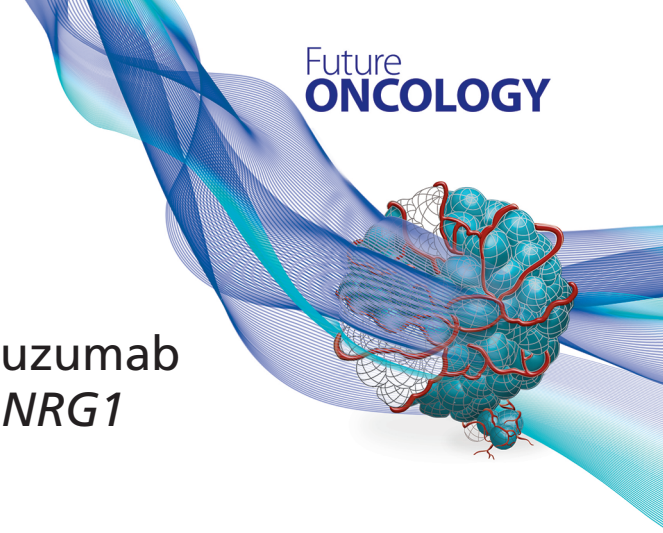
Clinical Trial Protocol

Future ONCOLOGY



The phase I/II eNRGy trial: Zenocutuzumab in patients with cancers harboring *NRG1* gene fusions

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Neuregulin 1 (*NRG1*) fusions are oncogenic drivers that have been detected in non-small-cell lung cancer (NSCLC), pancreatic ductal adenocarcinoma (PDAC) and other solid tumors. *NRG1* fusions are rare, occurring in less than 1% of solid tumors. Patients with *NRG1* fusion positive (NRG1+) cancer have limited therapeutic options. Zenocutuzumab is a novel, bispecific IgG1 antibody that targets both HER2 and HER3 proteins and inhibits NRG1 binding through a 'Dock & Block®' mechanism of action. Here, we describe the rationale and design of the phase II component of the eNRGy trial, part of the overall, open-label phase I/II, multicenter trial exploring the safety, tolerability, pharmacokinetics, pharmacodynamics, immunogenicity and antitumor activity of zenocutuzumab in patients with NRG1+ NSCLC, PDAC or other solid tumors.

Plain language summary – eNRGy: a clinical trial of zenocutuzumab for cancer caused by NRG1 gene fusions: *NRG1* gene fusions are rare mutations that cause cancer cells to grow. These fusions are found in many different types of cancer. Tumors with *NRG1* gene fusions do not respond well to standard treatment options. Zenocutuzumab, or Zeno, is a treatment that is being tested to see if it can stop cancer that is growing because of *NRG1* gene fusions. Here, we describe the reasoning for and design of an ongoing clinical trial (eNRGy) designed to study the efficacy

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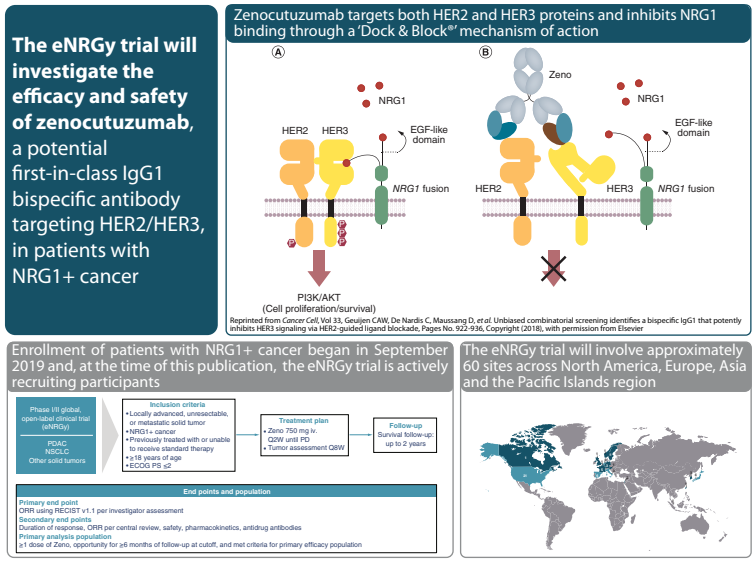
(how well it works) and safety of Zeno in patients with cancer that has *NRG1* gene fusions. The eNRGy trial is recruiting patients with cancer that has *NRG1* gene fusions, including non-small-cell lung cancer, pancreatic cancer and others. Patients who join this trial will receive Zeno once every 2 weeks until their cancer grows. The main goal (primary end point) of this trial is to determine the percentage of patients whose tumors decrease in size by 30% or more. The eNRGy trial is currently enrolling patients. For more information, refer to ClinicalTrials.gov (Identifier: NCT02912949), visit https://nrg1.com/, or call 1-833-NRG-1234.

