CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761352Orig1s000

MULTI-DISCIPLINE REVIEW

NDA/BLA Multi-disciplinary Review and Evaluation

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

Application Type	BLA
Application Number(s)	761352
Priority or Standard	Priority
Submit Date(s)	March 5, 2025
Received Date(s)	March 5, 2025
PDUFA Goal Date	February 4, 2025 (extended from November 4, 2024)
Division/Office	Division of Oncology 2/ Office of Oncologic Diseases
Review Completion Date	Refer to electronic stamp date
Established Name	Zenocutuzumab
(Proposed) Trade Name	BIZENGRI®
Pharmacologic Class	Bispecific HER2- and HER3-directed antibody
Code name	MCLA-124
Applicant	Merus N.V.
Formulation(s)	Injection: 375 mg/18.75 mL (20 mg/mL) in a single-dose vial
Dosing Regimen	750 mg intravenous infusion every 2 weeks until disease progression or unacceptable toxicity
Applicant Proposed Indication(s)/Population(s)	• Adult patients with advanced unresectable or metastatic non-small cell lung cancer (NSCLC) harboring a neuregulin 1 (NRG1) gene fusion following progression with prior systemic therapy (b) (4) (b) (4) • Adult patients with advanced unresectable or metastatic pancreatic adenocarcinoma (PDAC) harboring an NRG1 gene fusion following progression with prior systemic therapy (b) (4) (b) (4)
Recommendation on Regulatory Action	Accelerated Approval

Recommended Indication(s)/Population(s) (if applicable)	• 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 neuregulin 1 (*NRG1*) gene fusion with disease progression on or after prior systemic therapy.

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OPQ=Office of Pharmaceutical Quality

OPRO=Office of Program and Regulatory Operations

RBPM=Regulatory Business Process Manager

OPQAIII=Office of Product Quality Assessment III

DS=Drug Substance

DP=Drug Product

OPDP=Office of Prescription Drug Promotion

OSI=Office of Scientific Investigations

OSE= Office of Surveillance and Epidemiology

DEPI= Division of Epidemiology

DMEPA=Division of Medication Error Prevention and Analysis

DRISK=Division of Risk Management

Glossary

AC	advisory committee
ADA	antidrug antibody
ADC	antibody-drug conjugate
ADCC	Antibody-dependent cellular cytotoxicity
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ALP	alkaline phosphatase
AUC	Area under the drug concentration-time curve
BC	Breast cancer
BICR	Blinded independent central review
BLA	biologics license application
BMI	Body mass index
BOR	Best overall response
BP	blood pressure
BPM	Beats per minute
BTD	Breakthrough therapy designation
BTDR	Breakthrough therapy designation request
CBR	Clinical benefit rate
CDER	Center for Drug Evaluation and Research
CDK4/6	Cycline-dependent kinase 4/6
CDRH	Center for Devices and Radiological Health
CFR	Code of Federal Regulations
CI	Confidence interval
CL	Clearance
CLIA	Clinical Laboratory Improvements Amendments

Cmax	Maximum observed drug concentration
CMC	chemistry, manufacturing, and controls
CR	Complete response
CRC	Colorectal cancer
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CT	Computed tomography
CTCAE	Common terminology criteria for adverse e
DBP	Diastolic blood pressure
DCR	Disease control rate
DRC	Data review committee
DNA	Deoxyribonucleic acid
EC	Endometrial cancer
ECG	electrocardiogram
ECHO	Echocardiogram
eCTD	electronic common technical document
EDC	Electronic data capture
EGF	Epidermal growth factor
EOI	End of infusion
EOP	End of phase
EOT	End of treatment
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
FDG	Fluorodeoxyglucose
FFPE	Formalin-fixed paraffin-embedded
GC/GEC	Gastric cancer
GCP	good clinical practice

GLP	good laboratory practice
ICF	Informed consent form
ICH	International Conference on Harmonization
IMA	Invasive mucinous adenocarcinoma
IND	Investigational New Drug
IO	Immunotherapy
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
IV	Intravenous (IV)
KRAS	Kirsten rat sarcoma virus
LVEF	Left ventricular ejection fraction
MAPK	Mitogen-activated protein kinase
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
mmHg	Millimeter of mercury
mTOR	Mammalian target of rapamycin
MUGA	Multigated acquisition
NC	Not calculable
NCI	National Cancer Institute
NE	Not evaluable
NGS	Next-generation sequencing
NME	new molecular entity
NRG1	Neurgulin (human gene encoding heregulin protein) 1
NRG1+	Neuregulin 1 gene fusion-positive
NSCLC	Non-small cell lung cancer
OC	Ovarian cancer
ORR	Overall response rate

OS	Overall survival
PARP	Poly (ADP-ribose) polymerase
PCR	Polymerase chain reaction
PD	pharmacodynamics
PD-(L)1	Programmed death-(ligand) 1
PDAC	Pancreatic ductal adenocarcinoma
PERCIST	Positron Emission Tomography Response Criteria in Solid Tumors
PES	Primary Efficacy Set
PET	Positron emission tomography
PFS	Progression-free survival
PI3K	Phosphatidylinositol-3-kinase
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PO	Per os (oral)
PS	Performance status
PT	Preferred term
QRS	Q-, R-, S-wave
QTc	Corrected QT interval
QTcB	Corrected QT interval by Bazett
QTcF	Corrected QT interval by Fridericia
QTL	Quality tolerance limit
QxW	Once every x weeks
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria In Solid Tumors
REMS	risk evaluation and mitigation strategy
RNA	Ribonucleic acid
RP2D	Recommended Phase 2 dose

SAE	serious adverse event
SAF	Safety Analysis Set
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SD	Stable disease
SES	Supportive efficacy set
SOC	Standard of care
$T_{1/2}$	Apparent terminal half-life
TBL	Total bilirubin
TEAE	treatment emergent adverse event
TKI	Tyrosine kinase inhibitor
t_{max}	Time of observed maximum drug concentration
TMF	Trial master file
TTR	Time to response
ULN	Upper limit of normal
US(A)	United States (of America)
Vs	Versus
Vss	Apparent volume distribution at steady state
VEGF	Vascular endothelial growth factor
WHO	World Health Organization

1 Executive Summary

1.1. Product Introduction

Zenocutuzumab (MCLA-128) is a bispecific antibody that binds to the extracellular domains of HER2 and HER3 expressed on the surface of cells, including tumor cells. When bound to its target, zenocutuzumab blocks HER2:HER3 dimerization and prevents *NRG1* binding to HER3, inhibiting downstream signaling.

In this new biologics license application (BLA), the Applicant proposed the following indications for zenocutuzumab:

- Adults with advanced, unresectable or metastatic non-small cell lung cancer (NSCLC) harboring a neuregulin 1 (NRG1) gene fusion following progression with prior systemic therapy (b) (4)
- Adults with advanced, unresectable or metastatic pancreatic adenocarcinoma (PDAC) harboring a neuregulin 1 (NRG1) gene fusion following progression with prior systemic therapy (b) (4)

The recommended indications are,

- 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 neuregulin 1 (NRG1) gene fusion with disease progression on or after prior systemic therapy.

The recommended dosage of zenocutuzumab is 750 mg every 2 weeks until disease progression or unacceptable toxicity.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The review team recommends accelerated approval of zenocutuzumab for the treatment of adult patients with advanced unresectable or metastatic NSCLC or PDAC harboring an *NRG1* fusion with disease progression on or after prior systemic therapy.

In accordance with the provisions of 21 CFR 314.510 Subpart H, the recommendation for accelerated approval is primarily supported by overall response rate (ORR) and duration of response (DOR) results of Study MCLA-128-CL01 (eNRGy), which are considered reasonably likely to predict clinical benefit.

The eNRGy study is a multicenter, single-arm trial investigating zenocutuzumab in patients with NSCLC, PDAC, and other solid tumors harboring an *NRG1* fusion with disease progression on or after prior systemic therapy or who do not have satisfactory alternative treatment options.

Patients with tumors harboring other targetable genetic alterations were not eligible. Eligible patients had at least one measurable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, and an unresectable or metastatic solid tumor with a documented *NRG1* gene fusion identified through a molecular assay such as a next generation-sequencing-based assay [DNA or RNA], as routinely performed at CLIA or other similarly-certified laboratories. The primary objective to demonstrate the efficacy of zenocutuzumab for this population was ORR according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 as assessed by blinded independent central review (BICR). DOR was a key secondary endpoint.

The primary efficacy population consisted of 64 patients with NSCLC and 30 patients with PDAC. Of the NSCLC patients, 56% received prior treatment with platinum-based chemotherapy and prior anti-PD-1/PD-L1 therapy; 95% received prior platinum-based chemotherapy and 64% received prior anti-PD-1/PD-L1 therapy. The confirmed BICR-assessed ORR in the primary efficacy population of patients with NSCLC was 33% (95% CI: 22, 46) with a median DOR of 7.4 months (95% CI: 4.0, 16.6) for the 21 responders; a total of 43% of responders had a DOR ≥ 6 months. The ORR as assessed by BICR in the PDAC population was 40% (95% CI: 23, 59). The percentage of responders with a DOR of ≥6 months was 67%, and the percentage of responders with a DOR of ≥12 months was 17%.

FDA considers ORR, supported by DOR, to be an appropriate early clinical endpoint for these populations as it is a direct measure of the intervention; in the absence of therapy, NSCLC and PDAC tumors do not typically regress on their own. There are no approved therapies specifically targeting NRG1+ NSCLC or PDAC. Patients with metastatic NRG1+ NSCLC and no other actionable mutations are treated with standard regimens approved for the unselected NSCLC population. For patients with disease progression after standard first-line therapy, which includes a PD-(L)1 inhibitor with or without platinum-based chemotherapy, several chemotherapy regimens are available. The highest reported ORR in this setting is approximately 23% with docetaxel plus ramucirumab (Garon et al, *Lancet* 2014). Likewise, patients with NRG1+ PDAC are treated with standard of care chemotherapy, based on survival benefit observed with combination regimens. The ORR for the only approved regimen in the refractory disease setting, nal-irinotecan in combination with fluorouracil, is 7.7% (Onivyde USPI).

The observed ORR and DOR with zenocutuzumab, which appear to exceed the ORR and DOR observed with available second and later-line therapies for both NSCLC and PDAC, represent a clinically meaningful treatment effect in patients with previously-treated NRG1 fusion-positive NSCLC and PDAC and provide substantial evidence of effectiveness for both settings. Additionally, the improvement over available therapy takes into account that zenocutuzumab acts through a novel mechanism of action with a safety profile that is different than alternative treatments and manageable through appropriate labeling, particularly in the context of the improved efficacy compared to available therapy.

The Applicant also provided efficacy data from 11 patients with treatment-naïve NSCLC (ORR 36% [95% CI: 11, 70]); (b) (4) these results are considered generally supportive of

those observed in the primary efficacy population (b) (4)

A review extension was issued on November 4, 2024 to extend the Prescription Drug User Fee Act (PDUFA) goal date from November 4, 2024 to February 4, 2025. The basis for review extension was the submission of additional chemistry, manufacturing, and control (CMC) information on October 30, 2024 which required additional time to review. Both issues were fully resolved and support the review team's final recommendation.

The submitted evidence meets the statutory evidentiary standard for accelerated approval of zenocutuzumab for the treatment of patients with advanced unresectable or metastatic NSCLC or PDAC harboring an NRG1 fusion with disease progression on or after prior systemic therapy, and represents the first approval of a targeted therapy for NRG1 fusions. Continued approval for this indication may be contingent up upon verification and description of clinical benefit based on further characterization of response rate and durability through additional patient enrollment and longer follow-up from the ongoing eNRGy trial as a post-marketing requirement (PMR). The use of single arm data to support accelerated approval is considered appropriate in this case given the rarity of *NRG1* fusions and the improved ORR observed in the eNRGy trial relative to that of available second or later line therapies for NSCLC and PDAC rendering conduct of a randomized trial in these populations infeasible.

The Consolidated Appropriations Act (2023) provides the FDA with the authority to require that confirmatory studies to verify clinical benefit be underway prior to accelerated approval. The eNRGy trial continues to enroll patients at a rate expected to support timely completion, with an estimated final report submission within two years. As such, the review division considers the confirmatory study for this accelerated approval to be underway.

In this context, the efficacy and safety findings support a favorable benefit:risk assessment, and the review team recommends accelerated approval for zenocutuzumab for the treatment of adult patients with NSCLC and PDAC harboring *NRG1* fusions with disease progression on or after prior systemic therapy.

1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

Metastatic non-small cell lung cancer (NSCLC) is a serious and life-threatening disease with an unmet medical need, as evidenced by 5-year overall survival rates ranging from approximately 4-8% (Bar et al, *J Oncol* 2021; Ganti et al, *JAMA Oncol* 2021). Unresectable or metastatic pancreatic ductal adenocarcinoma (PDAC) is also a serious disease with a dismal prognosis, with an estimated survival median survival of 11.1 months in patients who are able to receive intensive chemotherapy (Wainberg Z et al *Lancet 2023*). The *NRG1* gene encodes a protein which can present as a soluble ligand or as a fusion protein inserted in the cell membrane. The *NRG1* gene contains an epidermal growth factor (EGF)-like domain and can bind to receptors in the ErbB family. When bound to the HER3 receptor, *NRG1* induces HER2/HER3 dimerization and downstream pro-proliferative signaling. *NRG1* gene fusions are rare, occurring in approximately 0.3% of patients with NSCLC and most commonly occur in patients with adenocarcinoma histology, particularly invasive mucinous adenocarcinomas (IMAs) (Li et al *Front Oncol* 2024; Muscarella, *PCM* 2023); *NRG1* fusions are estimated to be below 0.5% of all cases in PDAC. NRG1+ fusions are associated with lower tumor mutational burden and PD-L1 expression, and there are reports that suggest NRG1+ NSCLC is more aggressive and less likely to respond to standard platinum-based chemotherapy and immunotherapy regimens (Duruisseaux, et al *JCO* 2019; Drilon et al, *J Clin Oncol* 2021).

There are no approved therapies specifically targeting NRG1+ NSCLC or PDAC. Patients with metastatic NRG1+ NSCLC and no other actionable mutations are treated with standard regimens approved for the unselected NSCLC population. For patients with disease progression after standard first-line therapy, which includes a PD-(L)1 inhibitor with or without platinum-based chemotherapy, several chemotherapy regimens are available. The highest reported ORR in this setting is approximately 23% with docetaxel plus ramucirumab (Garon et al, *Lancet* 2014). Likewise, patients with NRG1+ PDAC are treated with standard of care chemotherapy, based on survival benefit observed with combination regimens. The ORR for the only approved regimen in the refractory disease setting, nal-irinotecan in combination with fluorouracil, is 7.7% (Onivyde USPI).

This BLA for zenocutuzumab is supported by results from Study MCLA-128-CL01 (eNRGy), an ongoing, multicenter, open-label trial evaluating the safety and efficacy of zenocutuzumab in adult patients with advanced unresectable or metastatic NSCLC and PDAC harboring an *NRG1* fusion and with disease progression on or after prior systemic therapy, or who have no satisfactory alternative treatment options available. The primary efficacy population included 75 patients with NSCLC (64 previously treated and 11 treatment-naïve) and 30 patients with PDAC. All patients in the study had measurable disease and received zenocutuzumab 750 mg IV every 2 weeks until treatment progression or

unacceptable toxicity.

The primary objective to demonstrate the efficacy of zenocutuzumab for this population was overall response rate (ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 as assessed by blinded independent central review (BICR). Duration of response was a key secondary endpoint. The primary efficacy population consisted of 64 patients with NSCLC and 30 patients with PDAC. Of the NSCLC patients, 56% received prior treatment with platinum-based chemotherapy and prior anti-PD-1/PD-L1 therapy; 95% received prior platinum-based chemotherapy and 64% received prior anti-PD-1/PD-L1 therapy. The confirmed BICR-assessed ORR in the primary efficacy population of patients with NSCLC was 33% (95% CI: 22, 46) with a median DOR of 7.4 months (95% CI: 4.0, 16.6) for the 21 responders. A total of 43% of responders had a DOR ≥6 months. The ORR as assessed by BICR in the PDAC population was 40% (95% CI: 23, 59). The percentage of responders with a DOR of ≥6 months was 67%, and the percentage of responders with a DOR of ≥12 months was 17%.

The primary safety population for this BLA comprises 175 patients treated on the eNRGy trial at the recommended dosage, including 99 patients with NRG1+ NSCLC and 39 patients with NRG1+ PDAC. The most common adverse events (≥10%) were diarrhea (28%), musculoskeletal pain (23%), fatigue (20%), nausea (17%), infusion-related reactions (13%), dyspnea (14%), constipation (13%), vomiting (12%), rash, abdominal pain (11% each), and edema (10%). The most frequent Grade 3-4 adverse reactions (≥2%) were anemia, diarrhea, abdominal pain, dyspnea and fatigue. Serious adverse reactions occurred in 24% of patients in the primary safety population. The most frequent (≥2%) were pneumonia (n=6) and dyspnea (n=4). Fatal adverse reactions occurred in five (2.9%) patients in the primary safety population. Fatal adverse reactions in the NSCLC population included respiratory failure (n=2) and cardiac failure (n=1). Fatal adverse reactions in the PDAC population included respiratory failure (n=1) and COVID-19 (n=1). Important safety signals identified included infusion related reactions/hypersensitivity, interstitial lung disease/pneumonitis and left ventricular dysfunction. These safety concerns will be addressed in the Warnings and Precautions section of the USPI. The safety profile for zenocutuzumab is considered acceptable when assessed in the context of a life-threatening disease and with appropriate monitoring as described in the product label.

An FDA-approved test for detection of NRG1 fusions in NSCLC and PDAC for selecting patients for treatment with zenocutuzumab is not available. The clinical review team determined that it is in the best interest of U.S. patients to approve zenocutuzumab before a companion diagnostic assay is available. Since an application for an in vitro companion diagnostic device is still under review, a contemporaneous approval with this BLA is not possible. The approved labeling will state that there is no FDA-approved test for selecting patients for treatment with zenocutuzumab. A post-marketing commitment (PMC) will be issued for the Applicant to provide adequate analytical and clinical validation results from clinical trial data to support labeling of a companion diagnostic test to detect NRG1 fusions for identifying patients who may benefit from zenocutuzumab.

The results of the eNRGy trial demonstrate substantial evidence of effectiveness for the treatment of adult patients with advanced unresectable or metastatic NCLC or PDAC harboring an *NRG1* fusion with disease progression on or after prior systemic therapy and allow for a favorable benefit:risk assessment. The magnitude of the observed treatment effect on ORR and DOR is clinically meaningful and provides a therapeutic benefit over available therapies. Given the rarity of *NRG1* fusions, a randomized trial is not considered feasible. Additionally, the improvement over available therapy takes into account that zenocutuzumab acts through a novel mechanism of action with a safety profile that is different than alternative treatments and manageable through appropriate labeling, particularly in the context of the improved efficacy compared to available therapy.

Based on the results of the eNRGy trial, the totality of information submitted to this BLA, and the favorable benefit:risk profile for this population with a serious and life-threatening disease, the review team recommends accelerated approval for zenocutuzumab for the following indications**: 1) the treatment of adult patients with advanced unresectable or metastatic NSCLC harboring an *NRG1* fusion with disease progression on or after prior systemic therapy; and 2) the treatment of adult patients with advanced unresectable or metastatic PDAC harboring an *NRG1* fusion with disease progression on or after prior systemic therapy.** Continued approval for this indication may be contingent upon verification and description of clinical benefit based on additional efficacy and safety data from the ongoing eNRGy trial as a post-marketing requirement (PMR). The Consolidated Appropriations Act (2023) provides the FDA with the authority to require that confirmatory studies to verify clinical benefit be underway prior to accelerated approval. The eNRGy trial continues to enroll patients at a rate expected to support timely completion, with an estimated final report submission within two years. As such, the review division considers the confirmatory study for this accelerated approval to be underway.

Dimension	NSCLC Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Lung cancer is the leading cause of cancer death in the U.S. with non-small cell lung cancer (NSCLC) representing approximately 80-85% of cases. Patients with metastatic NSCLC at diagnosis have a poor prognosis, with an estimated 5-year survival rate of 4-9%. • *NRG1* fusions are rare in NSCLC, occurring in approximately 0.3% of cases. • Data on the prognosis of patients with NRG1+ NSCLC are limited,	NRG1+ advanced unresectable or metastatic NSCLC is a rare, serious and life-threatening condition with poor survival.

