and limited therapeutic options.

NSCLC: Nearly 70% of patients with NSCLC present with advanced-stage disease, for whom treatments with curative intent (surgery or radiotherapy) are no longer feasible. Targeted therapies provide effective tailored options for patients with NSCLC harboring relevant targets such as actionable mutations in EGFR, ALK and ROS1 rearrangements, BRAF V600E point mutations, and NTRK fusions, and in tumors for which programmed cell death ligand 1 (PD-(L)1) expression drives the use of ICIs. Other recently-approved therapies include those targeting KRAS G12C mutations (sotorasib, adagrasib), RET fusions (selpercatinib, pralsetinib), and ROS1 fusions (repotrectinib). Although targeted therapies have redefined the treatment of patients with molecularly-defined NSCLC, they are ineffective in tumors lacking these known genetic alterations, which represent the majority of NSCLC cases. This latter population represents the pool in which NRG1 gene fusions are most likely to be identified. In a retrospective series of 110 patients with NRG1+ NSCLC, the majority of cases had no or low PD-(L)1 expression and low tumor mutational burden (Drilon et al, 2021). Metastatic disease was reported in 40% of patients, 41% of whom received platinum-based chemotherapy, and taxane-based chemotherapy and immunotherapy were both administered in 21% of patients, chemo-immunotherapy in 23%, and afatinib in 45%. This retrospective analysis

highlighted the limited activity of systemic and targeted therapy in advanced NRG1+ lung cancer. Platinum-doublet and taxane-based (post-platinum doublet) chemotherapy achieved low ORRs (13% and 14%, respectively) and modest median PFS (5.8 and 4.0 months, respectively). Outcomes with chemoimmunotherapy were poor with an ORR of 0% and PFS of 3.3 months. The modest disease control achieved with afatinib is of note, with the most common response being disease progression, reported in 60% of patients.

Background File Document upload:

N/A

History of the development of the solution/product:

Clinical evidence: The primary objective of the eNRGy study was to assess the magnitude of antitumor activity of zenocutuzumab in patients with a neuregulin 1 (NRG1) gene fusion assessed locally, as evaluated by the overall response rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and local investigator assessment. The key secondary objective was to assess durability of antitumor activity of zenocutuzumab, as evaluated by duration of response (DOR) per RECIST 1.1 and local investigator assessment. This was a Phase 1/2 open-label, multicenter, multinational study, with a dose-escalation phase followed by a single-arm, multiple-indication expansion group assignment phase. 175 NRG1+ cancer patients were treated; 11 NRG1+ tumor types were identified; most patients (78.9%) had either NRG1+ NSCLC (99 patients [56.6%]) or NRG1+ PDAC (39 patients [22.3%]). All efficacy analyses were performed in the PES (ie, in patients with the opportunity for ≥ 24 weeks follow-up prior to the data cutoff date), composed of 129 patients, including 75 NRG1+ NSCLC patients and 29 NRG1+ PDAC patients. The confirmed ORR was 33.3% (95% CI: 25.2, 42.3) in the 126 all NRG1+ tumor types patients with measurable disease, 33.8% (95% CI: 23.2, 45.7) in the 74 NRG1+ NSCLC patients, and 44.8% (95% CI: 26.4, 64.3) in the 29 NRG1+ PDAC patients. Responses were durable with a median DOR of 11.1 months (95% CI: 7.4, 17.1) for the 42 responders in the all NRG1+ tumor types population (range 1.7-24.0), and a Kaplan-Meier estimate of DOR at 6 months of 79.8% (95% CI: 63.7, 89.4) with 29/42 responders (69.0%) having a response lasting >6 months and 9 patients (21.4%) having a response lasting >12 months.

Development File Document upload:

N/A

Why this drug or device is innovative, the broad implications for future research, and/or how it will improve the human condition:

NRG1+ cancer is a unique biomarker-defined disease comprised of cancers of multiple

histologic subtypes that are driven by the actionable NRG1 fusion. Functional NRG1 fusion proteins bind to HER3 on cancer cells, triggering HER2/HER3 heterodimerization and activating several downstream signaling pathways which inhibit apoptosis and drive proliferation. Thus, targeting NRG1 fusions should be an effective therapeutic approach regardless of cancer histology and provides the opportunity to manage a wide variety of cancer patients using a selection biomarker rather than by cancer histology.

No NRG1-specific therapies are currently approved for patients with NRG1+ cancer, who are otherwise managed with standard-of-care therapies used to treat cancer patients in general. The majority of standard therapies for treating cancer (including those with a higher prevalence of NRG1 fusions) are associated with low ORRs, short median DORs or PFS, and significant toxicity (ie, high rates of Grade 3 or higher AEs). These poor clinical outcomes highlight the great unmet clinical need in patients with advanced NRG1+ cancer.

Zenocutuzumab, an HER2/HER3 bispecific antibody, demonstrated robust and clinically meaningful antitumor activity in patients with advanced or metastatic NRG1+ cancer. Early and durable confirmed responses were observed in NRG1+ NSCLC and NRG1+ PDAC patients who were previously treated with standard-of-care therapy, as well as across multiple other tumor types and fusion partners. Zenocutuzumab offers substantial improvement over available therapies for patients with advanced or metastatic NRG1+ NSCLC and NRG1+ PDAC, cancer populations with a high unmet need.

Innovation File Document upload:

N/A

Please provide appropriate references (PubMed, Abstract, Website):

1. Efficacy of Zenocutuzumab in NRG1 Fusion-Positive Cancer. Schram et al. The New England Journal of Medicine (NEJM) DOI: 10.1056/NEJMoa2405008, published 05 Feb 2025. <https://www.nejm.org/doi/full/10.1056/NEJMoa2405008>
2. The phase I/II eNRGy trial: Zenocutuzumab in patients with cancers harboring NRG1 gene fusions. Kim et al. Future Medicine doi: 10.2217/fon-2023-0824, published 14 Feb 2024. <https://www.tandfonline.com/doi/full/10.2217/fon-2023-0824>
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