Tweetable abstract: eNRGy is a global phase I/II trial currently recruiting patients with NRG1+ NSCLC, PDAC or other solid tumors to assess zenocutuzumab, an investigational bispecific IgG1 antibody that inhibits NRG1-activated HER2/HER3 oncogenic signaling.

Graphical abstract:



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Keywords: eNRGy trial • HER2 • HER3 • NRG1+ • *NRG1* fusion • NSCLC • PDAC • recruiting • Zeno • Zenocutuzumab

Neuregulin 1 (NRG1) belongs to a family of growth factors that, under healthy conditions, aid in the growth and development of epithelial, glial and muscle cells by promoting human epidermal growth factor receptor 2 (HER2)/human epidermal growth factor receptor 3 (HER3) signaling [1]. An *NRG1* fusion positive (NRG1+) cancer was first described in 2014 by Fernandez-Cuesta *et al.* in lung adenocarcinoma, and subsequent studies have provided evidence supporting the oncogenic role of these fusions in multiple tumor types [2–4]. The role of *NRG1* fusions as oncogenic drivers is further supported by their occurrence in the absence of other canonical cancer cell driver mutations in the vast majority of NRG1+ cancer reported to date [3,5–7]. Additionally, they have been shown to play critical roles in the initiation and maintenance of cancer stem cell-like properties [3,8,9].

NRG1 fusions have been detected with a wide range of fusion partners, both within and between various cancers [6]. However, *NRG1* fusions are rare, and identification of patients with NRG1+ cancer has proved challenging [10]. *NRG1* fusions are best detected through RNA sequencing, as DNA-based methods can fail to detect up to half of fusions due to insufficient sensitivity, variable intron splicing positions, and the presence of novel fusion partners [11,12].

NRG1 fusion partners may possess a transmembrane domain, which can lead to a high, localized concentration of NRG1 near HER2/HER3, resulting in constituent activation of HER2/HER3 signaling [10]. Zenocutuzumab (Zeno) has shown the ability to suppress tumor growth in preclinical models, even under conditions of high NRG1 concentrations; based on these results, Zeno was tested in preclinical xenograph models of mice harboring

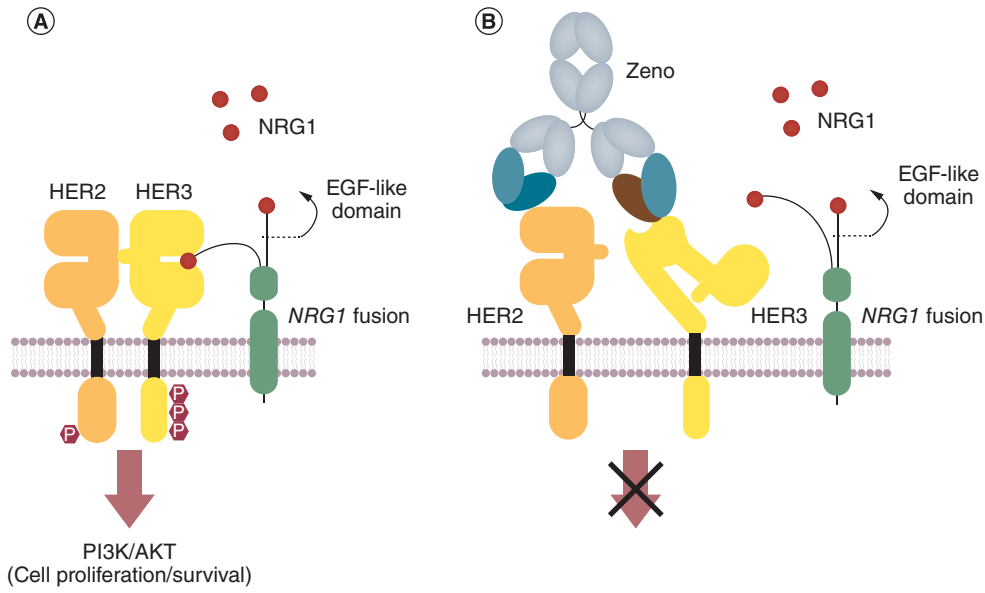

Figure 1. Zeno mechanism of action. (A) *NRG1* fusion proteins function as ligands for HER3 (similar to NRG1) and bind to HER3 with high affinity to promote HER2/HER3 dimerization and downstream signaling. **(B)** Zeno inhibits the NRG1/HER3 interaction via its 'Dock & Block®' mechanism, whereby one arm of the antibody binds to the HER2 receptor, optimally positioning the anti-HER3 arm to block the ligand/receptor interaction and prevent HER2/HER3 dimerization.
EGF: Epidermal growth factor; HER2: Human epidermal growth factor receptor 2; HER3: Human epidermal growth factor receptor 3; NRG1: Neuregulin 1; Zeno: Zenocutuzumab.
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NRG1+ cancer and demonstrated significant tumor shrinkage [13]. In addition to Zeno, other compounds targeting HER2/HER3 signaling, including seribantumab, HMBD-001, and afatinib, have been subject to investigation or retrospective studies in NRG1+ cancer [14–17].

eNRGy trial

Here, we describe the rationale and design for the phase II component of the eNRGy (ClinicalTrials.gov Identifier: NCT02912949) trial, part of the overall open-label phase I/II trial, which aims to evaluate the efficacy, safety, pharmacokinetics (PK), and pharmacodynamics (PD) of Zeno in patients with NRG1+ cancer. This trial is sponsored by Merus NV.