Dimension	NSCLC Evidence and Uncertainties	Conclusions and Reasons
	however; there are reports that tumors harboring *NRG1* fusions are more aggressive and less responsive to standard chemo-immunotherapy.	
Current Treatment Options	• Treatment options for patients with NRG1 fusion-positive metastatic NSCLC are the same as those utilized for patients with NSCLC with no targeted mutations. • After progression on standard of care first-line therapy consisting of a PD-(L)1 inhibitor with or without platinum-based therapy, there are several chemotherapy regimens available for the general population of patients with metastatic NSCLC, including NRG1 fusion-positive NSCLC. Of these, the highest ORR (23%) is reported with ramucirumab in combination with docetaxel.	There is an unmet medical need for patients with metastatic NRG1+ NSCLC based on the observed ORRs, DORs, and overall survival (OS) reported for the non-targeted therapies available for treatment of this patient population. There are no approved targeted therapies for *NRG1* fusions in NSCLC.
Benefit	• The efficacy of zenocutuzumab was evaluated in the eNRGy trial, an ongoing, multicenter, single arm, open-label trial in patients with advanced unresectable or metastatic NRG1+ NSCLC with progression after prior therapy or who have no satisfactory alternative treatment options. The primary efficacy population included 64 patients with previously-treated NSCLC. • Per BICR assessment, the ORR per RECIST v1.1 was 32% (95% CI: 21, 46) with a median DOR of 7.4 months (95% CI: 4.0, 16.6); a total of 43% of responders had a DOR of ≥6 months.	The submitted evidence meets the statutory evidentiary standard for accelerated approval in the previously-treated NRG1 fusion-positive NSCLC population. The magnitude of treatment effect and durability of responses provide evidence that zenocutuzumab provides a meaningful therapeutic benefit over available therapies in this genetically defined, rare subgroup of patients with metastatic NSCLC, and are higher than that observed with currently available therapies. Continued approval for this indication may be contingent upon verification

Dimension	NSCLC Evidence and Uncertainties	Conclusions and Reasons
		and description of clinical benefit based on additional efficacy and safety data from the ongoing eNRGy trial as a PMR. The eNRGy trial continues to enroll patients at a rate expected to support timely completion, with an estimated final report submission within two years. As such, the review division considers the confirmatory study for this accelerated approval to be underway.
Risk and Risk Management	• The safety database for this application comprises 175 patients treated with zenocutuzumab in the eNRGy trial. The data described below are for the 99 patients with NRG1+ NSCLC treated in the eNRGy trial. • Serious adverse reactions occurred in 25 (25%) patients with NRG1-fusion positive NSCLC. The most frequent (occurring in ≥2% of patients) were pneumonia (n=4), dyspnea and fatigue (n=2 each). • The most common adverse events (≥10%) included diarrhea, musculoskeletal pain, dyspnea, fatigue, cough, rash, infusion-related reactions, decreased appetite, edema and nausea.	Although zenocutuzumab can cause serious adverse reactions, these safety concerns will be addressed by information in the Warnings and Precautions and Dosage and Administration sections of product labeling. A PMR will be issued for an integrated safety analysis of data from patients with NRG1 fusion positive solid tumors to further characterize the long-term incidence, severity and outcome of the known serious risks of infusion-related reactions/hypersensitivity/anaphylaxis, interstitial lung disease/pneumonitis, and left ventricular dysfunction. The clinical review team determined that it is in the best interest of U.S. patients to approve

Dimension	NSCLC Evidence and Uncertainties	Conclusions and Reasons
		zenocutuzumab before a companion diagnostic assay is available. Since review of an application for an in vitro companion diagnostic device is still ongoing, a contemporaneous approval with this BLA is not possible. The approved labeling will state that there is no FDA-approved test for selecting patients for treatment with zenocutuzumab. A post-marketing commitment (PMC) will be issued for the Applicant to provide adequate analytical and clinical validation results from clinical trial data to support labeling of a companion diagnostic test to detect NRG1 fusions for identifying patients who may benefit from zenocutuzumab.

Dimension	NRG1+ Pancreatic Adenocarcinoma - Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Pancreatic adenocarcinoma (PDAC) is the 10th most common cancer in the US (3.3% of all cancers). In 2024, it is estimated that there will be 66,440 new cases of pancreatic cancer and an estimated 51,750 people will die of this disease (SEER Cancer Stat Fact: Pancreatic Cancer, accessed 9/20/2024). The prognosis is generally poor, with a median estimated overall survival for patients diagnosed with metastatic	*NRG1*+ advanced unresectable or metastatic PDAC is a rare, serious and life-threatening condition with poor survival.

Dimension	NRG1+ Pancreatic Adenocarcinoma - Evidence and Uncertainties	Conclusions and Reasons
	disease of less than a year. • *NRG1* fusions are very rare in PDAC (estimated to be below 0.5% of all cases). • There are very limited data on the prognosis of patients with *NRG1+* PDAC, and it does not appear that the presence of the fusion confers a particular predictive value to response to standard of care therapy, nor a general prognostic value.	
Current Treatment Options	• Treatment of patients with unresectable or metastatic PDAC is palliative. For patients who are eligible, the first-line treatment is combination chemotherapy, and the agents to be used are selected based on the general status of the patient and physician/institutional preferences. The most commonly regimens used in the US are fluoropyrimidine-, oxaliplatin, and irinotecan-based regimens (FOLFIRI and NALIRIFOX) and the combination of gemcitabine and nab-paclitaxel (GNP). The use of these regimens is supported by overall survival benefit observed in randomized controlled trials. For patients with poor health status, if eligible, gemcitabine is also indicated. • Treatment of patients with disease progression is determined by the prior first-line therapy received. If eligible, patients treated with FOLFIRINOX or NALIRIFOX may receive GNP and vice versa. The only approved therapy for relapsed/refractory disease is the combination of nal-irinotecan, fluorouracil, and leucovorin, which provided survival benefit in the NAPOLI-1 trial. NAPOLI-1 was a randomized study in patients with disease progression after prior gemcitabine therapy. Patients were randomized to receive nal-	Current treatment options for patients with relapsed/refractory PDAC are limited and provide a limited benefit; patients with this disease have an unmet medical need. There are no currently approved treatments for patients with *NRG1+* PDAC.

Dimension	NRG1+ Pancreatic Adenocarcinoma - Evidence and Uncertainties	Conclusions and Reasons
	irinotecan, fluorouracil, and leucovorin or fluorouracil and leucovorin. The study showed a median overall survival of 6.1 months (95% CI 4.8, 8.5) in the nal-irinotecan, fluorouracil, and leucovorin arm compared with 4.2 months (95% CI 3.5, 5.3) in the comparator arm (HR 0.68, 95% CI 0.50, 0.93). The ORR with nal-irinotecan, fluorouracil, and leucovorin was 7.7% (Onivyde USPI). • There are no approved therapies for patients with *NRG1*+ PDAC.	
Benefit	• The efficacy of zenocutuzumab was evaluated in the eNRGy trial, an ongoing, multicenter, single arm, multi-cohort, open-label study. The *NRG1*+ PDAC cohort enrolled 30 patients with advanced unresectable or metastatic disease; all but one patient had received prior systemic therapy. • Per BICR assessment, the ORR per RECIST v1.1 in the treatment-naïve setting was 40% (95% CI 23, 59). The median duration of response was not reached; 67% of responders had a DOR of ≥6 months.	The magnitude of effect on ORR observed in the eNRGy trial cohort with *NRG1*+ relapsed/refractory PDAC is higher than that observed with current standard of care with nal-irinotecan, fluorouracil, and leucovorin (7.7% in the NAPOLI-1 trial). The duration of responses observed in patients with *NRG1*+ PDAC was clinically meaningful in the context of a disease with estimated survival of 6 months. The submitted evidence meets the statutory evidentiary standard for accelerated approval. Continued approval for this indication may be contingent upon verification and description of clinical benefit based on additional efficacy and safety data from the ongoing eNRGy trial as a PMR. Merus has agreed to a PMR to submit data from a single-arm trial to verify and confirm the clinical benefit of zenocutuzumab

Dimension	NRG1+ Pancreatic Adenocarcinoma - Evidence and Uncertainties	Conclusions and Reasons
		in patients with *NRG1*+ PDAC. Due to the rarity of the disease, a randomized study is not feasible.
Risk and Risk Management	• The safety database for this application comprises 175 patients treated with zenocutuzumab in the eNRGy trial. The data presented below are for the 39 patients with *NRG1*+ PDAC treated in the eNRGy trial. • The most frequently observed (≥20%) adverse events were diarrhea, musculoskeletal pain, nausea, vomiting, and fatigue. The most common (≥2%) Grade 3-4 adverse events were hemorrhage, abdominal pain, fatigue, nausea, diarrhea, and vomiting. Serious adverse reactions occurred in 23% of patients, but no event was observed more than once. There were 2 fatal events, one due to COVID-19 and one due to respiratory failure. Due to the single-arm nature of the trial, there is uncertainty regarding the relation of some of the adverse events to zenocutuzumab (e.g., as compared to the background rate of adverse events in patients with advanced PDAC). Certain adverse reactions; however, such as infusion reactions or LVD, are unlikely to occur in the absence of drug therapy.	The observed safety profile is acceptable when assessed in the context of the treatment of a life-threatening disease. Most of the adverse reactions to zenocutuzumab were manageable with supportive care and treatment interruptions. The significant and potentially serious adverse reactions of infusion related reactions/hypersensitivity/anaphylaxis, interstitial lung disease/pneumonitis, and left ventricular dysfunction are adequately addressed in the Warnings and Precautions section and the dose modification recommendations included in product labeling; a PMR will be issued as described above in the NSCLC table. The clinical review team determined that it is in the best interest of U.S. patients to approve zenocutuzumab before a companion diagnostic assay is available. Since review of an application for an in vitro companion diagnostic device is still under review, a

Dimension	NRG1+ Pancreatic Adenocarcinoma - Evidence and Uncertainties	Conclusions and Reasons
		contemporaneous approval with this BLA is not possible. The approved labeling will state that there is no FDA-approved test for selecting patients for treatment with zenocutuzumab. A post-marketing commitment (PMC) will be issued for the Applicant to provide adequate analytical and clinical validation results from clinical trial data to support labeling of a companion diagnostic test to detect NRG1 fusions for identifying patients who may benefit from zenocutuzumab.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply): N/A, patient experience data was not submitted as part of this Application.

□	The patient experience data that was submitted as part of the application, include:					Section where discussed, if applicable
	□	Clinical outcome assessment (COA) data, such as				[e.g., Section 6.1 Study endpoints]
			□	Patient reported outcome (PRO)		
			□	Observer reported outcome (ObsRO)		
			□	Clinician reported outcome (ClinRO)		
			□	Performance outcome (PerfO)		
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)				
	□	Patient-focused drug development or other stakeholder meeting summary reports				[e.g., Section 2.1 Analysis of Condition]
	□	Observational survey studies designed to capture patient experience data				
	□	Natural history studies				
	□	Patient preference studies (e.g., submitted studies or scientific publications)				
	□	Other: (Please specify)				
□	Patient experience data that was not submitted in the application, but was considered in this review.					

X

Cross-Disciplinary Team Leader

Amy Barone, MD

2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

Neuregulin 1 (NRG1)

Neuregulin 1 (*NRG1*) the human gene encoding the heregulin protein, belongs to a group of ligands for the ERBB family of transmembrane receptor tyrosine kinases. NRG1 can be expressed by cancer cells or by cells in the tumor microenvironment as different isoforms and as an NRG1 fusion protein on tumor cells. NRG1 interacts with human epidermal growth factor receptor (HER) 3 (HER3; ERBB3) and HER4 (ERBB4), stimulating downstream growth and proliferation signaling pathways. Activation of HER2/HER3 heterodimers occurs via NRG1 ligand binding to HER3, and results in transphosphorylation of the 6 docking sites for the p85 subunit of phosphatidylinositol-3-kinase (PI3K) on the cytoplasmic domain of HER3, via the HER2 kinase (Fernandez-Cuesta et al, 2014).

Fusion proteins occur when a chromosomal translocation between 2 genes results in the transcription and translation of an in-frame mRNA transcript, with a resulting chimeric protein that can drive tumor progression (Mitelman et al, 2007). Multiple NRG1 fusion partners have been reported, including *CD74, ATP1B1, SDC4*, and *RBPMS*. A large range of gene fusion partners is seen both between and within tumor types (Jonna et al, 2019).

Functional studies of *NRG1* fusions support their role as oncogenic drivers across a range of in vitro and in vivo models. Functional NRG1 fusion proteins contain the carboxy terminus of the NRG1 protein, including an epidermal growth factor (EGF)-like domain. This EGF-like domain can bind to HER3 on the same or adjacent cells, triggering HER2/HER3 heterodimerization and activation of potent downstream signaling via the mitogen-activated protein kinase (MAPK) and PI3K mitogenic signaling pathways, promoting migration, proliferation, and tumor growth (Drilon et al, 2018; Fernandez-Cuesta et al, 2014).

The role of *NRG1* fusions as oncogenic drivers of cancer cell growth is further supported by their occurrence in the absence of other canonical cancer driver mutations in the vast majority of NRG1+ cancer reported to date (Chang et al, 2021; Dhanasekaran et al, 2014; Jones et al, 2019; Jonna et al, 2019). Studies in patients with NRG1 gene fusion-positive (NRG1+) cancer have highlighted the potential actionability of these fusions (Drilon et al, 2018; Fernandez-Cuesta et al, 2014; Geuijen et al, 2018; Heining et al, 2018; Jones et al, 2019; Schram et al, 2019).

NRG1 gene fusions have been detected at a low frequency across a wide range of tumor types (Jonna et al, 2020). In a genomic profiling study, *NRG1* fusions were reported in a range of cancer

types including non-small cell lung cancer (NSCLC), pancreatic ductal adenocarcinoma (PDAC), gallbladder cancer, renal cell carcinoma (RCC), ovarian cancer, breast cancer, sarcoma, bladder cancer, and colorectal cancer (CRC). Cancer types with relatively higher frequency and/or prevalence of *NRG1* fusions include NSCLC and PDAC (Fernandez-Cuesta et al, 2014; Heining et al, 2018).

The natural history and prognostic significance of cancer harboring an *NRG1* fusion is largely unknown because of the recent identification of this biological entity, its rarity, and the absence of prospective clinical studies. Data for patients with NRG1+ cancer are emerging in retrospective series and individual case reports.

Non-Small Cell Lung Cancer

Lung cancer has been one of the most common cancers worldwide for several decades, accounting for 12% of all new cancers diagnosed, and nearly 1 in 5 cancer deaths in 2018 (Bray et al, 2018). In the United States (US), lung malignancies are the leading cause of cancer deaths in both men and women, with an estimated 127,070 deaths and 238,340 diagnosed cases projected for 2023. Estimated complete prevalence of NRG1+ NSCLC in the US in 2024 was 6,085 patients (EpidStrategies, 2024).

Survival is particularly low among patients diagnosed with metastatic disease, with the 5-year overall survival (OS) rate of metastatic (stage IV) NSCLC below 10% (Siegel et al, 2023). In a retrospective analysis of real-world data in a US database registry, patients with treatment-naïve metastatic NSCLC without the actionable targets of mutated EGF receptor *(EGFR*) or anaplastic lymphoma kinase (*ALK*) rearrangements had a median OS of 11.1 months (95% confidence interval [CI]: 10.8, 11.5) (Simeone et al, 2019).

***NRG1* Fusion-Positive NSCLC**

The largest descriptive analysis to date of NRG1+ lung cancer was published in 2021 (Drilon et al, 2021). Among the NRG1+ NSCLC cases, the majority were adenocarcinomas, of which more than half were invasive mucinous adenocarcinomas (IMA). 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 overall response rates (ORRs; 13% and 14%, respectively) and modest median progression-free survival (PFS; 5.8 and 4.0 months, respectively). Outcomes with chemo-immunotherapy 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 best overall response (BOR) being disease progression, reported in 60% of patients. *NRG1* fusions were mutually exclusive with other known oncogenic drivers in the large majority of patients.

In another retrospective study, a comprehensive molecular and clinicopathologic analysis of tumor tissue from 144 invasive mucinous adenocarcinoma (IMA) lung cancers was performed (Chang et al, 2021). Compared to 104 patients with *KRAS* mutant IMA, the 12 patients with

NRG1+ IMA were characterized by more aggressive clinical features (larger primary tumor size, significantly higher rate of metastasis, particularly with extra-thoracic metastasis), as well as histologic features (desmoplastic stromal invasion or tumor necrosis), which correlate with worse prognosis in patients with IMA (Chang et al, 2020), and was consistent with the significantly shorter overall and recurrence-free survival seen in the patients with NRG1+ IMA compared to those with KRAS mutant IMA.

Pancreatic Adenocarcinoma

Pancreatic ductal adenocarcinoma is the most common type of pancreatic cancer and is currently the third leading cause of cancer deaths in the United States (US) in both men and women, with 50,550 estimated total deaths, and more than 64,050 estimated new cases in 2023 (Siegel et al, 2023). NRG1+ PDAC is a rare cancer with an estimated frequency of 1.01% in the PDAC population, as described in a recent meta-analysis, with estimated complete prevalence in the US in 2024 of 627 patients (EpidStrategies, 2024).

Patients with PDAC have one of the lowest 5-year survival rates of all solid tumor malignancies (Ducreux et al, 2015). Treatment options are extremely limited and disease management is especially challenging. While surgical resection with or without adjuvant chemotherapy offers the only chance of cure, only 15% to 20% of patients have resectable disease at diagnosis, with the majority having either locally advanced unresectable or metastatic cancer (Ducreux et al, 2015). While surgery, chemotherapy, and radiotherapy can improve survival and/or relieve symptoms, the prognosis of pancreatic cancer is dismal, with a 5-year overall survival (OS) rate of 3% for metastatic disease reported in the US (Siegel et al, 2023).

***NRG1* Fusion-Positive Pancreatic Adenocarcinoma**

In patients with PDAC, *NRG1* fusions have generally been detected in the absence of other concomitant cancer driver mutations, and have been seen mostly in *KRAS* wildtype PDAC, suggesting that the *NRG1* fusion acts as the principal oncogenic driver. Three reports summarizing case series of patients with NRG1+ PDAC have been published (Heining et al; 2018; Jones et al; 2019; Thavaneswaran et al, 2022). All 7 patients were younger than 60 years and had liver metastases. Five had received prior treatment, all of whom received FOLFIRINOX (5-fluorouracil [5-FU]/oxaliplatin/irinotecan) and/or gemcitabine-based therapy and experienced progression within 7 months of their last line of treatment. With the exception of younger age, the patient and tumor characteristics of NRG1+ PDAC were not different from those of the general pancreatic cancer patient population, including disease location, extent of disease, and outcome of prior treatment.

The FDA's Assessment:

NSCLC

While *NRG1* fusions are largely mutually exclusive of other oncogenic drivers in NSCLC as stated in the Applicant's section, recent literature indicates that *NRG1* fusions may co-occur with *KRAS* mutations in lung adenocarcinoma. Among the 110 patients included in the eNRGy1 Global Multicenter Registry, 7 (6%) had a concurrent driver identified, with *KRAS* mutations being the most common (Li et al *Front Oncol* 2024; Drilon et al *J Clin Oncol* 2021).

The referenced literature reports in the Applicant's section and FDA's literature search suggest that the activity of standard chemotherapy and combined chemotherapy and immune therapy may be inferior in NRG1+ NSCLC. However, the review team notes that understanding of the behavior of NRG1+ NSCLC is still evolving, and the response rates in the study by Drilon *et al* cited by the Applicant are derived from a very small sample of patients. For example, the response rate of 13% in patients with NRG1+ NSCLC receiving platinum doublet-based chemotherapy is based on a sample size of 15 patients, while the response rate of 0% in patients treated with chemo-immunotherapy is based on a sample size of 9 patients. A recent publication evaluating real-world outcomes of patients with NRG1+ solid tumors retrospectively reported objective responses in 8/11 (73%) patients with NRG1+ NSCLC treated with standard frontline chemotherapy or chemo-immunotherapy (Liu et al, 2024). Thus, while some data suggest NRG1+ NSCLC is more aggressive and less likely to respond to standard frontline treatment, more information is needed before definitive conclusions can be reached.