Background & rationale

A functional *NRG1* fusion product must be in-frame and produce a protein capable of activation of the HER2/HER3 signaling pathway [6,9]. Such fusions have been observed in cancers, including non-small-cell lung cancer (NSCLC), pancreatic ductal adenocarcinoma (PDAC) and other solid tumors [6,7,17–21]. *NRG1* fusions have been reported in 0.3–1.7% of lung cancer, 0.5–1.8% of pancreatic cancer, and <1% in other solid tumors (e.g., breast cancer, cholangiocarcinoma, colorectal cancers) [6,9,17,22,23]. However, certain cancer types, such as invasive mucinous adenocarcinoma (IMA) of the lung and *KRAS* wildtype (*KRAS*^{WT}) PDAC, exhibit an increased incidence of oncogenic *NRG1* fusions, with up to 30% of IMA and up to 18% of *KRAS*^{WT} PDAC harboring *NRG1* fusions [9,21]. NRG1 has been found to create fusions with a wide range of partners in NSCLC (including, but not limited to, *CD74*, *SDC4*, *SLC3A2*, *TNC*, *MDK*, *ATP1B1*, *DIP2B*, *RBPMS*, *MRPL13*, *ROCK1*, *DPYSL2*, *PRAP8*) and PDAC (e.g., *ATP1B1*, *CDH1*, *VTCN1*) [6].

Suboptimal responses to conventional therapeutic options have been reported in patients with NRG1+ cancer, including NSCLC, which demonstrates poor responses to afatinib and chemotherapy, with or without immunotherapy, and PDAC, which responds poorly to approved therapies [7,12,21,24]. Zeno is a potent bispecific IgG1 antibody that targets the extracellular domains of both HER2 and HER3 proteins and inhibits *NRG1* fusions through a 'Dock & Block®' mechanism of action (Figure 1) [13]. Zeno docks onto the more abundant HER2 protein, leading to high local concentrations on the cell surface; blocking *NRG1* fusion interactions with HER3, HER3 interactions

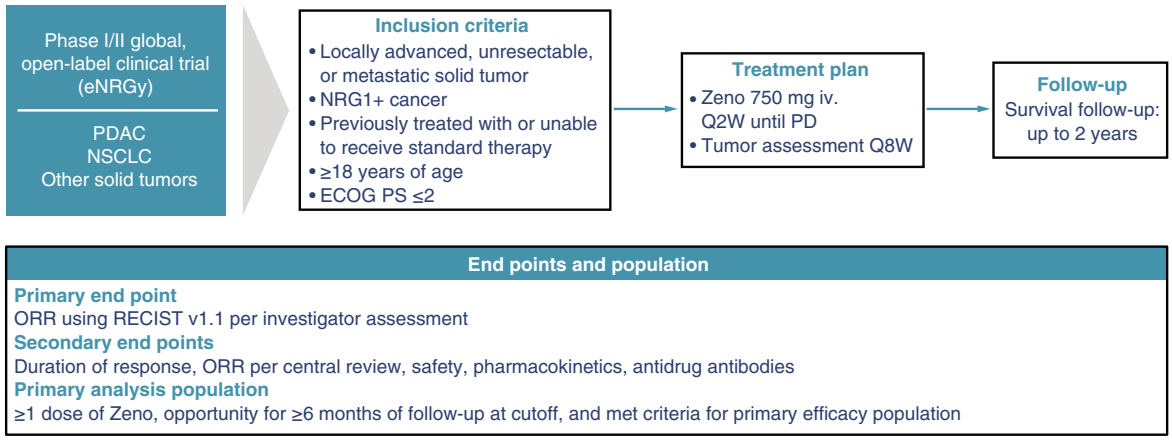

Figure 2. eNRGy trial design.
ECOG PS: Eastern Cooperative Oncology Group performance status; iv.: Intravenous; NRG1: Neuregulin 1; NSCLC: Non-small-cell lung cancer; ORR: Overall response rate; PD: Progressive disease; PDAC: Pancreatic ductal adenocarcinoma; RECIST: Response Evaluation Criteria in Solid Tumors; Q2W: Every 2 weeks; Q8W: Every 8 weeks; Zeno: Zenocutuzumab.

with HER2, and downstream HER2/HER3 signaling; and resulting in suppression of tumor cell proliferation and tumor cell survival through the PI3K-AKT-mTOR oncogenic signaling pathway [13]. Further, *in vitro* studies have demonstrated that Zeno induces enhanced antibody-dependent cellular cytotoxicity due to a glycoengineered modification of the IgG1 subunit to enhance affinity for Fc receptors [13,25,26].

Trial design

The eNRGy trial is a phase I/II, open-label, multicenter trial with multiple indication expansion cohorts. The purpose of the eNRGy trial is to assess the safety, tolerability, PK, PD, immunogenicity and antitumor activity of Zeno in patients with NRG1+ cancer. This trial is designed in two parts: Part 1 (now complete) was dose escalation, and Part 2 is dose expansion, which further evaluates the safety and antitumor activity of Zeno. Part 2 initially evaluated the safety and efficacy of Zeno in non-NRG1+ cancer with aberrant HER2/HER3 signaling, such as breast cancer, ovarian cancer, gastric/gastroesophageal cancer and endometrial cancer. Currently, the eNRGy trial is focused on evaluating the safety and efficacy of Zeno in NRG1+ cancer (Figure 2). The eNRGy trial currently involves approximately 60 sites across North America, Europe, Asia, and the Pacific Islands (Figure 3).

Eligibility criteria

Eligible patients are ≥18 years of age, have ≥1 evaluable or measurable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST v1.1), were previously treated with or unable to receive standard therapy, and have recovered from the toxicities of prior therapy. Patients are required to have a histologic or cytologic diagnosis of locally advanced, unresectable, or metastatic solid tumor malignancy with a documented *NRG1* fusion, identified through molecular-based assays, such as next-generation sequencing (NGS)-based assays (DNA- or RNA-based methods); however, as previously discussed, DNA-based testing may be suboptimal to detect *NRG1* fusions. Patients with cancer harboring *NRG1* fusions that are prospectively assessed as nonfunctional during study screening will not be eligible for enrollment. If nonfunctional *NRG1* fusions are identified after enrollment during the independent retrospective review, the associated patient data will not be included in the primary efficacy analysis of this trial. The key eligibility criteria of the eNRGy trial are summarized in Table 1.

Screening for *NRG1* fusions can be conducted at either a local or central laboratory. A fresh tumor sample, formalin-fixed paraffin-embedded (preferred sample type), or an archival tumor sample (preferably collected within 2 years of starting trial treatment) is required for eligibility. For patients who received prior afatinib or other HER-targeting agents, a biopsy after the last line of treatment is strongly preferred to assess for mechanisms of acquired resistance.