PDAC

The referenced literature reports in the Applicant's section and FDA's literature search are supportive of the rarity of *NRG1* alterations in patients with mPDAC. In a prospective clinical trial of whole genome sequencing (WGS) and whole transcriptome analysis on 47 patients with mPDAC, only samples from 3 patients did not have *KRAS* mutations. In all three patients with *KRAS* wild-type tumors, translocations affecting the *NRG1* gene were reported (Jones MR, 2019). In another study in a small cohort of 17 patients, four tumors were *KRAS* wild-type and 3 of the *KRAS* wild-type pancreatic cancers harbored an *NRG1* fusion (Heining C, 2018). In a sample population of 21,858 tumor specimens evaluated for fusion testing (Jonna S, 2017), among 623 PDAC specimens, 3 samples (0.5%) presented *NRG1* fusions; all NRG1 fusion positive tumors were *RAS* wild type.

Although the *RAS* wildtype population appears to be enriched for *NGR1* alterations, approximately 90-95% of PDAC samples carry *RAS* mutations (*RAS* Initiative, NCI). In an integrated genomic characterization of PDAC from the Cancer Genome Atlas Research Network (2017), 150 specimens were tested and only 10 samples did not carry *KRAS* mutations. Samples from patients with wild-type *KRAS* tumors harbored alterations in other *RAS* pathway genes and other oncogenic drivers, including *RET, ALK, BRAF, NTRK*, etc.

The review team agrees that *NRG1* gene alterations in patients with PDAC are rare.

2.2. Analysis of Current Treatment Options

The Applicant's Position:

NRG1+ Cancer

No specific therapies have been approved for NRG1+ cancer, and patients are managed according to current treatment guidelines specific for the underlying tumor histology and disease setting. Available therapies for many solid tumors in the advanced/metastatic setting, including driver-mutation negative NRG1+ NSCLC and NRG1+ PDAC, offer limited antitumor activity and are often associated with toxicity.

***NRG1* Fusion-Positive NSCLC** (Module 2.5 NSCLC)

Nearly 70% of patients with NSCLC present with advanced-stage disease, for which 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 neurotrophic tyrosine receptor kinase (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 treatment management for 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.

The combination of platinum-based chemotherapy with a PD-(L)1 inhibitor is a preferred regimen for the treatment of patients with newly diagnosed advanced unresectable or metastatic NSCLC without known oncogenic drivers. Per these National Comprehensive Cancer Network (NCCN) guidelines for NSCLC, this approach is recommended for patients with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1 and without contraindications to treatment with PD-(L)1 inhibitors. For patients with an ECOG PS of 2, platinum-based chemotherapy without immunotherapy is preferred.

For patients with advanced unresectable or metastatic NSCLC without known oncogenic drivers who have progressed on frontline systemic therapy with chemotherapy or chemo-immunotherapy, Food and Drug Administration (FDA)-approved treatment options are limited to docetaxel or pemetrexed administered as monotherapy, or a combination of docetaxel plus ramucirumab. Pemetrexed treatment of non-squamous histology resulted in an ORR of 8.5% with median PFS of 2.9 months (Alimta® PI, 2019), while docetaxel monotherapy resulted in an ORR of 5.5% with median PFS of 2.8 months (Taxotere PI, 2020). Addition of ramucirumab to docetaxel monotherapy resulted in a 23% ORR and median PFS of 4.5 months, however this regimen leads

to more toxicity and limited clinical benefit and an additional modest survival benefit of only 1.4 months (Cyramza PI, 2022; Garon et al, 2014).

The integration of immunotherapy with immune checkpoint inhibitors into the NSCLC treatment paradigm has resulted in a steady improvement in survival. Nonetheless, patients with unresectable advanced or metastatic NRG1+ NSCLC who have progressed after standard therapy have a poor prognosis and limited therapeutic options, highlighting the high unmet medical need of this population.

***NRG1* Fusion-Positive PDAC** (Module 2.5 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. Although up to 90% of PDAC tumors harbor activating *KRAS* mutations, molecularly targeted therapeutic strategies have not yet been approved for *KRAS* mutant PDAC (Mann et al, 2016).

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-fluorouracil (5-FU)/leucovorin (LV), is the first and only agent to be FDA-approved for patients with metastatic PDAC that has progressed following gemcitabine-based therapy. Approval was based on the pivotal Phase 3 NAPOLI study, demonstrating a significant median survival advantage of ~2 months compared with 5-FU/LV alone. This study reported a 7.7% confirmed response rate, median progression-free survival (PFS) of 3.1 months, and median OS of 6.1 months. High frequencies of Grade 3 and 4 AEs were observed, including neutropenia (27%), diarrhea (13%), vomiting (11%), and fatigue (14%) (Onivyde™ PI, 2015; Wang-Gillam et al, 2016).

The American Society of Clinical Oncology treatment guideline recommendations for metastatic pancreatic cancer include germline and somatic testing for microsatellite instability high/mismatch repair deficiency (MSI-H/dMMR), breast cancer gene mutations, and *NTRK* alterations, among others, to allow treatment with approved therapies or enrollment in ongoing clinical studies (Sohal et al, 2020). In the context of a tissue agnostic therapeutic approach, the following precision medicines with FDA approvals for tissue-agnostic indications can be used for pancreatic cancer: pembrolizumab for MSI-H/dMMR or TMB-H tumors; dostarlimab for dMMR tumors; selpercatinib for tumors harboring a rearranged during transfection (RET) gene fusion; NTRK inhibitors larotrectinib and entrectinib for tumors that harbor *NTRK1*, *NTRK2*, or *NTRK3* gene fusions; and dabrafenib in combination with trametinib for tumors with a *BRAF* V600E mutation.

No specific therapies have been approved for NRG1+ PDAC, and patients are treated according to the current treatment guidelines for PDAC generally. 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.

Table 1. Applicant – Summary of outcomes with FDA-approved therapies for previously-treated advanced unresectable/metastatic NSCLC

Regimen	Histology	Study Design	No. of Patients	ORR (95% CI)	mPFS (95% CI)	mOS (95% CI)	Reference
Docetaxel	Not specified	Docetaxel (D) vs Best supportive care (BSC)	N=104 (D: 55; BSC: 49)	5.5% (1.1, 15.1) vs NA	12.3 wks (9, 18.3) vs 7 wks (6.0, 9.3)	7.5 wks (5.5, 12.8) vs 4.6 wks (3.7, 6.1) HR: 0.56 (0.35, 0.88) p=0.01	Taxotere® USPI, 2021
Pemetrexed	Non-squamous	Pemetrexed (P) vs Docetaxel (D)	N=571 (P: 283; D: 288)	8.5% (5.2, 11.7) vs 8.3% (5.1, 11.5)	2.9 mo (2.4, 3.1) vs 2.9 mo (2.7, 3.4) HR: 0.97 (0.82, 1.16)	8.3 mo (7.0, 9.4) vs 7.9 mo (6.3, 9.2) HR: 0.99 (0.82, 1.20)	Alimta® USPI, 2022
Ramucirumab/ Docetaxel	Non-squamous and squamous NSCLC	Ramucirumab/docetaxel (R/D) vs Placebo/docetaxel (P/D)	N=1253 (R/D:628; P/D: 625)	23% (20, 26) vs 14 (11, 17) p<0.001	4.5 mo (4.2, 5.4) vs 3.0 mo (2.8, 3.9) HR: 0.76 (0.68, 0.86) p<0.001	10.5 mo (9.5, 11.2) vs 9.1 mos (8.4, 10.0) HR: 0.86 (0.75, 0.98) p<0.024	Cyramza® USPI, 2022 Garon et al, 2014
Pembrolizu-mab	Non-squamous and squamous	Pembrolizumab (Pb) vs Docetaxel (D)	N=1034 (Pb: 346; D: 343)	18% vs 9% p=0.0002	4 mo vs 4 mo HR: 0.79 (0.66, 0.94) p=0.004	12.7 mo vs 8.5 mo HR: 0.61 (0.49, 0.75) p<0.0001	Herbst et al, 2016
Nivolumab	Squamous	Nivolumab (N) vs Docetaxel (D)	N=272 (N: 135; D: 137)	20% (14, 28) vs 9% (5, 15) p=0.0083	3.5 mo vs 2.8 mo HR: 0.62 (0.47, 0.81) p=0.0004	9.2 mo (7.3, 13.3) vs 6.0 mo (5.1, 7.3) p=0.0002	Opdivo® USPI, 2023
Nivolumab	Non-squamous	Nivolumab (N) vs Docetaxel (D)	N=582 (N: 292; D: 290)	19% (15, 24) vs 12% (9, 17) p=0.02	2.3 mo (2.2, 3.3) vs 4.2 mo (3.5, 4.9) HR: 0.92 (0.77, 1.1) p=0.39	12.2 mo (9.7, 15.0) vs 9.4 mo (8.1, 10.7) HR: 0.73 (0.59, 0.89)	Opdivo® USPI, 2023

Regimen	Histology	Study Design	No. of Patients	ORR (95% CI)	mPFS (95% CI)	mOS (95% CI)	Reference
Atezolizumab	Non-squamous and squamous	Atezolizumab (A) vs Docetaxel (D)	N=850 (A: 425, D: 425)	14% (11, 17) vs 13% (10, 17)	2.8 mo (2.6, 3.0) vs 4.0 mo (3.3, 4.2) HR: 0.95 (0.82, 1.10)	13.8 mo (11.8, 15.7) vs 9.6 mo (8.6, 11.2) HR: 0.74 (0.63, 0.87) P=0.0004	Tecentriq® USPI, 2023

HR = hazard ratio

Table 2. Applicant – Summary of outcomes with FDA approved therapy for previously treated advanced unresectable/metastatic PDAC

Study (reference)	Prior treatment	Study therapies	N patients	ORR (%)	Median PFS (months)	Median OS (months)
NAPOLI-1 (Onivyde™ PI, 2015; Wang-Gillam et al, 2016)	Gemcitabine[1] (45% monotherapy)	Liposomal irinotecan/5-FU/LV	117	7.7 / 16[2]	3.1	6.1
		vs				
		5-FU/LV	149	1	1.5	4.2

[1] 13% of patients received gemcitabine in the neoadjuvant, adjuvant, or locally advanced setting without prior treatment for metastatic disease
[2] 7.7% confirmed ORR (Onivyde™-PI, 2015); 16% unconfirmed ORR (Wang-Gillam et al, 2016)
5-FU = 5-fluorouracil; LV = leucovorin; ORR = overall response rate; OS = overall survival; PFS = progression-free survival

New targeted therapies are therefore needed in patients with *NRG1* fusion-positive cancers, for whom there is no standard of care and who represents a population with unmet medical need. Zenocutuzumab, with its unique mechanism of action, is expected to address this unmet medical need, and represents the first NRG1-directed therapy that demonstrate clinically meaningful and durable efficacy in patients with NRG1+ NSCLC and NRG1+ PDAC. Zenocutuzumab is very-well tolerated (i.e., with low rates of discontinuation due to AEs), and the overall number, type and frequency of AEs and SAEs indicate its favorable safety profile.

The FDA's Assessment:

The review team agrees with the Applicant's description of available therapies for NSCLC and mPDAC; however, see Section 2.1 for additional discussion on FDA's assessment of response to available therapy. FDA notes that the Applicant's statement on the efficacy, safety, and tolerability of zenocutuzumab includes terminology such as "unique," "very-well tolerated," "low rates of discontinuation" and "favorable safety profile." This language should be avoided as it is vague, subjective and overly promotional. FDA's review of efficacy and safety can be found in Sections 7 and 8.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:

Zenocutuzumab is currently not marketed (or approved) in the United States or any other country. The clinical development program for zenocutuzumab is being conducted under IND 156484 within the Division of Oncology 2.

The FDA's Assessment:

FDA agrees with the Applicant's position.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

The IND was opened with DO1 to initate the first in human phase 1 study (IND 131752). At the request of FDA, the Sponsor then submitted IND 156484 to DO2 as an administrative split for the pivotal Phase 2 Study with the eNRGy protocol. The Pre-IND 165120 was opened with DO3 in order to be able to interact concerning the PDAC population.

Table 3. Applicant - Summary of Regulatory Communications with FDA

Interaction Type	Interaction Date	Primary Outcome
Study May Proceed	**16 Dec 2016**	**The sponsor submitted a new IND (131752) to DO1 for zenocutuzumab on 18 Nov 2016. FDA sent a study my proceed letter**
Orphan Drug Designation	**22 Jul 2020**	**The sponsor submitted an Orphan Drug Designation to IND 131752 on 28 Apr 2020. Orphan Drug Status Granted for treatment of pancreatic cancer.**
Fast Track Designation	**18 Dec 2020**	**The sponsor submitted a Fast Track Designation Request to IND 131752 on 27 Oct 2020. Fast Track was designated for the treatment of patients with metastatic solid tumors harboring NRG1 gene fusions (NRG1+ cancer) that have progressed on standard of care therapy.**

Interaction Type	Interaction Date	Primary Outcome
IND Administrative Split & 30-day waiver grant letter	**09 Jun 2021**	**The sponsor submitted IND 156484 as an administrative split to DO2 on 10 May 2021. FDA waived the 30-day review period for this IND. The IND was hence considered safe to proceed.**
Type B (EOP1) Meeting	**08 Sep 2021**	**The FDA provided feedback on the nonclinical safety package, clinical pharmacology program, the eligibility criteria, patient identification methodology, dose, endpoints, statistical analysis plan. The FDA provided feedback on the clinical data needed to support an accelerated approval of a BLA.**
Type C (WRO) Meeting – Reproductive Risk Assessment	**29 Jun 2022**	**FDA agreed that the weight-of-evidence approach for reproductive risk assessment appeared acceptable and sufficient to support the filing of a BLA.**
Type C (WRO) Meeting – BLA Proposed Format & Content	**05 Jul 2022**	**FDA provided written responses on the proposed content and format. FDA agreed with the data standard and report format of the nonclinical safety studies, with the list of clinical pharmacology study reports, clinical studies, the data standards approach, and with the proposed patient narratives. FDA recommended ORR to be assessed by independent central review.**
Pediatric Study Plan	**13 Sep 2022**	**Full waiver for all pediatric age groups iPSP Agreement received**
Type B (Pre-BLA) Meeting	**31 Oct 2022**	**FDA indicated current data are not adequate to support a tissue agnostic indication. DO2 recommended Merus to consider tumor-specific for a future application.**
Type B (EOP) Meeting with DO3	**23 Feb 2023**	**DO3 held a Type B EOP meeting with Merus under Pre-IND 165120. FDA provided feedback that ORR may be acceptable in this rare population depending on magnitude of response and DOR.**

Interaction Type	Interaction Date	Primary Outcome
BTD Granted	**17 May 2023**	**A Breakthrough Therapy Designation Request for NRG1+ PDAC was submitted to Pre-IND 165120. A Breakthrough Therapy Designation was granted 17 May 2023 for NRG1+ PDAC.**
BTD Granted	**03 Jul 2023**	**A Breakthrough Therapy Designation Request for NRG1+ NSCLC was submitted to IND 156484. A Breakthrough Therapy Designation was granted 03 Jul 2023 for NRG1+ NSCLC.**
Initial Comprehensive Multidisciplinary BTD Type B Meeting	**12 Sep 2023**	**FDA indicated that the proposed sample size may be adequate to support the initial BLA. FDA requested sponsor to provide endpoint analyses by blinded central review and investigator assessment. FDA agreed to 1 BLA with 2 indications.**
Type B (Pre-BLA) Preliminary Comments	**30 Nov 2023**	**The sponsor provided a summary of topline clinical results and the FDA provided preliminary comments. FDA agreed to the March 2024 BLA submission date (based on a 31 July 2023 data cutoff date) and agreed to receiving updated safety and efficacy data with an 90-day Safety Update Report (based on a 31 January 2024 data cutoff date). FDA provided feedback on clinical content of the BLA submission and CMC. FDA agreed that the data provided appears adequate to support filing a BLA.**
Type B (Pre-BLA) Meeting	**7 Dec 2023**	**FDA acknowledged Merus responses and additional data regarding response rate, prior therapies and information on differential median DOR. FDA agreed with rolling submission and timelines.**

BTD: Breakthrough Therapy Designation; CMC: Chemistry, Manufacturing and Controls; DOR: duration of response; EOP1: end of phase 1; IND: investigational new drug; NSCLC: Non-Small Cell Lung Cancer; PDAC: pancreatic ductal adenocarcinoma; ORR: objective response rate

The FDA's Assessment:

FDA agrees with the Applicant's characterizations of key regulatory milestones that occurred during the planning and conduct of studies for the development programs related to zenocutuzumab. Additionally, FDA has the following clarifications for key meetings.

The following topics were discussed during the October 21, 2022 Pre BLA meeting with DO2:

- Merus proposed that the primary efficacy population for the proposed BLA be comprised of patients with all NRG1+ solid tumors who received zenocutuzumab 750 mg Q2W in the eNRGy study or the Early Access Program (EAP). FDA recommended that Merus consider pursuing separate tumor-specific development programs for zenocutuzumab in NSCLC and PDAC, and/or continue enrollment of patients with other tumor types harboring NRG1 fusions on the eNRGy study to support a future marketing application for a tissue agnostic indication.
- FDA stated that there was not sufficient data to conclude that standard FDA-approved treatment regiments for patients without actionable genomic alterations are not efficacious in treatment-naïve patients with NRG1 fusion-positive cancer.

Summary of Regulatory Communications Regarding NSCLC Indication

The following topics were discussed during the September 14, 2023 BTD meeting with DO2:

- Merus stated their plan to submit a BLA to support accelerated approval for zenocutuzumab for the treatment of patients with advanced unresectable or metastatic NSCLC harboring an NRG1 gene fusion following progression with prior systemic therapy (b) (4) FDA recommended that the proposed indication statement be modified (b) (4) FDA requested that Merus include data for all patients with NSCLC in the BLA submission, as data from treatment-naïve patients may be considered supportive. Merus acknowledged FDA's recommendation and stated their plan to include data from treatment-naïve patients in the Pre-BLA meeting package, (b) (4)
- Merus proposed that the conversion of initial accelerated approval to full approval may be based on additional follow-up of efficacy and safety data from the ongoing patients included in the clinical datasets in the initial BLA. FDA stated that the size and scope of post-marketing requirements and commitments will be determined during the BLA review and recommended continuing enrollment of patients with NRG1+ NSCLC in the eNRGy trial. Merus acknowledged FDA's comments and stated that they are continuing to enroll NSCLC patients on the eNRGy trial.
- FDA stated that Merus should provide the analysis of endpoints by blinded central review and by investigator assessment in each CSR.
- FDA and Merus agreed that safety data from the eNRGy study and the Early Access Program (EAP) would not be pooled.

The following topics were discussed during the December 7, 2023 Pre BLA meeting with DO2:

- FDA requested that Merus include patients who did not have measurable disease at baseline as part of the assessment of response by both BICR and investigator, and to provide these data before BLA submission. Merus agreed and provided the requested information.

- Merus proposed to exclude patients treated less than 24 weeks prior to the data cutoff date from the primary efficacy set. FDA requested that Merus perform a sensitivity analysis with inclusion of these patients. Merus proposed that these patients be included in the supportive efficacy set as per the Statistical Analysis Plan of the eNRGy Study. Merus also proposed to include efficacy data for patients treated at least 24 weeks prior to the January 31, 2024, data cutoff date as part of the 90 day safety update report.
- FDA requested that Merus clarify the number of patients with NSLC who received prior platinum chemotherapy, prior immunotherapy and prior platinum chemotherapy and immunotherapy, and to provide efficacy results for these population subgroups. Merus clarified that prior immunotherapy was received by 41 NSCLC patients, and out of these 41 patients 36 patients also received prior platinum-based chemotherapy, either sequentially or concurrently with immunotherapy. Merus agreed to provide efficacy data for these subgroups.
- FDA requested that Merus provide an analysis of the discrepancy between BICR and investigator's assessment of duration of response in patients with PDAC in the BLA submission. Merus agreed that the BLA submission will include a summary accounting for the discrepancy in DOR by BICR and investigator.

Summary of Regulatory Communications Regarding PDAC Indication

The following topics were discussed on the February 23, 2023 meeting with DO3:

- Merus proposed to submit data to support an indication in patients with NRG1+ PDAC based on 25 patients enrolled in the PDAC cohort of the eNRGy study followed for at least 6 months. Additional data from NRG1+ patients with PDAC in the EAP (targeting maximum of 10 patients) was to be included as supportive efficacy data. To verify and confirm clinical benefit following an accelerated approval, Merus proposed to continue enrollment across cohorts of NRG1+ patients with cancer, including NRG1+ positive patients with PDAC and submit the efficacy data from an additional 25 (total 50) NRG1+ patients with PDAC from the eNRGy study.
- Merus provided additional data on enrollment. In Merus' experience, up to 12 patients with NRG1+ PDAC may be enrolled in one year, despite having > 60 clinical centers across 17 countries. Merus stated that over a 3 year period, the ORR in patients with NRG1+ PDAC patients treated with zenocutuzumab has been consistent and stable (ORR: 41.7 – 45.0% by local investigator assessment). Per Merus, enrollment of additional patients would improve marginally the lower bound of the 95% confidence interval for ORR (projected to be 21%), which exceeds current standard of care in refractory PDAC.
- FDA requested further clarification on the sample size, as the study enrolled patients who were not included in the efficacy analysis. Merus stated that specific exclusions from the primary analysis population were consistent with those described in the protocol and eligibility for inclusion in the primary analysis population was determined prior to

receiving investigational drug. FDA stated that the Agency does not object to the approach that prespecifies (prior to treatment) which patients will be included in the analysis population; submissions to the FDA should clearly describe the clinical effects of zenocutuzumab in the primary analysis population and in patients excluded from the primary analysis population (i.e., separately).

- Although FDA acknowledged the rarity of the population, FDA stated that the sample size of 25 patients did not appear sufficient to characterize the effects on response rate and duration of response, and limited information would be available to characterize treatment effects in different subgroups of patients (e.g., based on age).
- FDA clarified that to evaluate single-arm trial results, FDA does not consider inferential procedures.

The following topics were discussed on the September 12, 2023 Type B meeting with DO3:

- Merus proposed a potential conversion of the initial accelerated approval to full approval based on additional follow-up of efficacy and safety data of the ongoing patients included in the clinical datasets in the initial BLA. FDA did not agree with this proposal and stated that for the PDAC indication, additional patients would be requested to adequately characterize the long-term efficacy (including duration of response) and safety of treatment with zenocutuzumab. Further, FDA clarified that if granted accelerated approval for the NRG1+ PDAC indication, the size and scope of the postmarketing requirements and commitments will be discussed during the BLA review and recommended that Merus continue enrollment of patients with PDAC in the eNRGy trial.
- Although FDA did not object to use of a protocol-prespecified criteria for selection of patients to be included in the PDAC analysis population, FDA stated that the approach taken in the eNRGy study, in which an independent body determines whether the NRG1 fusion is predictive to be functional, is not informative to practitioners in the absence of an approved FDA test. FDA requested that Merus summarize in the pre-BLA meeting a plan to inform selection of patients in product labeling (i.e., with respect to additional driver mutations and NRG fusion functionality).
- In addition, although FDA agreed with the exclusion of patients for whom prospectively (or retrospectively in a blinded manner) the NGR fusion is not considered to be activating or who have other driving mutations, FDA stated that the efficacy population should include patients enrolled in the eNRGy trial (who received at least one dose of zenocutuzumab) for whom no baseline scans were available (these patients should be considered as non-responders) and patients who were identified as having non-measurable disease retrospectively by the IRC (who were identified as having measurable disease by the investigator). FDA also stated patients who discontinued treatment due to toxicity or clinical progression (or other reasons) should be considered as non-responders.
- FDA did not agree with the planned pooling of data from the eNRGy study and the EAP. The pooled efficacy should only include patients treated under the eNRGy protocol and the EAP population should be analyzed separately.

At the December 7, 2023, pre-BLA meeting, the following was discussed regarding the PDAC indication:

- The Kaplan-Meier estimate of median DOR in the 12 patients with PDAC who responded was 16.6 months (95% CI: 3.7, not calculable) per BICR and was 7.4 months (95% CI: 5.5, 11.2) in the 13 patients who responded per investigator assessment. FDA requested Merus to provide in the BLA an analysis of the discrepancy between BICR and investigator's assessment of duration of response in patients with PDAC. Merus clarified these differences are related to differences in assessment of onset and end of response and attribution of response in 3 patients. Merus stated that the BLA submission will include a summary accounting for the discrepancy in DOR by BICR and investigator.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

No significant issues were identified. Two clinical investigators, Drs. Alison Schram (Site # 3001), and Koichi Goto (Site # 6001), as well as the (b) (4) Contract Research Organization (CRO), (b) (4), and the study sponsor, Merus NV, were inspected. Inspections of Drs. Schram and Goto, Merus NV, and, (b) (4), revealed no significant discrepancies or regulatory violations. Based on these inspections, the eNERGy trial appears to have been conducted adequately and the data generated by the inspected clinical investigators and the imaging CRO as submitted by the Applicant, appear acceptable in support of the proposed indication. Please see Clinical Inspection Summary for more detail.

4.2. Product Quality

Zenocutuzumab-zbco is a sterile, clear to slightly opalescent, colorless to slightly yellow, preservative-free concentrate for infusion, formulated as 375 mg/18.75 mL (20 mg/mL) zenocutuzumab-zbco, 34.9 mg histidine, 51.1 mg L-histidine hydrochloride monohydrate, 3.7 mg polysorbate 20, 1412 mg trehalose, and water for injection at pH 6.0. Zenocutuzumab-zbco is provided in a Type (b) (4) glass vial, stoppered with an elastomeric stopper, and sealed with an aluminum cap for intravenous infusion. Each carton contains two vials of zenocutuzumab-zbco for one 750 mg dose.

The Office of Pharmaceutical Quality, CDER, recommends approval of BLA 761352 for Zenocutuzumab-zbco manufactured by Merus N.V. The data submitted in this application are adequate to support the conclusion that the manufacture of zenocutuzumab-zbco is well-controlled and leads to a product that is pure and potent for the duration of the shelf-life. It is recommended that this product be approved for human use under conditions specified in the package insert.

Refer to the OPQ Executive Summary dated November 15, 2024, for full details.

The CMC post-marketing commitments (PMCs) listed below should be included in the action letter.

1. Develop a validated functional cell-based assay representative of the mechanism of action of zenocutuzumab, including blocking of NRG1:HER3 binding and HER2:HER3 dimerization, for drug substance and drug product release and stability testing of potency and establish acceptance criteria for release and

stability for this test. Analyze sample retains from clinical batches and stability samples to support proposed acceptance criteria.

Fulfillment date: December 31, 2025

2. Validate an appropriate test to control for zenocutuzumab [(b) (4)] and establish a drug substance release acceptance criterion based on the levels of the [(b) (4)] observed in clinical batches.

Fulfilment date: March 31, 2025

3. Analyze zenocutuzumab drug substance and drug product sample retains for the antibody dependent cell-mediated cytotoxicity (ADCC) reporter assay activity using a qualified reference standard. Reevaluate drug substance and drug product release and stability acceptance criteria for the ADCC reporter assay based on available retain, release, and stability results. Provide a justification to support selection of the revised acceptance criteria.

Fulfillment date: March 31, 2025

4. Optimize and re-validate the HER3 binding assay for drug substance and drug product release and stability testing of potency. Robustness assessments for critical reagents and parameters for the HER3 binding assay in the re-validation will be included.

Fulfillment date: December 15, 2025

5. Perform a supplemental validation for the imaged capillary isoelectric focusing and ultra-performance size exclusion chromatography drug substance and drug product methods to confirm the reportable range in accordance with ICH Q2(R2). Validate a lower limit of quantification (LLOQ) for [(b) (4)] impurities by the drug product imaged capillary isoelectric focusing method.

Fulfillment date: July 31, 2025

6. Establish an appropriate drug substance release acceptance criterion for Oligosaccharide mapping test based on levels of relevant glycosylated species observed in clinical batches.

Fulfillment Date: April 30, 2025

7. Establish appropriate drug substance and drug product release and stability specifications for total impurities by reduced capillary gel electrophoresis methods based on levels observed in clinical batches.

   Fulfillment Date: March 31, 2025

8. Establish appropriate drug substance and drug product release and stability specifications for total impurities by non-reduced capillary gel electrophoresis methods based on levels observed in clinical batches.

   Fulfillment Date: July 31, 2025

9. Conduct a supplemental drug product validation study to reassess the homogeneity of the fill study. Include formulation and product critical quality attributes that could be impacted by the fill process in your assessment.

   Fulfillment Date: June 30, 2025

4.3. Clinical Microbiology

No significant issues were identified. See CMC review for full details.

4.4. Devices and Companion Diagnostic Issues

A companion diagnostic assay for zenocutuzumab is currently not available. Since review of an application for an in vitro companion diagnostic device is still ongoing, a contemporaneous approval with this BLA is not possible. The approved labeling will state that there is no FDA-approved test for selecting patients for treatment with zenocutuzumab. A post-marketing commitment (PMC) will be issued for the Applicant to provide adequate analytical and clinical validation results from clinical trial data to support labeling of a companion diagnostic test to detect NRG1 fusions for identifying patients who may benefit from zenocutuzumab. Refer to Section 13, Postmarketing Requirements and Commitment.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Zenocutuzumab (MCLA-128) is a low-fucose, humanized, immunoglobulin G1 (IgG1) bispecific antibody that binds to the extracellular domains of human epidermal growth factor 2 (HER2) and HER3 expressed on the surface of cells, including tumor cells, inhibiting HER2:HER3 dimerization and preventing neuregulin 1 (NRG1) binding to HER3, subsequently inhibiting downstream pro-proliferative signaling pathways. The Applicant proposes to use zenocutuzumab at 750 mg every 2 weeks until disease progression or unacceptable toxicity. The intended route of administration is intravenous (IV) infusion. The proposed indication is for the treatment of adult patients with advanced, unresectable, or metastatic non-small cell lung cancer (NSCLC) harboring a NRG1 gene fusion with disease progression on or after prior systemic therapy; and the treatment of adult patients with advanced, unresectable, or metastatic pancreatic adenocarcinoma (PDAC) harboring a NRG1 gene fusion with disease progression on or after prior systemic therapy.

The established pharmacological class for zenocutuzumab is bispecific HER2- and HER3-directed antibody. Crystallography and small angle X-ray scattering conducted in the absence of NRG1 showed that the anti-HER2 and anti-HER3 antibody-binding fragment (Fab) arms of zenocutuzumab bind to the extracellular domains (ECDs) of HER2 and HER3. In addition, the anti-HER3 Fab of zenocutuzumab binds to HER3 in its inactive conformation and its epitope partially overlaps with the NRG1-binding domain, thus, preventing NRG1 binding to HER3. Zenocutuzumab bound to human and monkey HER2 and HER3, but the anti-HER2 antibody-binding fragment (Fab) did not bind to HER2 in rodents in in vitro assays. Sequence homology assessments showed high amino acid sequence similarity of HER2 and HER3 between monkeys and humans (98–99%), with lower sequence homology between human and rodent HER2 (85–88%) and HER3 (91–93%). Together, these results support the use of cynomolgus monkeys as the pharmacologically relevant species for zenocutuzumab toxicity assessment. Zenocutuzumab blocked NRG1-induced HER2:HER3 dimerization in a reporter assay. In cellular assays, zenocutuzumab inhibited the growth/proliferation of NRG1 fusion-expressing and NRG-1-stimulated cancer cells, including pancreatic cell models and immortalized human bronchial epithelial cells (HBECs). This suppression of cell proliferation, specifically using NRG1-expressing pancreatic cells and HBECs, was associated with inhibition of the phosphoinositide 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) signaling pathway. Zenocutuzumab mediated antibody-dependent cellular cytotoxicity (ADCC) in breast cancer cell lines, but did not induce complement-dependent cytotoxicity (CDC). In vivo, zenocutuzumab showed antitumor activity in a HER2-positive breast cancer cell line xenograft model, which was associated with inhibition of HER2:HER3 dimerization and PI3K/Akt signaling. Zenocutuzumab also showed antitumor activity in NRG1 fusion-positive lung and pancreatic cancer patient-

derived xenograft (PDX) models. These studies support the proposed mechanism of action of zenocutuzumab.

In vitro cytokine release studies using whole human blood from healthy donors showed only slight increases in cytokine levels. However, the co-incubation of HER2/HER3-expressing breast cancer cells and peripheral blood mononuclear cells (PBMCs) in the presence of zenocutuzumab induced the significant release of interferon gamma (IFN-g), interleukin 6 (IL-6), IL-8, and tumor necrosis factor alpha (TNF-a).

The Applicant evaluated the safety of zenocutuzumab in GLP-compliant 1-month and 13-week repeat-dose toxicology studies in cynomolgus monkeys with the intended IV route of administration. In the 1-month study, increased white blood cells and neutrophils correlated histologically with increased myelopoiesis in the bone marrow, unilateral focal extramedullary hemopoiesis in the mandibular lymph node, and polymorphonuclear leukocytic infiltration in the mesenteric lymph node. Additional target organs of toxicity included the thymus, adrenal gland, sternum, skin, and injection site. In the 13-week study, two animals in the mid- and high-dose groups were prematurely euthanized due to an immune-mediated infusion reaction and diarrhea refractory to treatment related to intestinal lesions, respectively. The Applicant suggests that these findings were unrelated to zenocutuzumab as comparable findings were not observed in animals that showed higher zenocutuzumab exposure compared to the mid-dose animal, and intestinal lesions have been reported in monkeys (Brady and Carville, 2012; Johnson et al., 2022; Sasseville and Diters, 2008). Of note, the mid-dose animal exhibiting an immune-mediate infusion reaction was positive for anti-drug antibodies (ADAs). While we recognize that intestinal lesions have been previously reported in monkeys, we also note that diarrhea is one of the most common adverse reactions reported in patients treated with zenocutuzumab. In animals that survived to scheduled necropsy, increased spleen and adrenal gland weights correlated histologically with increased cellularity of germinal centers and adrenal cortical hypertrophy, respectively. Additional target organs of toxicity included the lymph nodes (axillary, mesenteric, iliac), gallbladder, small and large intestines, injection site, and skin. Findings consistent with clinical experience included skin toxicity (thinning hair; histological findings of erosion, ulceration, mononuclear cell infiltration, inflammation), infusion-related reaction, and elevated alanine aminotransferase (ALT) and aspartate transaminase (AST).

Carcinogenicity and genetic toxicology studies with zenocutuzumab were not conducted as they are generally not appropriate for antibody-based therapies.

The Applicant did not conduct reproductive or embryo-fetal developmental toxicology studies with zenocutuzumab. Rather, the Applicant provided a literature-based weight-of-evidence (WOE) assessment of the potential reproductive toxicity of zenocutuzumab based on its mechanism of action, consistent with the alternative approach described in the FDA Guidance for Industry, Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations. Animal data from the literature demonstrate that HER2 and HER3 are

critically important in embryo-fetal development, including effects on cardiac, vascular and neuronal development, and survival. Furthermore, published articles show that treatment with a HER2-directed antibody during pregnancy has resulted in cases of oligohydramnios in humans manifesting as fatal pulmonary hypoplasia, skeletal abnormalities, and neonatal deaths (Gougis et al., 2023; Andrikopoulou et al., 2021). In addition, zenocutuzumab has the potential to be transmitted from the mother to a developing fetus because human IgG1 is known to cross the placenta. Therefore, the pharmacology/toxicology team, in conjunction with the clinical team, included a box warning for embryo-fetal toxicity in the label for BIZENGRI. Due to the potential of zenocutuzumab to cause fetal harm, the Applicant proposed effective contraception use for female patients during treatment with BIZENGRI and for 2 months after the last dose based on five times the half-life of zenocutuzumab of 8 days. The Applicant did not evaluate the presence of zenocutuzumab in milk; however, maternal IgG is known to be present in human milk. The effects of local gastrointestinal exposure and limited systemic exposure in the breastfed child to BIZENGRI are unknown. The developmental and health benefits of breast feeding along with the mother's clinical need for BIZENGRI should be considered when deciding on nursing. If a decision is made not to breastfeed, a washout period of 2 months may be considered.

Recommendation:
The nonclinical pharmacology and toxicology data submitted to this BLA are adequate to support the approval of BIZENGRI for the proposed indication. Referenced NDAs, BLAs, DMFs.

5.2. Referenced NDAs, BLAs, DMFs

The Applicant's Position:

Not applicable.

The FDA's Assessment:

FDA agrees.

5.3 Pharmacology

Primary pharmacology

The Applicant's Position:

Zenocutuzumab (MCLA-128) is a bispecific antibody that binds to the extracellular domains of HER2 and HER3 expressed on the tumor cell surface. In in vitro and in vivo studies, MCLA-128 blocks HER2:HER3 dimerization, and prevents HER3 from associating with HER2 by blocking NRG1 binding to HER3. NRG1 fusions are involved in oncogenesis and dysregulation, which

leads to tumor growth. In vitro and in vivo data demonstrate that the anticancer activity of MCLA-128 is due to blocking HER2:HER3 dimerization and NRG1:HER3 binding, resulting in suppression of tumor cell proliferation and tumor cell survival through the PI3K-AKT-mTOR oncogenic signaling pathway. In vitro, MCLA-128 also mediates antibody-dependent cellular cytotoxicity (ADCC), leading to elimination of tumor cells.

In vitro studies

MCLA-128 is composed of the Merus Fab (MF) fragments MF(b) (4) (anti-HER2) and MF(b) (4) (anti-HER3), both harboring a common light chain. In vitro studies with MCLA-128 established binding affinity and specificity for both HER2 and HER3.

The affinity of MCLA-128 for HER2 and HER3, as well as that of the individual Fab arms, was tested by incubating the HER2-amplified breast cancer cell lines BT-474 and SK-BR-3, which both express HER3, with radioactively labeled antibodies. To determine the affinity of the individual HER2 and HER3 Fab arms, bispecific HER2×TT and HER3×TT antibodies were included in the experiment (the TT Fab arm binds to the irrelevant antigen tetanus toxoid). MCLA-128 (HER2×HER3), HER2×TT, and HER3×TT were radioactively labeled with 125I and incubated with cells in a serial titration. Unbound radioactivity was removed, and the cell-bound radioactivity was measured, allowing the calculation of values for the dissociation constant (KD) by Scatchard analysis (Table 4). The mean KD values for MCLA-128 were 3.2 nM in BT-474 cells and 2.0 nM in SK-BR-3 cells.

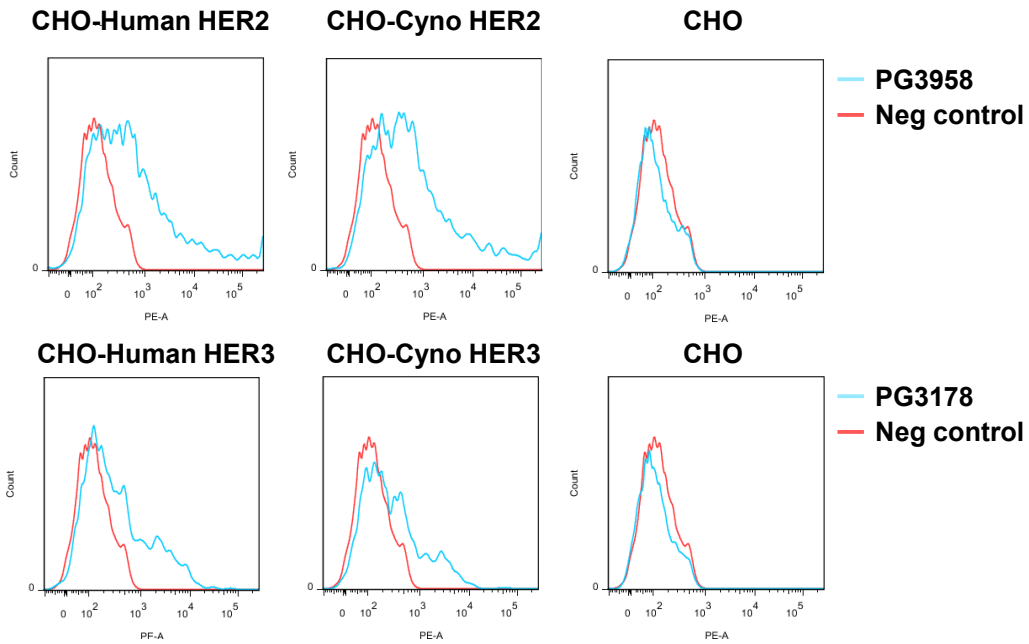
Table 4. Applicant - K_D values for binding affinities of indicated antibodies in two HER2-amplified breast cancer cell lines

Antibody	BT-474*	SK-BR-3*	Average Affinity#
MCLA-128	3.2 ± 0.5 nM	2.0 ± 0.4 nM	2.6 nM
HER2×TT	3.9 ± 0.6 nM	2.3 ± 0.7 nM	3.1 nM
HER3×TT	0.2 ± 0.1 nM	1.0 ± 0.4 nM	0.6 nM

** K_D values shown are mean ± SD of 3 experiments using each of the indicated cell lines; # average of mean K_D values determined in BT-474 and SK-BR-3 cells. Source: Report P1208-R33 (eCTD Module 2.6.2).*

Binding experiments using flow cytometry and enzyme-linked immunosorbent assay (ELISA) showed unequivocally that MF(b) (4) binds specifically to HER2, whereas MF(b) (4) binds specifically to HER3. Both MF(b) (4) and MF(b) (4) bind human and cynomolgus homologs of their target receptors (Figure 1).