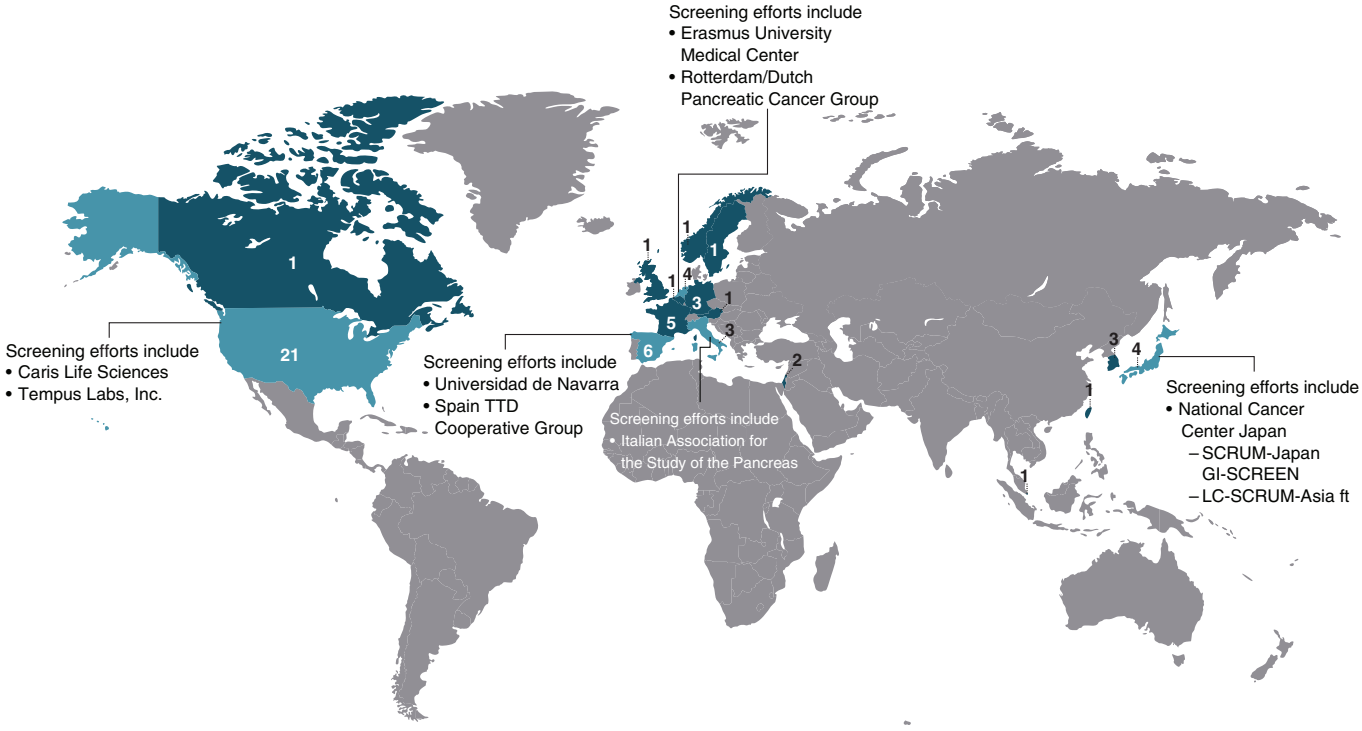

Figure 3. eNRGy trial sites. Active sites include Memorial Sloan-Kettering Cancer Center, National Cancer Center Hospital (NCCH) East, Seoul National University Hospital, Gustave Roussy, Hospital Universitario Vall d'Hebron, Hospices Civils de Lyon Cancer Institute – Louis Pradel Hospital, St. Marianna University Hospital, Institut Curie – René-Huguenin Hospital, Karmanos Cancer Institute, Princess Margaret Cancer Centre, Osaka International Cancer Institute, Netherlands Cancer Institute, Deutsches Krebsforschungszentrum, Dana-Farber Cancer Institute, Georgetown University Department of Medicine, University of California Irvine Medical Center (UCIMC) – Chao Family Comprehensive Cancer Center, Mayo Clinic Hospital – Phoenix, Samsung Medical Center, Severance Hospital – Yonsei Cancer Center, A.O. Niguarda Cà Granda Farmacia Ospedaliera – U.O. di Cardiología, Universitair Medisch Centrum Utrecht, Hospital Clinico Universitario de Valencia, The University of Texas MD Anderson Cancer Center, Mayo Clinic Cancer Center (MCCC) – Rochester, Emory Clinic, National Cancer Center Hospital (NCCH), Centro Integral Oncológico Clara Campal (CIOCC), National Cancer Centre of Singapore Pte Ltd, Hospital Universitario 12 de Octubre, Istituti Fisioterapici Ospitalieri, Mayo Clinic Hospital – Florida, Northwest Medical Specialties, Medical Oncology Associates, P.S., University of Pennsylvania – Penn Memory Center, St. James Healthcare, Hematology-Oncology Associates of Fredericksburg, Cancer Specialists of North Florida, Utah Cancer Specialists, and Billings, Montana.
TTD: Treatment of digestive tumors.

Trial procedures

Patients with NRG1+ cancer will receive Zeno 750 mg intravenous (iv.) given once every 2 weeks over a 4-week cycle. The infusion duration is 4 hours during Cycle 1; however, the infusion duration can be reduced to 2 hours in Cycles 2+ if there are no infusion-related reactions (IRR) of grade ≥2 reported in the first treatment cycle. Prior to each infusion of Zeno, premedication will consist of paracetamol (1000 mg oral or iv.), dexchlorpheniramine (5 mg iv.), and dexamethasone (10 mg iv.) to mitigate IRRs. Corticosteroids will only be mandatory as premedication for the first infusion and can be continued at the investigator's discretion. An H2 antagonist may optionally be prescribed as premedication, per the investigator's discretion.

Blood samples (~4 ml) will be collected to characterize the PK profile of Zeno at the following timepoints on Cycle 1 Day 1: predose, 2 hours (±15 minutes) postdose, 4 hours (±30 minutes) postdose, and 24 hours (±2 hours) postdose. Limited blood samples will be collected for PK profiles on selected infusion dates at the following timepoints after Cycle 1 Day 1: predose and end-of-infusion only. Tumor tissue samples will be collected from consenting patients. Testing may include gene expression (DNA and RNA) and cancer gene mutations (including genes associated with HER2 and HER3); HER2 expression/gene amplification; and expression of HER2:HER3 dimer, phosphorylated HER (pHER)2, pHER3, phosphorylated protein kinase B (pAKT), and phosphorylated extracellular signal–regulated kinase (pERK)1/2. Blood samples will be collected at Cycle 1 Day 1 predose, Cycle 2 Day 1, every 2 cycles thereafter, and at the end of treatment for PD analyses; testing may include

Table 1. Key eligibility criteria for patients with NRG1+ cancer in the eNRGy trial.