Figure 1. Applicant - Flow cytometry results demonstrating binding of MF (b) (4) and MF (b) (4) to CHO cells expressing human and cynomolgus HER2 and HER3 receptors



Human or cynomolgus monkey HER2 or HER3-encoding expression vectors were used to transfect CHO cells, resulting in transient expression of HER2 or HER3 receptors. Transfected and control CHO cells were analyzed by flow cytometry. MF = Merus Fab; PG = protein IgG. *Source: Report P0712-R16 (eCTD Module 2.6.2).*

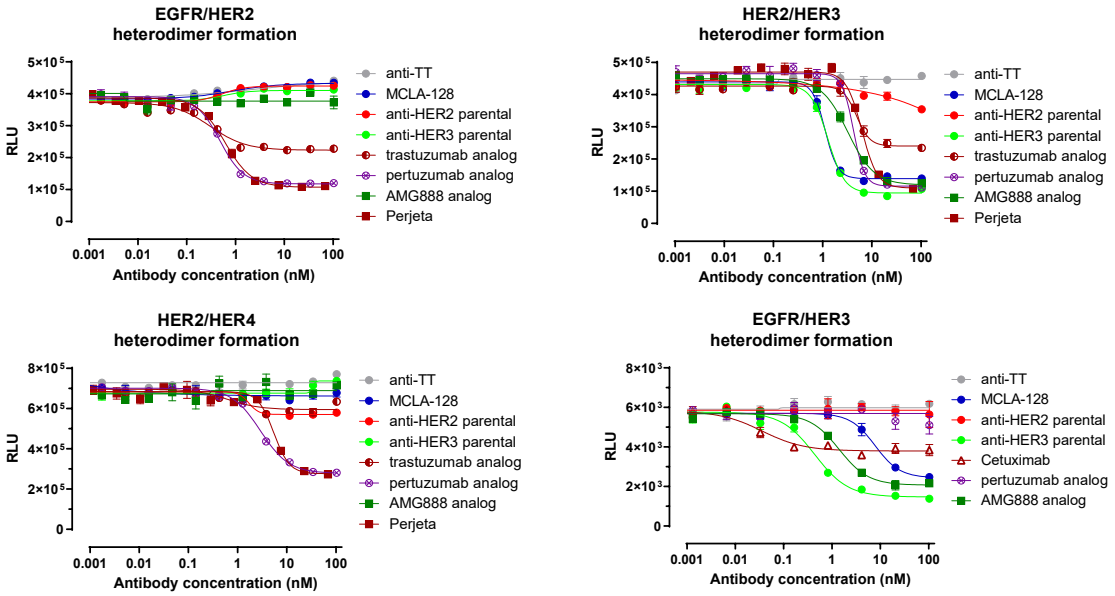
MCLA-128 fully inhibited HRG-induced HER2:HER3 dimerization with relatively high potency (Table 5). EGFR:HER3 formation was partially blocked by MCLA-128. In contrast, MCLA-128 inhibited neither EGFR:HER2 nor HRG-induced HER2:HER4 dimerization. (Figure 2 and Table 5). MCLA-128 thus selectively and efficiently inhibits the formation of HRG-induced HER2:HER3 dimers, when compared to monospecific antibodies targeting HER2 or HER3.

Table 5. Applicant - IC_{50} values for antibodies tested in RTK heterodimerization assays

IC_{50} (nM)	EGFR:HER2	HER2:HER3	HER2:HER4	EGFR:HER3
Anti-TT	-	-	-	-
MCLA-128	-	1.12	-	7.78
Anti-HER3 parental	-	1.27	-	0.44
Anti-HER2 parental	-	-	1.69	-

IC_{50} values were determined in Prism using non-linear regression (4 parameters). Source: Report P1208-R55 (eCTD Module 2.6.2).

Figure 2. Applicant - Specific inhibition of HRG-induced HER2:HER3 dimerization by MCLA-128

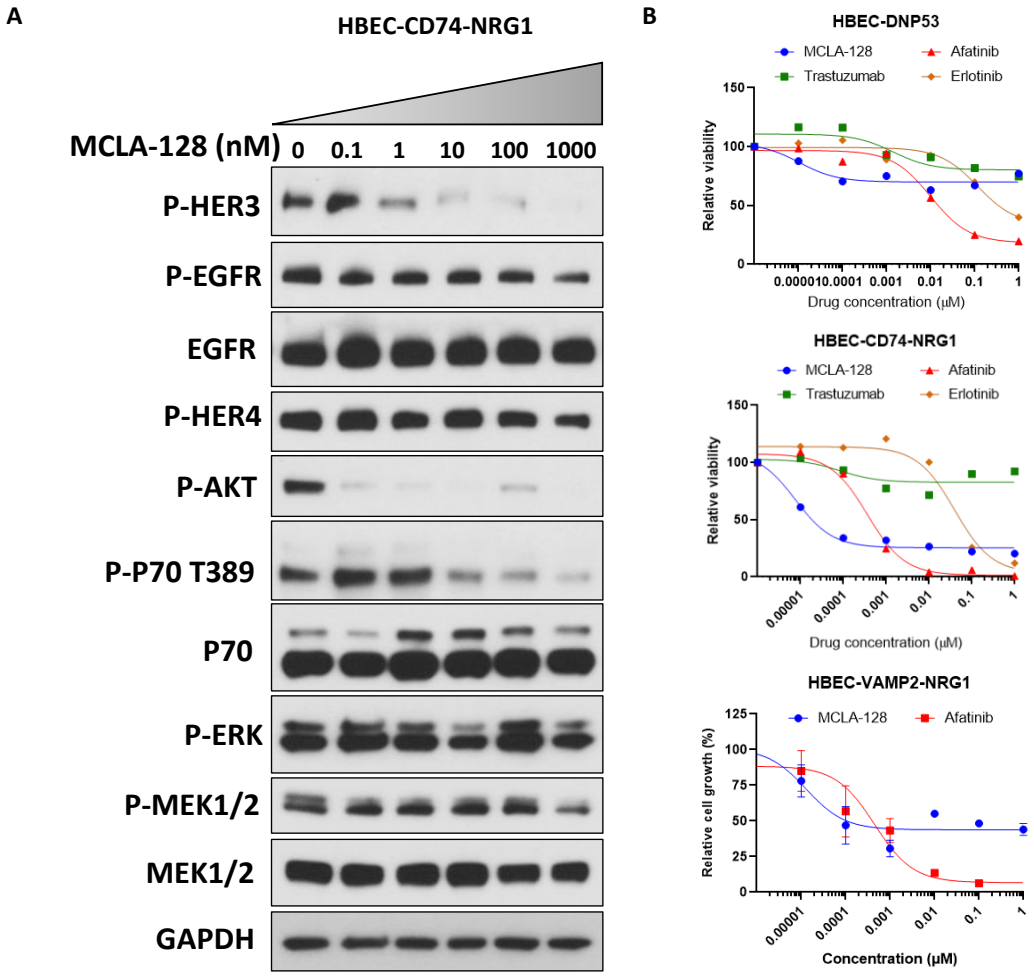


Antibody antagonist mode dose-response curves in EGFR:HER2, HER2:HER3, HER2:HER4, and EGFR:HER3 assays. Each data point represents the mean and standard deviation of four replicates per dose. Anti-TT was used as a negative control in all experiments. Trastuzumab and pertuzumab were used as HER2-specific controls; AMG888 was used as HER3-specific control; and cetuximab was used as anti-EGFR control. Data were plotted in GraphPad Prism and curve fits were performed using a log (inhibitor) versus response-variable response (4 parameters) fit to calculate the half-maximal inhibitory concentrations (IC_{50}) (see Table 5). *Source: Report P1208-R55 (eCTD Module 2.6.2).*

To map signaling pathways activated by NRG1 fusions, the effect of MCLA-128 on PI3K-AKT signaling was assessed in a series of cell lines expressing an NRG1 fusion protein (Report P1801-S12; Schram et al, 2022).

In NRG1-overexpressing human bronchial epithelial cells (HBEC), exposure to MCLA-128 for 3 hours demonstrated a dose-dependent decrease in phosphorylation of the various components of the HER3-mediated PI3K-AKT signaling pathway (Figure 3. Viability assays also showed a marked reduction in cell counts of HBEC-CD74-NRG1 cells at relatively low concentrations of MCLA-128 (half-maximal effective concentration [EC50] 7.6×10-6 µM, 95% confidence interval [CI]: 3.2×10-6, 1.8×10-5 µM). For the VAMP2-NRG1 model, the potency of MCLA-128 in terms of EC50 was 1.3×10-5 µM (95% CI: 3.6×10-6, 4.8×10-5 µM). No significant inhibitory effects on cell viability were observed upon treatment of the NRG1-fusion-negative HBEC cell line (HBEC-DNP53).

Figure 3. Applicant - MCLA-128-induced inhibition of PI3K-AKT signaling and cell survival in NRG1-fusion-expressing immortalized HBEC cell lines

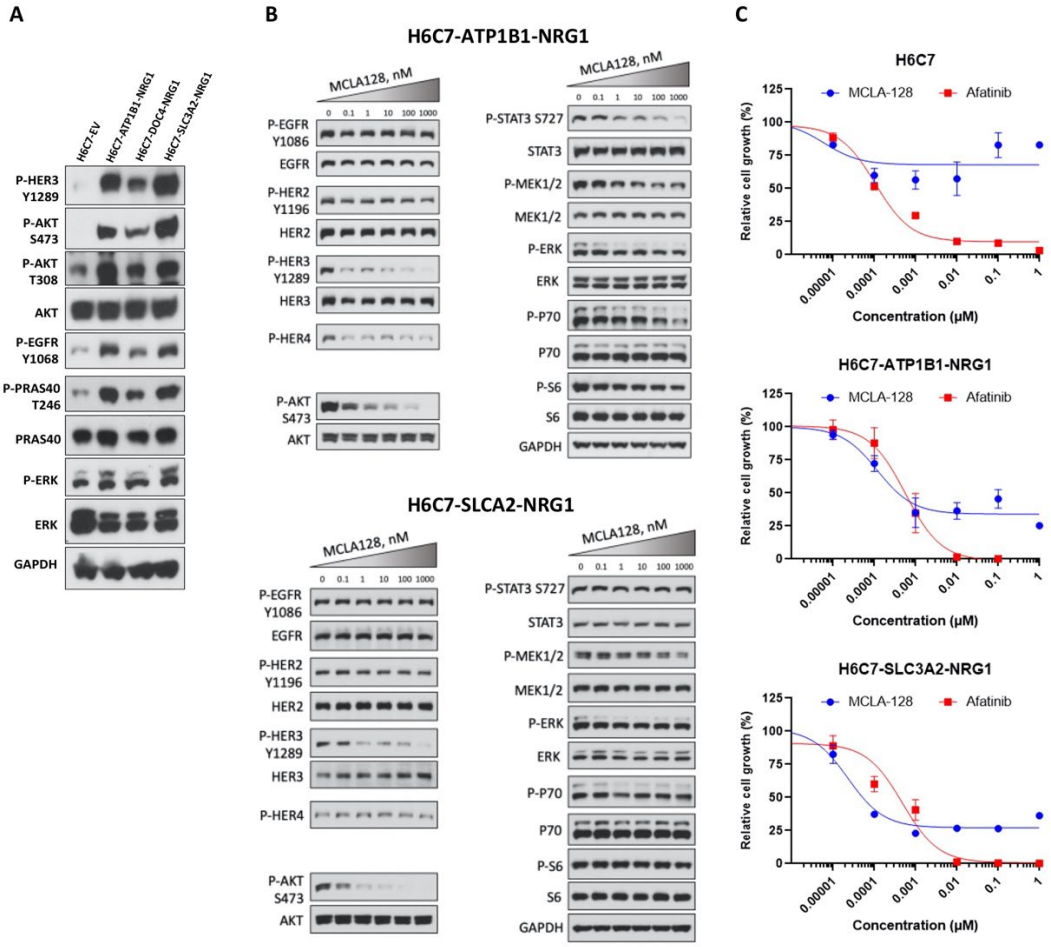


(A) Inhibition of *CD74-NRG1*-induced signaling. *CD74-NRG1*-expressing HBEC-DNP53 cells were cultured under serum-free conditions for 24 h before being treated with the indicated concentrations of MCLA-128 for 3 h and subjected to western blot analysis. (B) Inhibition of viability of cells expressing *NRG1* fusions. HBEC-DNP53 control cells (top), *CD74-NRG1*- and *VAMP2-NRG1*-expressing cells were cultured serum-free and subjected to the indicated concentrations of MCLA-128 or control substances for 3 days before performing an Alamar Blue viability assay. Trastuzumab: anti-HER2 benchmark antibody; Afatinib: EGFR/HER2 inhibitor; Erlotinib: EGFR inhibitor. Data points are shown as means (± standard error of the mean [SEM]) of 4 experiments (HBEC-DNP53 & HBEC-CD74-NRG1) or 3 experiments (HBEC-VAMP2-NRG1). *Source: Report P1801-S12 (eCTD Module 2.6.2).*

Immortalized human pancreatic ductal epithelial cells (H6C7 cell line) were also engineered to over-express NRG1 fusion proteins. Treatment of the H6C7-ATP1B1-NRG1 and H6C7-SLC3A2-NRG1 fusion cell lines with increasing concentrations of MCLA-128 led to a dose-dependent reduction in HER3-mediated PI3K/AKT signaling (Figure 4B). A marked reduction in viability

relative to control conditions was shown (Figure 4C) in both ATP1B1-NRG1 and SLC3A2-NRG1-induced cell growth after treatment with increasing concentrations of MCLA-128 (ATP1B1-NRG1: EC50 1.2×10-4 µM, 95% CI 6.0×10-5, 2.4×10-4 µM; SLC3A2-NRG1: EC50 2.3×10-5 µM, 95% CI 1.5×10-5, 3.7×10-5 µM).

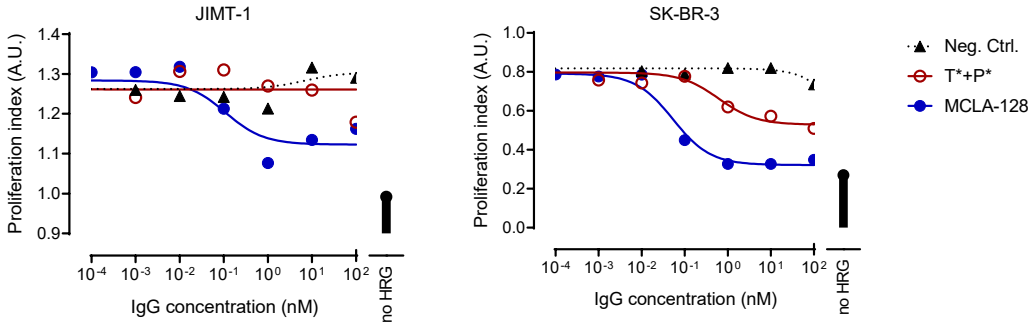
Figure 4. Applicant - MCLA-128-induced inhibition of PI3K/AKT signaling and cell survival in 3 *NRG1*-fusion-expressing pancreatic cell models



(A) HER3 PI3K/AKT signaling is upregulated in pancreas cells expressing *NRG1* fusions. H6C7 cell lines expressing 3 different *NRG1* fusion partners were cultured under serum-free conditions for 24 h before western blot analysis. (B) MCLA-128 inhibits *NRG1*-fusion-induced signaling. *ATP1B1-NRG1* and *SLCA2-NRG1*-expressing H6C7 cells were cultured under serum-free conditions for 24 h before being treated for 3 h with the indicated concentrations of MCLA-128 and subjected to western blot analysis. (C) Inhibition of viability of cells expressing *NRG1* fusions. Control cells (top) and *ATP1B1-NRG1* and *SLC3A2-NRG1*-expressing cells were cultured serum-free and subjected to the indicated concentrations of MCLA-128 or the EGFR/HER2 inhibitor afatinib for 3 days before performing an Alamar Blue viability assay. Data points are shown as means (± SEM) of 4 experiments. EV = empty vector. *Source: Report P1801-S12 (eCTD Module 2.6.2).*

MCLA-128 also inhibited the proliferation of the HER2-amplified breast cancer cell lines JIMT-1 and SK-BR-3 at high HRG concentrations (Report P1208-R47)(Figure 5). These data suggest that MCLA-128 is capable of completely suppressing ligand-driven growth in HER2-overexpressing cells at nanomolar to sub-nanomolar concentrations.

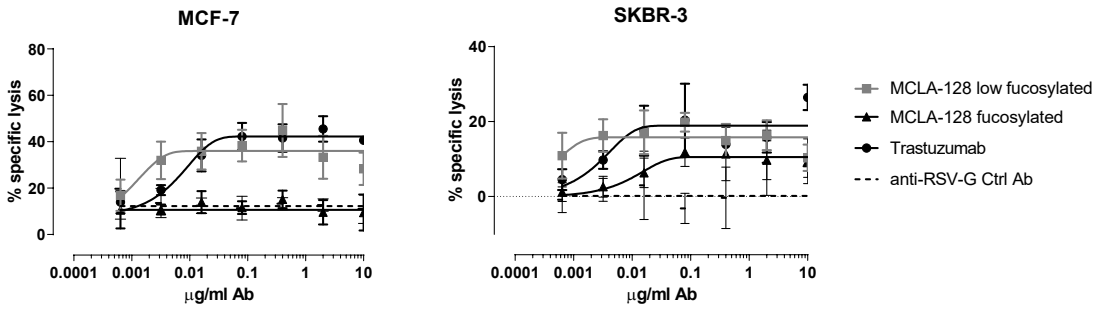
Figure 5. Applicant - Superior inhibitory activity of MCLA-128 in HER2-amplified breast cancer cells stimulated with high concentration of HRG (12.5 nM)



Cell cycle analysis was performed on breast cancer cell lines expressing intermediate (JIMT-1) and high (SK-BR-3) levels of HER2 while co-expressing similar levels of HER3. Cells were stimulated with no HRG or supramaximal (12.5 nM) HRG concentrations and titrations of the indicated antibodies. The proliferation index was calculated by dividing the percentage of cells in the G0/G1 and S phase by the percentage of cells in the G2/M phase. Neg. Ctrl. = anti-tetanus toxoid negative control antibody; no HRG = basal cell proliferation independent of HRG; T*+P* = equimolar combination of trastuzumab and pertuzumab analogs. *Source: Report P1208-R47 (eCTD Module 2.6.2).*

ADCC activity of MCLA-128 has been maximized by low-fucose glycoengineering (further details are described in eCTD Module 3.2.S.1.2). ADCC activity of low-fucosylated MCLA-128 was compared with that of a non-engineered (wild-type) variant using a standard 51Chromium release assay. Results showed that the PBMC-mediated ADCC activity of low-fucosylated MCLA-128 is superior to that of the non-engineered wild-type variant when using both a HER2 high-expressing cell line (SK-BR-3) and a HER2 low-expressing cell line (MCF-7) as target cells (Figure 6). The ADCC activity of low-fucosylated MCLA-128 was independent of the CD16 (FcγRIIIa) receptor polymorphism variants (158V/F) tested (selected based on commonly occurring polymorphisms in the human population) (Report P1208-R10). It was therefore decided to manufacture MCLA-128 using the low-fucose expression technology.

Figure 6. Applicant - Enhancement of MCLA-128 ADCC activity by low-fucose expression technology

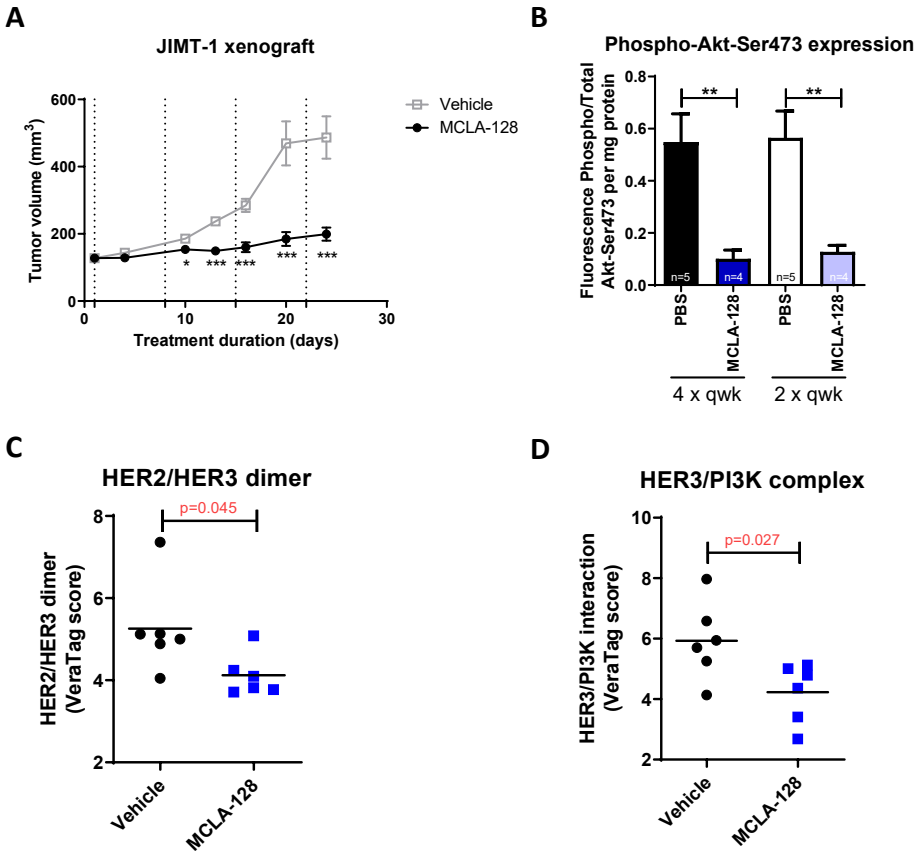


Breast cancer cells expressing low (MCF-7) or high (SK-BR-3) levels of HER2 were labeled with ^{51}Chromium and incubated with a titration of antibodies in the presence of human peripheral blood mononuclear cells (PBMCs). The ADCC activity of low-fucosylated MCLA-128 was compared with that of fucosylated MCLA-128, trastuzumab, and negative control antibody (Ctrl Ab). Data presented are from one donor (# (b) (6)) and are representative of data from four donors. Data points indicate means (± SD) of 3 experiments. *Source: Report P1208-R10 (eCTD Module 2.6.2).*

In vivo studies

Since MCLA-128 effectively inhibited proliferation of the JIMT-1 cell line in vitro, it was subsequently tested in an in vivo xenograft model. Clear antitumor efficacy was observed after treatment with MCLA-128 in mice bearing JIMT-1 tumors (Report P1208-R21). Further experiments were done to determine whether inhibition of the PI3K pathway leads to tumor growth inhibition (TGI) in this model, mice bearing JIMT-1 xenografts were treated with 2 or 4 weekly doses of MCLA-128 (Report P1208-S49). In mice treated with 4 weekly doses of MCLA-128, this resulted in 59% TGI relative to the vehicle group (Figure 7A). Forty-eight hours after the last dose, tumors were harvested and quantified for total and phosphorylated AKT levels by Luminex analysis. Phosphorylation of AKT was severely inhibited by MCLA-128 compared to vehicle control (Figure 7B). To determine whether this could be related to the inhibition of HER2-HER3 heterodimerization, the VeraTag assay was applied on formalin fixed paraffin embedded JIMT-1 tumor sections. Both HER2:HER3 heterodimerization (Figure 7C) and HER3:PI3K formation (Figure 7D) were significantly inhibited by MCLA-128. Overall, these in vivo mechanism of action studies correlate well with our in vitro findings and suggest that the inhibition of HER2:HER3 dimer formation and downstream AKT signaling is involved in the MCLA-128-induced tumor growth reduction in the JIMT-1 model.

Figure 7. Applicant - MCLA-128 mechanism of action in HER2-overexpressing tumor xenograft model



(A) JIMT-1 xenograft growth curves from MCLA-128 and vehicle treatment groups. MCLA-128 (25 mg/kg) and phosphate-buffered saline (PBS) was given once a week, four times (4 x qwk). Dotted lines indicate days of treatment administration. Tumor size between vehicle and MCLA-128-treated groups were compared with an unpaired t-test. * p<0.05, *** p<0.005 (n=10). **(B)** JIMT-1 tumors from mice treated with either 2 or 4 weekly doses of PBS or MCLA-128 (25 mg/kg) were extracted 48 h after the last dose and assessed for levels of phosphorylated proteins – EGFR, HER2, HER3, HER4, and AKT – by Luminex according to procedures established at [redacted] (b) (4). Bars show ratios for phosphorylated to total AKT (Ser473) (means ± SEM) determined in samples from 4 or 5 animals, as indicated. ** p≤0.01 (**C, D)** JIMT-1 tumor sections from mice treated with two weekly doses of PBS or MCLA-128 (25 mg/kg) were extracted 4 h after the second dose and analyzed by VeraTag assay for the formation of HER2:HER3 dimers and HER3:PI3K complexes. An unpaired two-tailed t-test was used to calculate p-values comparing vehicle and MCLA-128 groups. The horizontal lines in **(C)** and **(D)** represent the mean. *Source: Report P1208-S49 (eCTD Module 2.6.2).*

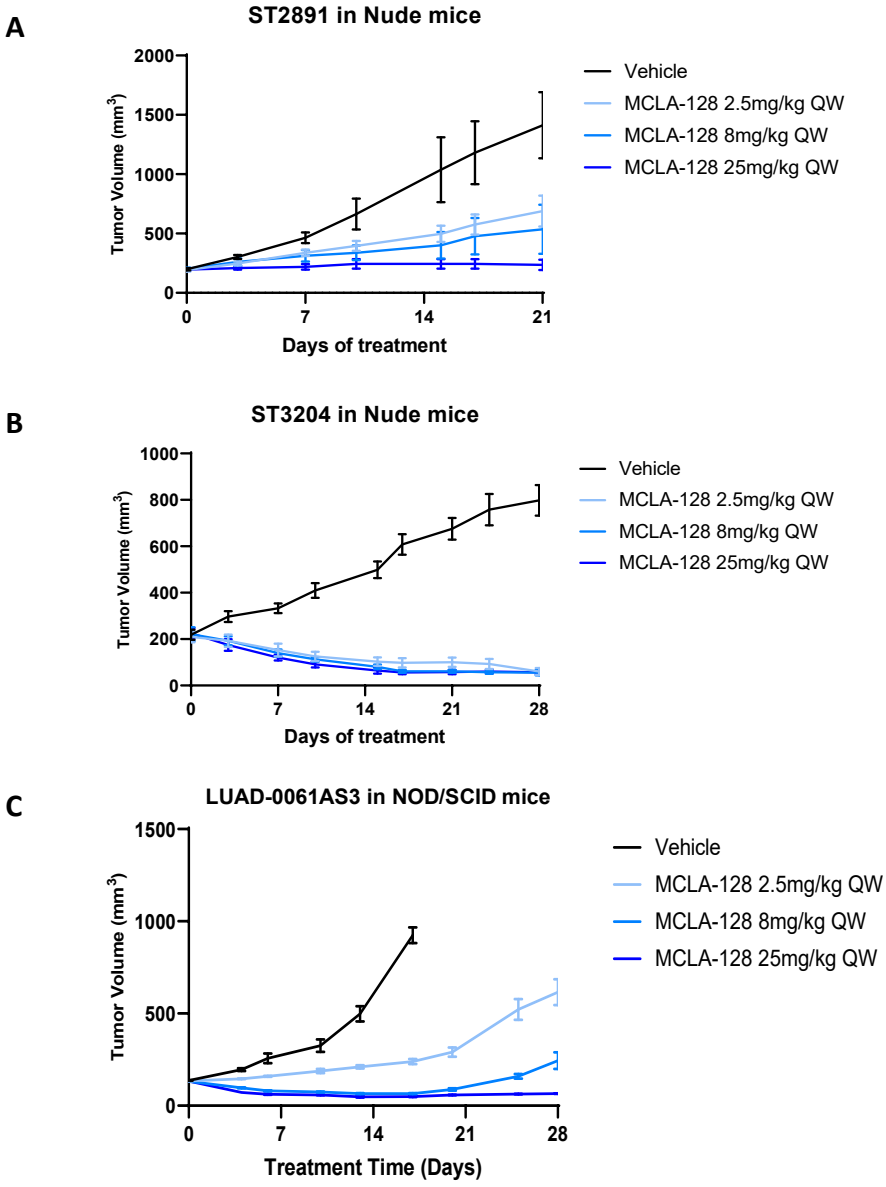
The efficacy of MCLA-128 was further assessed in vivo in several tumor models bearing an NRG1 gene fusion: 3 lung cancer models, 1 breast cancer model, and 2 ovarian cancer models. In the 3 lung cancer models shown here, antibodies were dosed at 2.5–25 mg/kg once a week over 4-5 weeks.

In lung cancer model ST2891 (CD74-NRG1 fusion), a significant dose-dependent reduction in tumor volume was reported with MCLA-128 towards ST2891 tumors at all tested dose levels ($p<0.05$ by one-way analysis of variance (ANOVA) on Day 21; Figure 8A)(Report P1801-R16).

In lung cancer model ST3204 (CD74-NRG1 fusion), a significant reduction in tumor volume was reported with MCLA-128 towards ST3204 tumors ($p<0.0001$ by one-way ANOVA on Day 28), including partial tumor regression at all tested dose levels (Figure 8B)(Report P1801-R16).

In lung cancer model LUAD-0061AS3 (SLC3A2-NRG1 fusion), tumor growth inhibition induced by MCLA-128 on Day 17 increased in a dose-dependent manner from 86% in the 2.5 mg/kg group to 109% in the 8 mg/kg group and 111% in the 25 mg/kg group (Figure 8C). (Report P1801-S12).

Figure 8. Applicant - Antitumor efficacy of MCLA-128 in *NRG1*-fusion-expressing lung cancer models



(A) ST2891 model: Tumor growth curves plotted over 21 days in mice (n = 10/group). **(B)** ST3204 model: Tumor growth curves plotted over 28 days in mice (n = 10/group). **(C)** LUAD-0061AS3 model: Tumor growth curves plotted over 28 days in mice (n = 5/group). Mice received weekly either vehicle or MCLA-128 at doses of 2.5, 8, or 25 mg/kg. Error bars represent SEM. *Sources: Reports P1801-R16, P1801-S12 (eCTD Module 2.6.2).*

The FDA's Assessment:

In general, FDA agrees with the Applicant's conclusions. However, the Applicant (b) (4)

Zenocutuzumab (MCLA-128) is composed of the Fab fragments MF (b) (4) (anti-HER2) and MF (b) (4) (anti-HER3). Shotgun mutagenesis technology mapped the epitope of the anti-HER2 Fab fragment to domain I of HER2 (Study No. P1208-R50), and the epitope of the anti-HER3 fragment to domain III of HER3 (Study No. P1208-R52), which is the major NRG1-binding domain of HER3. Consistent with this, crystal structures and small angle X-ray scattering with MF (b) (4) and MF (b) (4) and their respective receptor ECDs showed that the Fab fragments of zenocutuzumab binds to HER2 and HER3 ECDs, leading to inhibition of HER2:HER3 dimerization. In addition, MF (b) (4) binds to the inactive conformation of HER3 and the epitope of MF (b) (4) partially overlaps with the NRG1-binding domain; thus, binding of zenocutumab to HER3 may prevent NRG1 binding to activate HER3 (Study No. P1208-R45). As assessed by ELISA and flow cytometry, both the anti-HER2 and anti-HER3 Fab fragments bound to the human and cynomolgus homologs of their target receptors (Study Nos. P0712-R12, P0712-R16), but the anti-HER2 Fab fragment did not bind to HER2 in rodents (Study No. P0712-R12). In addition, sequence homology assessments of HER2 among human, cynomolgus monkey, mouse, rat, and hamster showed high amino acid sequence similarity of HER2 and HER3 between monkeys and humans for the full-length protein and extracellular domain (98–99%), with lower sequence homology between human and rodent HER2 (85–88%) and HER3 (91–93%) (Study No. P1305-S38). These results support the use of cynomolgus monkeys as the pharmacologically relevant species for zenocutuzumab toxicity assessment. Zenocutuzumab did not induce CDC against the HER2- and HER3-positive human breast cancer SK-BR-3 cell line (Study No. 200-888-003). In addition to lung, breast, and ovarian cancer models bearing an NRG1 gene fusion, the antitumor activity of zenocutuzumab was evaluated in an NRG1 fusion-positive PDX model of pancreatic cancer (Study No. P1801-S28). Athymic mice were inoculated with PDAC tumors with an NRG1 fusion and treated once weekly with zenocutuzumab at 25 mg/kg IP, followed by a 3-month observation period. Zenocutuzumab showed antitumor activity and tumor regression below baseline (>100% tumor growth inhibition) compared to the control group. There were no mortalities or adverse effects on body weights.

Secondary Pharmacology

The Applicant's Position:

No secondary pharmacology studies were performed.

The FDA's Assessment:

FDA agrees.

Safety Pharmacology

The Applicant's Position:

Stand-alone safety pharmacology studies were not conducted. Safety pharmacology was evaluated as part of the general toxicology studies performed with MCLA-128.

No effect was observed on ECG, blood pressure, respiration rate, body temperature or CNS safety pharmacology parameters evaluated as part of the general toxicology studies performed in cynomolgus monkeys with MCLA-128 up to 101 mg/kg/week (Report 612352, Report 49737 TCP, eCTD Module 2.6.2).

The FDA's Assessment:

FDA agrees with the Applicant's conclusions.

5.4. ADME/PK

The Applicant's Position:

Toxicokinetic (TK) characteristics of MCLA-128 (zenocutuzumab) were studied as part of single and repeated dose toxicity studies in cynomolgus monkeys, the pharmacologically relevant species.

- Systemic exposure increased in a fairly proportional manner over the dose range 10-101 mg/kg after a single IV infusion
- Serum elimination half-life tended to increase with dose and ranged from 73-210 hours
- The calculated volumes of distribution were in the range of 68.3-121 mL/kg
- In the 1-month repeated dose toxicity study, females at the low dose (10 mg/kg/week) showed a three-fold accumulation (based on AUC), whereas the males at this dose showed only slight accumulation (1.37-fold) after repeated dosing. At 30 mg/kg/week, there was no evidence of accumulation, with AUC values being similar on Days 1 and 22. At 100 mg/kg/week, only slight accumulation was observed (1.52 to 1.71-fold) after 4 weekly doses.

- In the 13-week repeated dose toxicity study, due to the formation of anti-drug antibodies (ADA) and accumulation of MCLA-128, dose proportionality after repetitive dosing could not be accurately assessed. By Week 13, MCLA-128 exposure had slightly accumulated (1.39 to 1.42-fold increase in AUC_{0-t}) for the 101 mg/kg dose level, while no relevant accumulation was observed for the 10 mg/kg and 30 mg/kg dose levels. Comparable observations were made for C_{max}.
- Among the 50 cynomolgus monkeys dosed with MCLA-128 in the single dose and the 1-month and 13-weeks repeated dose studies, 21 tested positive for the presence of anti-drug antibodies (ADA).
- Conventional studies on absorption, distribution, metabolism and excretion (ADME) have not been conducted for MCLA-128, since MCLA-128 is a biologic and pathways of protein degradation are known. It is believed that MCLA-128, like other proteins, is catabolized by lysosomal enzymes in the liver and/or kidney into amino acids that are then re-absorbed and/or re-incorporated into endogenous proteins.

Sources: *Reports 612347, 612352, 49737 TCP, eCTD Module 2.6.4.*

Table 6. Applicant's table

Absorption
Report 612347: A single dose pharmacokinetic (PK) and preliminary toxicity study of MCLA-128 by intravenous infusion in cynomolgus monkeys. See table below.
Distribution
No distribution studies were performed. Distribution studies are generally not applicable to biotechnology-derived pharmaceuticals, in line with the International Council for Harmonization (ICH) S6 (R1) guideline. Estimates of the volume of distribution following a single IV dose in cynomolgus monkeys suggest only limited distribution of MCLA-128 outside the vascular compartment (Report 612347, eCTD Module 2.6.4).
Metabolism
No metabolism studies were performed. Metabolism studies are generally not applicable to biotechnology-derived pharmaceuticals, in line with the ICH S6 (R1) guideline. It is considered that MCLA-128, like other proteins, is catabolized by lysosomal enzymes in the liver and/or kidney into amino acids that are then re-absorbed and/or re-incorporated into endogenous proteins (eCTD Module 2.6.4)
Excretion
No excretion studies were performed. Excretion studies are generally not applicable to biotechnology-derived pharmaceuticals, in line with the ICH S6 (R1) guideline (eCTD Module 2.6.4).
Summary PK parameters from pharmacokinetic studies
See tables below.
Integrative summary table of Cmax and AUC parameters across toxicology studies (general, reproductive, and carcinogenicity, if conducted).
Pharmacokinetics/toxicokinetics after a single dose (eCTD Module 2.6.5)

Test article: MCLA-128			
Report Number: 612347			
Species	Cynomolgus monkey		
Gender (M/F)/Number of animals	1M + 1F/dose level		
Feeding condition	Fed		
Vehicle/Formulation	0.9% sodium chloride		
Method of administration	Intravenous infusion over 1 hour		
Dose (mg/kg)	10, 30 and 100		
Sample (e.g., whole blood, plasma, serum)	Serum		
Analyte	MCLA-128		
Assay	ECLIA		
PK parameters † (Unit)			
Dose (mg/kg)	10	30	100
T_{max} (hours)	1.1	3.1	2.1
C_{max} (µg/mL)	222	642	1840
$AUC_{0\text{-}168h}$(h.µg/mL)	11850	39100	109000
$AUC_{0\text{-}t}$(h.µg/mL) (t=Day 43)	13200	55900	189000#
$t_{1/2}$ (hours)	73#	110#	210#
CL (mL/h/kg)	0.717#	0.537#	0.532#
V_{ss} (mL/kg)	68.3#	72.3#	121#
ADA-positive animals (Day 22)	2/2	1/2	0/2
ADA-positive animals (Day 43)	2/2	2/2	1/2

† PK parameters are given as the mean value for the male and female monkey; # Values are for a single animal at each dose level – insufficient data points in the elimination phase to calculate values for the other animal in the group. ADA = anti-drug antibody; AUC = area under the serum drug concentration versus time curve; CL = (apparent) serum clearance; C_{max} = maximum serum drug concentration; ECLIA = electrochemiluminescence linked immunoassay; $t_{1/2}$ = half-life; PK = pharmacokinetic; T_{max} = time of observed maximum serum drug concentrations; V_{ss} = estimated volume of distribution at steady state.

Toxicokinetics after 1-month repeated dose (eCTD Module 2.6.5)

Test article: MCLA-128	
Report Number.: 612352	
Species	Cynomolgus monkey

Gender (M/F)/Number of animals	3M + 3F/dose level (5M + 5F in high dose group).											
Feeding condition	Fed											
Vehicle/Formulation	MCLA-128 formulation buffer / 0.9% sodium chloride (50%/50%, V/V)											
Method of administration	Intravenous infusion over 1-hour on Days 1, 8, 15, 22 and 29											
Dose (mg/kg/week)	10, 30 and 100											
Sample (e.g., whole blood, plasma, serum)	Serum											
Analyte	MCLA-128											
Assay	ECLIA											
Dose (mg/kg/week)	**10**	**30**	**100**									
	Day 1	**Day 22**	**Day 1**	**Day 22**	**Day 1**	**Day 22**						
PK parameters (Unit)	M	F	M	F	M	F	M	F	M	F	M	F
C_{max} (µg/mL)	230	261	620	881	812	786	500	501	2320	2250	3120	2970
$AUC_{0\text{-}168h}$(h.mg/mL)	11.3	12.8	15.5	39.3	44.6	41.3	45.9	44.3	129	130	220	197
Accumulation ratio ($AUC_{Day\ 22}/AUC_{Day\ 1}$)	-	-	1.37	3.07	-	-	1.03	1.07	-	-	1.71	1.52
ADA-positive animals (Day 29)			3/3	1/3			0/3	1/3			0/5	1/5

V/V = volume per volume; M = male; F = female.