Inclusion criteria	Exclusion criteria
• Age ≥18 years • ≥1 measurable lesion according to RECIST v1.1 or evaluable disease for a limited number of patients (≤10) in the basket solid tumors with *NRG1* fusions cohort • Previously treated with or unable to receive standard therapy • Histologic or cytologic diagnosis of locally advanced, unresectable, or metastatic solid tumor malignancy with a documented *NRG1* fusion, as identified via molecular assays, such as NGS (DNA- or RNA-based) • ECOG PS ≤2 • Estimated life expectancy of ≥12 weeks • Patient ineligible to receive previous therapy or toxicities of previous anticancer therapy resolved to grade ≤1 except for toxicities that in the opinion of the investigator do not affect the assessment of AEs related to the trial drug • Patient has recovered from prior surgery or other procedure or complication to grade ≤2 or to baseline condition • Laboratory screening values: ◦ Absolute neutrophil count ≥1.5 × 10^9/l ◦ Platelets ≥100 × 10^9/l ◦ Hemoglobin ≥8 g/dl ◦ ALT and AST ≤3 × ULN or ≤5 × ULN in cases of metastatic liver involvement ◦ Total bilirubin ≤1.5 × ULN or ≤2 × ULN in cases of metastatic liver involvement ▪ Total bilirubin ≤3.0 × ULN or direct bilirubin ≤1.5 × ULN will be allowed for cases of antecedents of Gilbert's syndrome ◦ eGFR >30 ml/min • Able to provide a baseline tumor biopsy sample[†,‡]	• Pregnant or lactating • Recent treatment (≤14 days) with anticancer medication or investigational drugs • Active, uncontrolled infection or unexplained fever • Known hypersensitivity to any of the components of Zeno or history of severe hypersensitivity to human or humanized monoclonal antibodies • Known HIV or hepatitis B or C infection • Known symptomatic or unstable brain metastases[§] • Patients with leptomeningeal metastases • Previous or concurrent malignancy[¶] • NYHA class III or IV congestive heart failure, LVEF <50%, or a history of significant cardiac disease

[†]For patients who received afatinib or other HER-targeting agents, a biopsy collected after the last line of treatment is strongly preferred to assess for mechanisms of acquired resistance.
[‡]When archival tissue is not available and collection of a fresh biopsy is not safe or feasible during the screening period, patients with a locally confirmed *NRG1* gene fusion will be allowed to enroll in the eNRGy trial, provided they meet all other inclusion/exclusion criteria.
[§]Patients with asymptomatic brain metastases are eligible to participate if the metastases have been radiographically and clinically stable for ≥1 month. If on steroids for this indication, the patient must be on a stable dose for ≥1 month.
[¶]Excluding nonbasal cell carcinoma of the skin or carcinoma *in situ* of the uterine cervix, unless the tumor was treated with curative or palliative intent and, in the opinion of the investigator (with sponsor agreement), the previous or concurrent malignancy condition doesn't affect the assessment of safety and efficacy of the trial drug.
AE: Adverse event; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ECOG PS: Eastern Cooperative Oncology Group performance status; eGFR: Estimated glomerular filtration rate; HIV: Human immunodeficiency virus; LVEF: Left ventricular ejection fraction; NGS: Next-generation sequencing; NRG1: Neuregulin 1; NYHA: New York Heart Association; RECIST: Response Evaluation Criteria in Solid Tumor; ULN: Upper limit of normal; Zeno: Zenocutuzumab.

Fcγ receptor genotyping, enumeration of *NRG1* fusion analysis on circulating tumor cells, and determination of circulating tumor DNA and testing for mutations in cancer genes (including those associated with HER2/HER3 signaling).

Upon completion of the trial, patients may be followed for disease status and will be followed for survival status every 3 months for up to 2 years from discontinuation of treatment. Tumor markers will be assessed via collection of a blood sample at the initial screening and once per cycle, in addition to tumor tissue samples collected at initial screening and optionally at the end of Cycle 4 and at the end of treatment. Tumor markers will be assessed per institutional protocols or management of specific cancer types or per investigator discretion (e.g., CA19-9 in PDAC). Adverse events will be reported from the time of the patient's first dose through 30 days following the last Zeno treatment and graded according to Common Terminology Criteria for Adverse Events v4.03.