Toxicokinetics after 13-week repeated dose (eCTD Module 2.6.5)

Test article: MCLA-128	
Report Number: 49737 TCP	
Species	Cynomolgus monkey
Gender (M/F)/Number of animals	3 M + 3F/dose level (5M + 5F in high dose group)
Feeding condition	Fed
Vehicle/Formulation	MCLA-128 formulation buffer / 0.9% sodium chloride (50%/50%, V/V)
Method of administration	Intravenous infusion over 1-hour on Days 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78 and 85
Dose (mg/kg/week)	10, 30 and 101
Sample (e.g., whole blood, plasma, serum)	Serum
Analyte	MCLA-128

Assay	ECLIA							
Dose (mg/kg/week)	**10**							
	Week 1		**Week 5**		**Week 9**		**Week 13**	
PK parameters (Unit)	Male	Female	Male	Female	Male	Female	Male	Female
C_{max} (µg/mL)	255	261	147	200	103	257	161	156
$AUC_{0\text{-}168h}$(h.mg/mL)	12,100	13,300	6,660	7,080	16,300	15,000	13,200	7,100
Accumulation ratio ($AUC_{Week}/AUC_{Week\ 1}$)	-	-	0.543	0.482	1.33	0.996	1.08	0.467
ADA-positive animals	0/3	0/3	3/3	2/3	3/3	3/3	3/3	3/3

Dose (mg/kg/week)	**30**							
	Week 1		**Week 5**		**Week 9**		**Week 13**	
PK parameters (Unit)	Male	Female	Male	Female	Male	Female	Male	Female
C_{max} (µg/mL)	693	728	1,020	1,120	1,080	652	636	659
$AUC_{0\text{-}168h}$(h.mg/mL)	38,100	42,800	47,000	73,600	56,900	71,100	29,700	42,400
Accumulation ratio ($AUC_{Week}/AUC_{Week\ 1}$)	-	-	1.21	1.66	1.46	1.61	0.764	0.954
ADA-positive animals	0/3	0/3	2/3	1/3	1/2	1/3	2/2	1/3
Dose (mg/kg/week)	**101**							
	Week 1		**Week 5**		**Week 9**		**Week 13**	
PK parameters (Unit)	Male	Female	Male	Female	Male	Female	Male	Female
C_{max} (µg/mL)	2,380	2,600	3,180	2,980	3,040	2,580	3,770	4,110
$AUC_{0\text{-}168h}$(h.mg/mL)	142,000	141,000	227,000	168,000	226,000	176,000	207,000	198,000
Accumulation ratio ($AUC_{Week}/AUC_{Week\ 1}$)	-	-	1.5	1.19	1.56	1.23	1.42	1.39
ADA-positive animals	0/5	0/5	1/5	2/5	0/4	2/5	0/4	1/5
V/V = volume per volume								

The FDA's Assessment:

FDA agrees with the Applicant's summary of the nonclinical ADME/PK data. In the 1-month GLP-compliant repeat-dose toxicology study in monkeys, exposure to zenocutuzumab on Day 1 increased in an approximately dose-proportional manner. Exposure on Day 22 increased less than

dose proportionally between 10 and 30 mg/kg and greater than dose proportionally between 30 and 100 mg/kg. This lack of dose proportionality was likely the result of reduced exposure in individual animals due to ADA formation. There were no significant sex-related differences in exposure.

In the 13-week GLP-compliant repeat-dose toxicology study, exposure on Day 1 increased in an approximately dose-proportional manner. Exposure in Weeks 5 and 9 increased greater than dose proportionally between 10 and 30 mg/kg and dose proportionally between 30 and 101 mg/kg. In Week 13, exposure increased greater than dose proportionally across the dose range. There were no significant sex-related differences in exposure. The mean terminal elimination half-life ranged from 8.43 to 101 hours, clearance ranged between 0.00514 and 0.101 mL/min/kg, and the volume of distribution ranged from 0.0332 to 0.0883 L/kg.

5.5. Toxicology

5.5.1. General Toxicology

The Applicant's Position:

MCLA-128 is a bispecific antibody directed against HER2 and HER3 intended for the treatment of advanced cancers. The nonclinical safety program of MCLA-128 followed the International Council for Harmonisation (ICH) M3(R2), S3A, S5(R3), S6(R1), S7A, and S9 guidelines for the nonclinical evaluation for anti-cancer pharmaceuticals. The pivotal toxicology studies were conducted in accordance with the requirement of the United States (US) Food and Drug Administration (FDA) GLP regulations for Nonclinical Laboratory Studies (21CFR Part 58) and/or the principles of Organisation for Economic Co-operation and Development (OECD) GLP in countries that are part of the OECD Mutual Acceptance of Data process.

The cynomolgus monkey was utilized as the only pharmacologically relevant species for toxicity testing, in view of cross reactivity of MCLA-128 with the HER2/HER3 targets in this species.

Intravenous (IV) administration of MCLA-128 was well tolerated in cynomolgus monkeys following single and repeated dose (up to 13 weekly doses), with no test item-related clinical, laboratory, or pathological findings up to the highest dose tested (101 mg/kg). There was no evidence of test item-related cardiotoxicity or effects on thyroid function. There was some evidence of anti-drug antibodies (ADA) to MCLA-128 in a few treated animals in the repeated dose toxicity studies. However, all treated animals were exposed to MCLA-128 for all or most of the treatment period, such that the formation of ADA in isolated animals was not considered to have compromised the safety evaluation. The MCLA-128 infusion solution showed good local tolerability, with no evidence of local irritation at injection sites (apart from signs associated with the administration procedure) in the cynomolgus monkey toxicity studies.

Table 7. Applicant - Single dose toxicity

Report Title: A single dose pharmacokinetic (PK) and preliminary toxicity study of MCLA-128 by intravenous infusion in cynomolgus monkeys				**Test Article: MCLA-128**
Species/Strain:	Monkey/cynomolgus	**Duration of Dosing:**	Single dose	**Report No.:** 612347
Initial Age:	36-39 months	**Duration of Post Dose:**	42 days	**eCTD Location:** Module 2.6.7
		Method of Administration:	IV infusion (1 h) on Day 1	
		Vehicle/Formulation:	Formulation buffer/0.9% NaCl	**GLP Compliance:** Yes

Special Features:	None
Observed maximum non-lethal dose:	100 mg/kg

Dose – mg/kg	**10**		**30**		**100**	
Number of animals	**1M**	**1F**	**1M**	**1F**	**1M**	**1F**
Toxicokinetic data	See Section 5.4					
Noteworthy findings	No treatment effects on clinical signs, bodyweight or terminal organ weight/necropsy findings. Systemic exposure to MCLA-128 was dose-related. ADAs were detected on Days 22 and 43 for all animals at 10 and 30 mg/kg, and on Day 43 only for the male animal at 100 mg/kg.					

ADA = anti-drug antibody; F = female; IV = intravenous; M = male.

Table 8. Applicant - Repeat-dose toxicity (1-month)

Report Title: One-month repeated dose toxicity study by intravenous infusion in cynomolgus monkeys with an 8-week recovery period				**Test Article: MCLA-128**
Species/Strain:	Monkey/cynomolgus	**Duration of Dosing:**	5 weeks	**Report No.:** 612352
Initial Age:	29-40 months	**Duration of Post Dose:**	8 weeks	**eCTD Location:** Module 2.6.7
Date of First Dose:	22Apr14	**Method of Administration:**	IV infusion (1 h) on Days 1, 8, 15, 22, and 29	
		Vehicle/Formulation:	Formulation buffer/0.9% NaCl	**GLP Compliance:** Yes

Special Features:	None
No Observed Adverse Effect level:	100 mg/kg/week

Dose – mg/kg/week	**Control (0)**		**10**		**30**		**100**	
Number of animals	**5M**	**5F**	**3M**	**3F**	**3M**	**3F**	**5M**	**5F**
Toxicokinetic data	See Section 5.4							
Noteworthy findings:	0	0	0	0	0	0	0	0
Died or sacrificed moribund:	- -	- -	-	- -	- -	- -	-	- -

Dose – mg/kg/week	Control (0)		10		30		100	
Number of animals	**5M**	**5F**	**3M**	**3F**	**3M**	**3F**	**5M**	**5F**
Weight gain (Days 1-32) – kg	-	-	-	-	-	-	#	-
Clinical signs	-	-	-	-	-	-	-	-
Ophthalmoscopy	-	-	-	-	-	-	-	-
ECG (including QTc)	-	-	-	-	-	-	-	-
Blood pressure	-	-	-	-	-	-	-	-
Respiration rate	-	-	-	-	-	-	-	-
Body temperature	-	-	-	-	-	-	-	-
Hematology	-	-	-	-	-	-	-	-
Clinical chemistry	-	-	-	-	-	-	-	-
Urinalysis	-	-	-	-	-	-	-	-
Troponin I/thyroid hormones	-	-	-	-	-	-	-	-
Lymphocyte subset analysis	0/5 0/2	0/5 0/2	- 3/3	1/3 NA	0/3 NA	1/3 NA	- 0/5	1/5 1/2
Gross necropsy findings	0/2	0/2	NA NA	NA	NA	NA	0/2 2/2	1/2
Organ weights								
Histopathology								
ADA incidence – Day 29								
ADA incidence – Recovery Week 4								
ADA incidence – Recovery Week 8								

 # One male showed body twitches, increased heart rate, dilated pupils and heavy eyes during dosing on Day 29 – returned to normal within 15 min post dosing. Not considered adverse event or definitely treatment-related. "–" = No treatment-related findings; ADA = anti-drug antibodies; ECG = electrocardiogram; F = females; GLP = good laboratory practice; IV = intravenous; M = males; NA = not applicable; QTc = corrected QT interval.

Table 9. Applicant - Repeat-dose toxicity (13-weeks)

Report Title: 13-week repeated dose toxicity study by intravenous infusion in cynomolgus monkeys with a 6-week recovery period				**Test Article: MCLA-128**
Species/Strain:	Monkey/cynomolgus	**Duration of Dosing:**	13 weeks	**Report No.:** 49737 TCP
Initial Age:	24-33 months	**Duration of Post Dose:**	6 weeks	**eCTD Location:** Module 2.6.7
Date of First Dose:	15Mar22	**Method of Administration:**	IV infusion (1 h) on Days 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78, and 85	

Report Title: 13-week repeated dose toxicity study by intravenous infusion in cynomolgus monkeys with a 6-week recovery period							**Test Article: MCLA-128**	
				Vehicle/Formulation:	Formulation buffer/0.9% NaCl	**GLP Compliance:**	Yes	
Special Features:			None					
No Observed Adverse Effect level:			101 mg/kg/week					
Dose – mg/kg/week	**Control (0)**		**10**		**30**		**101**	
Number of animals	**5M**	**5F**	**3M**	**3F**	**3M**	**3F**	**5M**	**5F**
Toxicokinetic data	See Section 5.4							
Noteworthy findings:								
Died or sacrificed moribund:	0	0	0	0	1	0	1	0
Weight gain (Days 1-87) – kg	-	-	-	-	-	-	-	-
Clinical signs	-	-	-	-	-	-	-	-
Ophthalmoscopy	-	-	-	-	-	-	-	-
ECG (including QTc)	-	-	-	-	-	-	-	-
Blood pressure	-	-	-	-	-	-	-	-
Respiration rate	-	-	-	-	-	-	-	-
Body temperature	-	-	-	-	-	-	-	-
Hematology	-	-	-	-	-	-	-	-
Clinical chemistry	-	-	-	-	-	-	-	-
Urinalysis	-	-	-	-	-	-	-	-
Troponin I/thyroid hormones	-	-	-	-	-	-	-	-
Lymphocyte subset analysis	-	-	-	-	-	-	-	-
Gross necropsy findings	0/5	0/5	3/3	3/3	2/2	1/3	0/4	1/5
Organ weights	0/2	0/2	NA	NA	NA	NA	0/1	2/2
Histopathology	0/2	0/2	NA	NA	NA	NA	1/1	2/2
ADA incidence – Week 13								
ADA incidence – Recovery Week 4								
ADA incidence – Recovery Week 6								

" –" = No treatment-related findings; ADA = anti-drug antibodies; ECG = electrocardiogram; F = females; GLP = good laboratory practice; IV = intravenous; M = males; NA = not applicable; QTc = corrected QT interval.

The FDA's Assessment:

FDA generally agrees with the Applicant's high-level summary of the toxicology data; however, FDA does not agree that there were no zenocutuzumab-related findings of toxicological significance. In the 1-month GLP-compliant repeat-dose toxicology study in monkeys (reviewed under IND 131752), zenocutuzumab was intravenously administered at 10, 30, and 100 mg/kg once weekly for a total of 5 doses. Recovery from toxicity was assessed in animals at 100 mg/kg

after an 8-week recovery period. Dose-dependent changes in organ weight (relative to body weight) were observed in the spleen (13–37%), uterus (13–39%), and epididymis (17–35%) and were partially reversible. Gross pathology findings in the main study animals included a depressed area of the brain in one male at 100 mg/kg, and abnormal skin appearance or thinning hair in two females at 100 mg/kg; in recovery animals at 100 mg/kg, findings included enlargement of the parathyroid gland in one male, a mass in the kidney of one female, and abnormal consistency, pale discoloration, and/or adhesion(s) in the lung of several animals. Hematological changes indicative of toxicity (>50%) were observed at ≥10 mg/kg and included increased white blood cells and neutrophils, which correlated histologically with increased myelopoiesis in the bone marrow (femur), unilateral focal extramedullary hemopoiesis in the mandibular lymph node, and polymorphonuclear leukocytic infiltration in the mesenteric lymph node. Additional target organs of toxicity included the thymus, adrenal gland, sternum, skin, and injection site. Refer to Table 10 for selected histopathology findings. ADAs were detected in 6 of 22 animals (27%) on Day 29, 1 of 4 animals (25%) in recovery Week 4, and 3 of 4 animals (75%) in recovery Week 8.

Table 10: Selected Histopathology Findings (1-Month Study; Monkeys)

			Male				Female			
Organ/Tissue	Finding	Dose (mg/kg)	**0**	**10**	**30**	**100**	**0**	**10**	**30**	**100**
# of Monkeys Examined (Dosing/Recovery)			3/2R	3	3	3/2R	3/2R	3	3	3/2R
Adrenal gland	Vacuolation, decreased, zona fasciculata, diffuse, bilateral	Mild								1
	Mononuclear cell infiltration, cortex, focal	Minimal				1				1R
Femur	Myelopoiesis, increased	Moderate								1
Heart	Mixed inflammatory cell infiltration, focal	Minimal								1
Injection site	Inflammation, muscle, focal	Minimal				1/1R				
	Degeneration, perivascular, focal	Mild								1
Liver	Mononuclear cell infiltration	Minimal		2	3	1				
	Inflammatory cell infiltration, sinusoidal	Minimal								1
Lymph node, mandibular	Extramedullary hemopoiesis, focal, unilateral	Mild				1				
Lymph node, mesenteric	Polymorphonuclear leukocytic infiltration	Minimal								1
	Pigment deposits	Mild				1				
Pancreas, exocrine	Mononuclear cell infiltration, focal	Minimal				1		1		
Skeletal muscle	Mononuclear cell infiltration, focal	Minimal				1				
Skin and subcutis	Hyperplasia, epidermal	Mild								1

			Male				Female			
Organ/Tissue	Finding	Dose (mg/kg)	**0**	**10**	**30**	**100**	**0**	**10**	**30**	**100**
# of Monkeys Examined (Dosing/Recovery)			3/2R	3	3	3/2R	3/2R	3	3	3/2R
Spleen	Thickening, capsular, focal	Minimal			1					
Sternum	Myelopoiesis, increased	Mild								1
Stomach	Erosion, with hemorrhage, mucosal, multifocal	Minimal				1				
Thymus	Atrophy	Moderate								1
Thyroid gland	Mononuclear cell infiltration, unilateral, focal	Minimal		1	1					
	Cyst, in surrounding tissue, focal, unilateral	Minimal								1
	Cyst, unilateral	Mild						1		

R = recovery

In the 13-week repeat-dose toxicology study in monkeys, zenocutuzumab was intravenously administered at 10, 30, and 101 mg/kg once weekly for 13 weeks, followed by a 6-week recovery period. On Day 29, one male at 30 mg/kg died just before scheduled euthanasia and one male at 101 mg/kg was euthanized in moribund condition. In the male at 30 mg/kg, clinical signs appeared after the fifth infusion (e.g., lying on one side, non-sustained convulsions with foamy red vomitus, abnormal pupillary reflex). Clinical pathology findings at necropsy included increased white blood cell parameters (4x) and C-reactive protein (CRP, 15-fold) correlating histologically with focal vascular/perivascular inflammation; increased AST (99x), ALT (60x), creatine kinase (28x), and lactate dehydrogenase (7x) correlating histologically with muscular lesions; increased creatinine (2x), potassium (2x), and phosphorus (3x) correlating histologically with renal dysfunction/glomerulopathy; and decreased red blood cell parameters (0.6x) correlating histologically with hemorrhage in multiple organs (heart, tongue, gall bladder, injection site). Additional histological findings included increased cellularity in vessels from the lungs, liver, adrenal glands, and kidneys; and up to marked edema in the gall bladder and hepatic lymph nodes. Together, these findings are consistent with the features of an immune-mediated infusion reaction, which correlated with presence of ADAs. The relationship of these findings to zenocutuzumab is uncertain as they were not observed in the other animals, including those treated with higher doses. Hepatic changes including marked atrophy, marked diffuse congestion, and minimal degeneration/necrosis of hepatocytes were considered to contribute to the poor clinical state of the animal. The moribundity of the male at 101 mg/kg was attributed to diarrhea refractory to treatment, related to inflammatory and degenerative lesions in the large intestine. Protozoan parasites consistent with Balantidium coli were also observed in the lumen of the cecum and colon. The Applicant considered this finding to be unrelated to zenocutuzumab, as such intestinal lesions have been reported in untreated monkeys (Brady and Carville, 2012; Johnson et al., 2022; Sasseville and Diters, 2008). FDA review team verified these findings in the literature and agrees that the moribundity is most likely due to diarrhea and infection secondary to lesions; however,

we also note that in the clinic, diarrhea was reported as a common adverse event with zenocutuzumab.

In animals that survived to scheduled necropsy, increased spleen weight was observed in males at all dose levels (13–36%) and in females at 30 mg/kg (44%), compared with controls, which correlated histologically with increased cellularity of germinal centers. Increased adrenal gland weight was observed at all doses in males (27–55%) and females (9–39%), which correlated histologically with adrenal cortical hypertrophy. Organ weight changes in the adrenal gland were not reversible. Additional target organs of toxicity included the lymph nodes (axillary, mesenteric, iliac), gallbladder, small and large intestines, injection site, and skin. ADAs were detected in 11 of 32 animals (34.4%) in Week 5; 10 of 30 animals (33.3%) in Weeks 9 and 13; 2 of 7 animals (28.6%) in Week 17; and 3 of 7 animals (42.9%) at the end of recovery (Week 19).