Outcome measures/end points

For patients with NRG1+ cancer, the primary objective is to assess the magnitude of antitumor activity of Zeno, and the key secondary objective is to assess the durability of antitumor activity of Zeno (Table 2). Secondary objectives include the clinical benefit rate, duration of response, the time of onset of response, characterization of the safety and tolerability of Zeno, characterization of the PK profile of Zeno, immunogenicity of Zeno, and evaluation of progression-free survival and overall survival. The clinical activity and antitumor effect of Zeno will be evaluated according to RECIST v1.1 imaging (chest, abdomen, pelvis, head [if brain metastases detected] and additional sites for applicable tumor types) and will be obtained at the initial screening and every 8 weeks following the start of trial treatment. All imaging procedures will be performed according to standard local imaging protocols; imaging results for all patients with NRG1+ cancer will undergo independent review, read by a central imaging center. A confirmed response to treatment is defined as two consecutive assessments of complete or partial response assessed ≥4 weeks apart.

Table 2. Objectives and end points for Part 2 of the eNRGy trial.

Objective	End point
Patients with NRG1+ cancer	
Primary objective • To assess the magnitude of antitumor activity of Zeno in patients with *NRG1* fusions as assessed locally	• ORR[†,‡]
Key secondary objective • To assess the durability of antitumor activity of Zeno in patients with *NRG1* fusions as assessed locally	• DOR[†,‡]
Secondary objectives • To assess the magnitude and duration of antitumor activity of Zeno in patients with *NRG1* fusions as assessed centrally	• ORR[†,§] • DOR[†,§]
• To assess the CBR of Zeno in patients with *NRG1* fusions as assessed locally and centrally	• CBR[†,‡,¶] • CBR[†,§,¶]
• To assess time to onset of response in patients with *NRG1* fusions as assessed locally and centrally	• Time to response[†,‡] • Time to response[†,§]
• To characterize the safety and tolerability of Zeno	• Frequency and nature of AEs
• PK profile of Zeno	• Assessment of PK variables, including total exposure, C_{max}, V, V_{ss}, $t_{1/2}$, $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, and t_{max} • Population PK analysis
• Immunogenicity of Zeno	• Incidence and serum titers of antidrug antibodies against Zeno
• Evaluation of PFS and OS	

[†]Assessed per RECIST v1.1.
[‡]Assessed as per local investigator's assessment.
[§]Assessed as per central review.
[¶]Defined as the proportion of patients in whom a CR or PR is observed, or SD of a minimum duration of 24 weeks.
AE: Adverse event; $AUC_{0\text{-}t}$: Area under the curve from time zero to time t; $AUC_{0\text{-}\infty}$: Area under the curve from time zero to the time of the last quantifiable concentration; CBR: Clinical benefit rate; C_{max}: Maximum plasma concentration; CR: Complete response; DOR: Duration of response; NRG1: Neuregulin 1; ORR: Overall response rate; OS: Overall survival; PFS: Progression-free survival; PK: Pharmacokinetics; PR: Partial response; RECIST: Response Evaluation Criteria in Solid Tumor; SD: Stable disease; t_{max}: Time to reach maximum concentration; $t_{1/2}$: Half-life; V: Volume of distribution; V_{ss}: Volume of distribution at steady state; Zeno: Zenocutuzumab.

Statistics

Analysis method

Data from all participating centers will be combined and summarized for demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements, and all relevant PK/PD measurements. Quantitative data will be summarized using descriptive statistics, and qualitative data will be summarized with contingency tables. The full analysis population will comprise all patients to whom trial treatment was assigned and ≥1 dose of trial treatment was received. The primary efficacy evaluable population will comprise all patients who had a documented, functional *NRG1* fusion based on NGS testing in the absence of other driver mutations and who received the first dose of trial treatment ≥6 months prior to the cutoff date. Patients were also required to receive ≥1 infusion of Zeno at 750 mg once every 2 weeks, lack prior exposure to anti-HER3 targeting antibodies, and have ≥1 postbaseline response assessment or early discontinuation due to disease progression. The safety population will include all patients who received any trial treatment. The PK analysis population will include all patients who provide ≥1 evaluable PK concentration.

Sample size

Among patients with NRG1+ NSCLC, enrollment is planned to be limited to 100 patients. Enrollment of patients with NRG1+ PDAC is planned to be limited to 50 patients, and enrollment of patients with NRG1+ in other solid tumors into a basket cohort is planned to be limited to 100 patients across the various tumor types.

The eNRGy study in patients with *NRG1* fusions was designed to initially assess the presence of antitumor activity in patients with NSCLC, PDAC, or other tumor types, such as breast cancer and cholangiocarcinoma. The overall sample size was increased to a maximum of 250 patients to ensure a sufficient sample size to support a regulatory submission in NSCLC (to ensure at least 100 NSCLC patients previously treated with platinum-based combination), PDAC, and/or tumor agnostic setting, where a sufficient number of patients across multiple tumor types is expected to be treated to provide substantial evidence of effectiveness in a setting where a randomized trial will not be feasible.

Conclusion

Patients with advanced NRG1+ cancer have limited treatment options and suboptimal responses to conventional systemic treatment. The eNRGy trial will investigate the efficacy and safety of Zeno, a potential first-in-class IgG1 bispecific antibody targeting HER2 and HER3, in patients with NRG1+ cancer. Enrollment of patients with NRG1+ cancer began in September 2019 and, at the time of this publication, the eNRGy trial is still actively recruiting participants. Please refer to ClinicalTrials.gov (Identifier: NCT02912949), visit https://nrg1.com/, or call 1-833-NRG-1234 for more information.

Future perspective

Additional trials to detect the activity of Zeno in dysregulated HER3 signaling are ongoing (e.g., ClinicalTrials.gov Identifier: NCT05588609). Given the heterogeneity of *NRG1* gene fusions, it is likely that novel fusion partners will be detected and *NRG1* fusions will be identified in other solid tumors. With the broadening use of comprehensive molecular profiling (including RNA-based NGS) in clinical practice and incremental improvements in assay technology over time, the detection of driver alterations (including *NRG1* fusions) in clinical practice will continue to improve, providing the opportunity to match patients to targeted therapy. Identification of novel driver alterations and/or genetic signatures in advanced solid tumors will provide the opportunity for further development of targeted therapies.

Executive summary

- Neuregulin 1 (NRG1) is a ligand for HER2/HER3 signaling, which can promote the growth and development of epithelial, glial and muscle cells; chromosomal rearrangements can result in *NRG1* gene fusions, leading to dysregulated HER2/HER3 signaling.
- *NRG1* fusions can function as oncogenic drivers and are typically mutually exclusive of other common oncogenic drivers.

Background & rationale

- *NRG1* fusions have been described in numerous cancers, including non-small-cell lung cancer (NSCLC) and pancreatic ductal adenocarcinoma (PDAC).
- Although the incidence of cancers harboring *NRG1* fusions is relatively low, these cancers have limited therapeutics options.
- It has been shown that inhibiting HER2/HER3 signaling could provide therapeutic benefits to patients with NRG1+ cancer.
- Zenocutuzumab is a novel, bispecific IgG1 antibody that targets both HER2 and HER3 proteins and inhibits NRG1 binding through a 'Dock & Block®' mechanism of action.

eNRGy trial design & planned sample size

- The eNRGy trial is a phase I/II, open-label, multicenter trial exploring the safety, tolerability, pharmacokinetics, pharmacodynamics, immunogenicity and antitumor activity of zenocutuzumab in patients with NRG1+ NSCLC, PDAC, or other solid tumors.
- Planned enrollment in the eNRGy trial is approximately 100 patients with NRG1+ NSCLC, 50 patients with NRG1+ PDAC, and 100 patients with other NRG1+ solid tumors.
- The primary objective is to assess the magnitude of antitumor activity of zenocutuzumab, and the key secondary objective is to assess the durability of antitumor activity.

Conclusion

- The eNRGy trial will investigate the efficacy and safety of zenocutuzumab, a potential first-in-class IgG1 bispecific antibody targeting HER2/HER3, in patients with NRG1+ cancer.
- Enrollment of patients with NRG1+ cancer began in September 2019 and, at the time of this publication, the eNRGy trial is actively recruiting participants.

Author contributions

AM Schram: conceptualization, data curation, formal analysis, investigation, methodology, supervision, validation, writing – review & editing. D-W Kim: conceptualization, writing – review & editing. A Hollebecque: data curation, supervision, validation, writing – review & editing. K Nishino: resources, writing – review & editing. T Macarulla: conceptualization, investigation, methodology, validation, visualization, writing – review & editing. SY Rha: conceptualization, data curation, formal analysis, investigation, methodology, writing – review & editing. M Duruisseaux: validation, visualization, writing – review & editing. SV Liu: investigation, resources, writing – review & editing. M Najeeb Al Hallak: data curation, investigation, writing – review & editing. K Umemoto: writing – review & editing. C Wesseler: conceptualization, investigation, writing – original draft, writing – review & editing. JM

Cleary: investigation, project administration, resources, writing – review & editing. C Springfeld: writing – original draft, writing – review & editing. C Neuzillet: validation, writing – original draft, writing – review & editing. A Joe: writing – review & editing. S Jauhari: project administration, supervision, writing – original draft, writing – review & editing. J Ford: methodology, writing – review & editing. K Goto: investigation, writing – review & editing.

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D-W Kim reports uncompensated consultation or advisory role at Amgen, AstraZeneca, BMS/ONO Pharmaceutical, Daiichi Sankyo, GSK, Janssen, Merck, MSD, Oncobix, Pfizer, SK Biopharm, and Takeda. AM Schram reports serving on a Merus advisory board. All other authors have no other competing interests or relevant affiliations with any organization or entity with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Ethical conduct of research

The investigators have obtained appropriate institutional review board approval and have followed the principles outlined in the Declaration of Helsinki for all human experimental investigations. Written informed consent is required and has been obtained from the participants involved.

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