Table 10. Selected Histopathology Findings (13-Week Study; Monkeys)

			Male				Female			
Organ/Tissue	Finding	Dose (mg/kg)	**0**	**10**	**30**	**101**	**0**	**10**	**30**	**101**
	# of Monkeys Examined (dosing/recovery)		3/2R	3	3	3/2R	3/2R	3	3	3/2R
Gallbladder	Mononuclear cell infiltration	Minimal		2				2	1	2
Adrenal gland	Hypertrophy, cortical	Minimal		1		2		1	1	
Salivary gland, mandibular	Mononuclear cell infiltration	Minimal	1	1		2	2	1		2
Thyroid gland	Mononuclear cell infiltration	Minimal				1				1
	Dilatation; follicle	Minimal		1						1
Heart	Vacuolation; myofiber	Minimal				1				
	Mononuclear cell infiltration	Mild				1				
	Hypertrophy; myofiber	Minimal				1				
	Fibrosis	Mild				1				
Kidney	Cellularity, increased	Minimal				1				
	Mononuclear cell infiltration	Minimal		3	2		1	2	3	1
		Mild				1				
Liver	Mononuclear cell infiltration	Mild								1
Lymph node, axillary	Erythrocytosis	Minimal			1	2	1		2	1
	Cellularity, increased; lymphoid	Minimal		2		1				
		Mild			1					1
		Moderate				1				
Lymph node, iliac	Cellularity, increased; lymphoid	Minimal				1				
		Mild				1				
Lymph node, mesenteric	Erythrocytosis	Minimal			1	1				1
	Cellularity, increased; lymphoid	Minimal						2	1	1
		Mild			1				2	1

			Male				Female			
Organ/Tissue	Finding	Dose (mg/kg)	**0**	**10**	**30**	**101**	**0**	**10**	**30**	**101**
	# of Monkeys Examined (dosing/recovery)		3/2R	3	3	3/2R	3/2R	3	3	3/2R
	Aggregate; macrophage	Minimal								1
Spleen	Cellularity, increased; lymphoid	Minimal		2	1	3	1		1	1/1R
Small intestine, duodenum	Degeneration/necrosis; glandular	Mild				1				
	Atrophy; glandular	Mild				1				
Large intestine, cecum	Microabscess	Minimal				1				
Large intestine, colon	Hyperplasia; mucosal	Minimal				1				
Infusion site, saphenous, left	Hemorrhage	Minimal				1			1	
	Hemorrhage; perivascular	Minimal	1		2			1	1	1
		Mild				1	2	1	1	2
	Fibroplasia; perivascular	Minimal								1
Infusion site, saphenous, right	Hemorrhage; perivascular	Minimal				1	2	1		1
		Mild								2
		Moderate				1				
	Mixed cell infiltration; perivascular	Minimal								3
		Mild			1	1				
Skin	Erosion	Mild				1				
	Ulceration	Minimal								1
	Mononuclear cell infiltration	Minimal				1				
	Inflammation; subacute, subcutaneous tissue	Mild				1				

R = recovery

FDA did not review the single-dose toxicology study in monkeys; thus, the Applicant's conclusions from this study were not verified by FDA.

5.5.2. Genetic Toxicology

The Applicant's Position:

Standard genotoxicity studies are not considered appropriate for this class of biological product, in line with the ICH S6 (R1) guideline.

The FDA's Assessment:

FDA agrees that genotoxicity studies are not warranted to support this BLA submission.

5.5.3. Carcinogenicity

The Applicant's Position:

Carcinogenicity studies have not been performed with MCLA-128 as they are not considered appropriate for this class of biological product, in line with the ICH S6 (R1) and ICH S9 guidelines.

The FDA's Assessment:

FDA agrees that carcinogenicity studies are not warranted to support this BLA submission.

5.5.4. Reproductive and Developmental Toxicology

The Applicant's Position:

Reproductive and developmental toxicology studies have not been performed. The Sponsor is of the opinion that sufficient data are available in the public domain to assess a hazard to reproduction for MCLA-128 to inform the risk-benefit assessment for MCLA-128, and that the assessments of the potential toxicity of MCLA-128 on fertility as well as early embryonic development and prenatal and postnatal development in animals are not required to support the Biologics License Application (BLA) for the proposed indication. No adverse effects on reproductive organs and tissues were observed in the repeated dose toxicity study with 5 weekly IV dosing of MCLA-128 in nonhuman primates (NHPs) up to 100 mg/kg. Also in a 13-week repeated dose toxicity study with IV dosing of MCLA-128 in NHPs, no adverse events on the reproductive system were seen. Data from this study are included in the reproductive risk assessment supporting the BLA. In accordance with ICH S5(R3) and S6(R1) and the US FDA guidance for Oncology, a weight of evidence (WOE) assessment based on the literature is provided to justify Sponsor's position. In addition, due to the specificity of MCLA-128, NHPs are considered to be the only pharmacologically relevant species to perform reproduction toxicity studies. Since the data in the public domain indicate that antibodies targeting HER2 and/or HER3 can cause embryotoxicity, and in accordance with the recent FDA Guidance "Nonclinical Considerations for Mitigating Nonhuman Primate Supply Constraints Arising from the COVID-19 Pandemic", the use of NHPs to obtain additional information on the reproduction toxicity of MCLA-128 is not warranted and not ethical.

The FDA's Assessment:

To address the potential effects of zenocutuzumab on embryo-fetal development, the Applicant submitted an assessment of reproductive and developmental risk using a WOE approach. FDA agreed in June 2022 that this approach appeared reasonable. The WOE risk assessment referenced published literature showing that HER2 and HER3 are critically important for embryo-fetal development. Mice with HER2 knocked out or expressing catalytically inactive HER2 have been shown to die at mid-gestation due to cardiac dysfunction (Chan et al., 2002; Shin et al., 2011). In addition, HER2 knockout mice have shown abnormal sympathetic nervous system development due to a lack of neural crest precursor cells in the primary sympathetic ganglion chain (Britsch et al., 1998). Studies have also shown the involvement of HER2 in gonad development in human embryos (Quenby et al., 1999), male fertility in mice (Shin et al., 2011), and proper cardiac development in mouse embryos (Lee et al., 1995). The literature suggests a role for HER3 in developing tissues and organs in tissues (Srinivasan et al., 2001) and supports a role for HER3 in cardiovascular (Armstrong and Bischoff, 2004; Casalini et al., 2004) and neuronal (Riethmacher et al., 1997) development in mice, and proper mammary gland ductal morphogenesis in mice (Jackson-Fisher et al., 2008). In addition, knockout of HER3 has been shown to cause embryo lethality on Day 13.5 due to cardiac and vascular defects as well as abnormalities in the neural crest, pancreas, stomach, and adrenal gland (Erickson et al. 1997).

Additionally, based on published literature, a HER-2-directed antibody given to women during pregnancy caused oligohydramnios that led to fatal pulmonary hypoplasia, skeletal abnormalities, and neonatal deaths (Gougis et al., 2023; Andrikopoulou et al., 2021). Human experience with HER-2-directed products was included in the label.

Lastly, human IgG1 is known to cross the placenta. Given that zenocutuzumab is an IgG1-based bispecific antibody, zenocutuzumab has the potential to be transmitted from the mother to the developing fetus.

Based on the mechanism of action of zenocutuzumab and embryo-fetal harm reported with HER-2-directed products, FDA recommends including a box warning for embryo-fetal toxicity and advising females of reproductive potential to use effective contraception during treatment with zenocutuzumab and for 2 months after the last dose.

5.5.5 Other Toxicology Studies

The Applicant's Position:

Local tolerance
No injection site reactions were observed which were considered related to the administration of MCLA-128 up to 101 mg/kg at a concentration of 10.1 mg/mL (Report 612352, Report 49737 TCP, eCTD Module 2.6.6).

In vitro hemocompatibility
The MCLA-128 infusion solution (in the concentration range of 1-4 mg/mL) is compatible with human whole blood and plasma (eCTD Module 2.6.6).

Tissue cross reactivity
The observed staining of human tissues with MCLA-128 was consistent with known expression patterns of HER2 and HER3, and no significant "off-target" staining likely to be of clinical importance was observed. This was confirmed by the histopathological examination of tissues from the 1-month and 13-weeks repeated dose toxicity studies in cynomolgus monkeys, which showed no treatment-related changes following up to 13 weekly IV doses of MCLA-128 at dosages up to 101 mg/kg/week (Report 612352, Report 49737 TCP, eCTD Module 2.6.6).

In silico immunogenicity
The DRB scores for MCLA-128 (a humanized antibody) are within the range of those for 4 marketed humanized benchmarking antibodies. Therefore, MCLA-128 is not considered to have an increased risk for immunogenicity when compared to marketed benchmark humanized IgG1 antibodies (Report R06423, eCTD Module 2.6.6).

Cytokine release
There is a low potential for MCLA-128 to induce cytokine release in human whole blood ex vivo (Report (b) (4)-14/150-002, eCTD Module 2.6.6). Based on an in vitro assay, MCLA-128 has the potential to release cytokines when target and effector cells are brought together by MCLA-128 (Report 200-8888-002, eCTD Module 2.6.6).

Cardiomyocyte toxicity
Based on an in vitro model system, MCLA-128 does not effect cardiomyocyte viability (Report P1208-R13, eCTD Module 2.6.6).

The FDA's Assessment:

FDA agrees with the Applicant's assessments of the GLP-compliant vitro hemocompatibility study, and non-GLP-compliant in silico immunogenicity and in vitro cardiomyocyte viability studies.

FDA disagrees that no injection site reactions were observed in the repeat-dose toxicology studies in monkeys. In the 1-month study, histological findings of minimal to mild focal perivascular degeneration and focal muscle inflammation were observed at the injection site at 100 mg/kg. In the 13-month study, histological findings of perivascular hemorrhage, fibroplasia, and/or mixed inflammatory cell infiltration were observed at ≥10 mg/kg.

The GLP-compliant tissue cross-reactivity study was reviewed by the FDA under IND 131752. Zenocutuzumab concentrations of 2 and 10 mg/mL were applied to cryosections of human tissues from three donors. Positive membrane/cytoplasmic staining was observed in the endothelium, mesothelium, mononuclear cells (including alveolar macrophages), smooth muscle

myocytes, peripheral nerve cells, spindle cells, glial cells, arachnoid cap cells, ovarian stromal cells, decidual cells, cardiomyocytes, interstitial cells of the testis, and glomerular tuft cells of the kidney. According to the Applicant, this staining pattern is consistent with known HER2/HER3 expression, with the exception of the staining observed in the renal glomerular tuft cells and mesothelium, which was mainly cytoplasmic and thus may be of limited relevance in vivo.

FDA agrees with the Applicant's assessments of the cytokine release assays, which were reviewed under IND 131752. In the GLP-compliant cytokine release study (Study No. 0X-14/150-150-002), zenocutuzumab induced only slight increases in cytokine levels from whole blood samples from 12 donors. In the non-GLP-compliant cytokine release study (Study No. 200-8888-002), cytokine release was evaluated in an ADCC assay by co-incubating HER-expressing target cells (SKBR-3 breast cancer cells) and human effector cells (PBMCs). Zenocutuzumab induced the significant release of IFN-g, IL-6, IL-8, and TNF-a with EC20 values of 2.5, 8.2, 0.1, and 7.5 ng/mL, respectively.

(b) (4)

Summary: (b) (4)-related compounds were identified as leachables that will result in a maximum daily exposure (PDE) of (b) (4) µg/day in patients. The impurities were stated to be (b) (4) with molecular weights (MWs) of approximately (b) (4). No relevant nonclinical or clinical data are available to assess the acceptability of the (b) (4) µg/day of the leachables; however using data from related compounds, the level is acceptable for the current BLA.

Toxicology assessment:
In the sterile filtration process for the manufacture of zenocutuzumab drug product, two 0.22 µm (b) (4) membrane filters were used. The Applicant conducted a filter leachable study, in which they identified (b) (4)-related compounds as leachables and showed that the maximum concentration detected in the filtered product in the worst-case exposure scenario is (b) (4) ppm. The maximum daily exposure was calculated to be (b) (4) µg/day ((b) (4) ppm * 37.5 mL/day [maximum volume administered to patients]). This value was compared to the PDE, which was calculated based on concepts from the ICH Q3C guidance using the NOAEL from a toxicity study conducted in rats. According to the Applicant, the (b) (4) identified in the leachable study was most likely (b) (4) with a MW of approximately (b) (4) m/z. As toxicological data for (b) (4) are not available, the Applicant used toxicological data for (b) (4) in general for their assessment.

The Applicant justified the use of (b) (4) using results from a (b) (4) in compliance with the guidelines for the EPA's Toxic Substances Control Act and EPA GLP Regulations, to calculate the PDE for (b) (4). According to the Applicant's high-level summary of this study, a (b) (4)

(b) (4) Body and organ weights, food consumption, clinical signs, and blood chemistry were all within the normal range. Histopathological findings in the lung tissues included signs of (b) (4). Based on the high-level description provided, it was unclear if histopathology was conducted in other organs. A NOAEL of (b) (4) mg/m^3 was used to calculate a PDE of (b) (4) µg/person/day as follows:

(b) (4)

The FDA also calculated a PDE of (b) (4) µg/day; however, because there is not intersubject variability with drugs administered IV with regard to systemic exposure and because bioavailability was not provided for rat study, we used an F2 = 1 and an F6 = 10, respectively. The FDA review team also took into consideration other supportive publications on toxicologic assessment of (b) (4)

Given that the maximum daily exposure for (b) (4)-related compounds is (b) (4) µg/day and below the PDE; that the indication for zenocutuzumab is advanced, unresectable, or metastatic cancers (NSCLC and pancreatic adenocarcinoma); and that patients will receive zenocutuzumab once every 2 weeks, the proposed specification limit in the drug product is acceptable from the pharmacology/toxicology perspective.

X X

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Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

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6 Clinical Pharmacology

6.1 Executive Summary

The FDA's Assessment:

The clinical pharmacology key review question focused on the appropriateness of the proposed recommended dosage of zenocutuzumab for the general patient population.

The primary evidence of efficacy and safety was obtained from Study MCLA-128-CL01 (eNRGy), a multicenter, single-arm trial investigating zenocutuzumab in patients with NSCLC, PDAC, and other solid tumors harboring an *NRG1* fusion with disease progression on or after prior systemic therapy or who do not have satisfactory alternative treatment options. The patients with advanced, unresectable or metastatic NSCLC and PDAC harboring an NRG1 gene fusion received zenocutuzumab 750 mg every 2 weeks (Q2W) as an intravenous (IV) infusion. The Applicant's proposed dosage is zenocutuzumab 750 mg Q2W as an IV infusion. Based on the clinical pharmacology review, although there is a lack of dosage optimization in the current proposed patient population, the recommended dosage of zenocutuzumab in the proposed patient population is acceptable based on the review considerations described below.

Efficacy:

- Clinically meaningful objective response rates were observed in patients with advanced, unresectable or metastatic NSCLC and PDAC harboring an NRG1 gene fusion (NGR1+).
- A positive trend for exposure-response (ER) relationships was observed between exposure (Cave,ss) and response (overall response rate and duration of response) based on 129 patients from the eNRGy trial at the proposed dosage.
- Zenocutuzumab activity in initial dose finding cohorts was only observed in the narrow sub-group of patients with NSCLC and PDAC harboring an NRG1 gene fusion (NGR1+), and not in broader patient groups with solid tumors.

Safety:

- Zenocutuzumab monotherapy was studied over a dose range of 40 to 900 mg Q3W, at 400 mg Q1W (with 800 mg loading dose) and 750 mg Q2W, and the maximum tolerated dose (MTD) was not reached.
- No positive trend of exposure (Cavg,ss and Cmax,ss) for treatment emergent adverse events (TEAEs) Grade ≥ 3, TEAE any grade, diarrhea and left ventricular ejection fraction (LVEF) reduction was observed.

The clinical pharmacology review team assessed the Applicant's population pharmacokinetic (PopPK) report. The assessment concluded that the evaluated intrinsic or extrinsic factors (including age, sex, race [White or Asian], body weight, albumin level, mild or moderate renal impairment, and mild hepatic impairment) are unlikely to have clinically meaningful effects on zenocutuzumab exposure. The effect of moderate to severe hepatic impairment or severe renal impairment on the PK of zenocutuzumab is unknown. Given that zenocutuzumab is a bispecific antibody, and there is a lack of exposure response relationships for safety, the currently available data do not suggest that PMRs for moderate to severe hepatic impairment, or severe renal impairment are needed.

The effect of anti-drug antibodies (ADAs) on the PK, PD, safety, and efficacy of zenocutuzumab remains unknown due to i) the low occurrence of ADAs; and ii) the absence of neutralizing antibody results due to a pending neutralizing antibody assay validation. The clinical pharmacology review team concluded that given the absence of neutralizing antibody assay, a PMC will be issued to request new neutralizing antibody (NAb) data generated from the validated neutralizing antibody assay.

Recommendations

The Office of Clinical Pharmacology has reviewed the information and data submitted in BLA 761352. This BLA is approvable from a clinical pharmacology perspective. The key review issues with specific recommendations and comments are summarized in the table below.

Table 6.1: Review Issues and Recommendations/Comments

Review Issue	Recommendations and Comments
Pivotal and Supportive evidence of effectiveness	The primary evidence of effectiveness comes from the Phase 1/2, first in human Study MCLA-128-CL01 (Part 2 Expansion ("eNRGy trial")) in patients with advanced, unresectable or metastatic NSCLC and PDAC harboring an NRG1 gene fusion (NRG1+). In the eNRGy trial, at the target dosage of 750 mg Q2W, there were a clinically meaningful objective response rate (ORR) in patients with NRG1+ NSCLC and NRG1+ PDAC (Se section 8.1). A positive trend for efficacy-exposure relationship between exposure (Cavg,ss) and response (overall response rate & duration of response) at one dose level at 750 mg was observed; however, the interpretation of the efficacy-exposure relationship should be approached with caution due to potential confounding factors and data limitations, as only one dose level was tested.

General dosing instructions	The recommended dosage of zenocutuzumab is 750 mg every 2 weeks (750 mg Q2W), administered by intravenous infusion (initial infusion over 4 hours.
Dosing in patient subgroups (intrinsic and extrinsic factors)	Based on PopPK analyses, the evaluated intrinsic or extrinsic factors (including age, sex, race [White or Asian], body weight, albumin level, mild or moderate renal impairment, and mild hepatic impairment) are unlikely to have clinically meaningful impact on the exposure. There is no data available for patients with moderate to severe hepatic impairment and severe renal impairment.
Immunogenicity	In patients who received zenocutuzumab at the approved recommended dosage, 4.6% patients developed anti-zenocutuzumab antibodies. Because of the low occurrence of ADAs, the effect of these antibodies on the PK, PD, safety, and efficacy of zenocutuzumab is unknown. The current neutralizing antibody (NAb) assay is not adequate due to inadequate validation. A PMC will be issued to request new Nab data generated from an adequately developed and validated NAb assay.
Drug-drug interactions	Not applicable to bispecific antibodies.
Labeling	The proposed labeling is acceptable upon the Applicant's agreement to the FDA revisions to the label. Clinical pharmacology labeling recommendations are detailed in Section 12 of the label.
PMCs	The following PMC will be issued to request new NAb data generated using an adequately developed and validated NAb assay. *Develop and validate a neutralizing antibody (NAb) assay and submit a full validation report of the developed NAb assay. The assay format should be adequately justified to be suitable for the detection of NAbs. This NAb assay will be used to test available confirmed anti-drug antibody (ADA) positive samples from banked and ongoing clinical studies. Include the updated NAb results analyzed using the validated NAb assay to address the effects of neutralizing antibody on pharmacokinetics (PK), pharmacodynamics (PD), safety, or effectiveness of zenocutuzumab*.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1 Pharmacology and Clinical Pharmacokinetics

The Applicant's Position:

The clinical pharmacology analyses in support of this initial application for monotherapy indication in NRG1+ cancer patients primarily focused on data collected on zenocutuzumab monotherapy from MCLA-128-CL01.

Characterization of the pharmacokinetics (PK) of zenocutuzumab by NCA showed that PK parameters increased in a dose-proportional manner over a dose range from 480 to 900 mg Q3W. The PK of zenocutuzumab was also characterized using a population PK analysis approach with concentration data collected from 318 patients with various cancers who received zenocutuzumab doses of 40 to 900 mg Q3W, 400 mg Q1W (with loading dose of 800 mg) or 750 mg Q2W. PK was described with a typical two-compartment model with linear and non-linear clearance. The linear part of the clearance changed in a time-dependent manner. There were no clinically relevant differences in clearance, volume of distribution and other PK parameters of zenocutuzumab based on tumor type (NSCLC vs. PDAC vs. others).

For the subpopulation of NRG1+ cancer patients, steady-state concentrations of zenocutuzumab were reached by a median time of 8 weeks after repeated dosing with 750 mg Q2W regimen and the median accumulation ratio was 1.6-fold. The geometric mean value for volume of distribution at steady state is 6.1 L (90% interval: 5.3-7.4). Zenocutuzumab clearance is approximately 36% lower [geometric mean 22.1 ml/h (90% interval: 14.1-37)] at steady state than that after the first dose [34.7 mL/h (90% interval: 25.5-49.7)]. This decrease in clearance over time was not considered clinically relevant. At steady state the geometric mean half-life was 8.0 days (90% interval: 5.2-11).

A range of intrinsic and extrinsic factors at baseline were evaluated for impact on PK. The magnitude of covariate effects on PK exposures was generally modest. Most of the statistically significant covariates had a minor impact on exposures (≤ 20% change). Males had 23% lower exposures compared to females (median (90% CI) of geometric mean ratios of $AUC_{0-2week,ss}$ for males versus females: 0.77 (0.72-0.84)) and patients with below median BSA had 29% higher exposure compared to above median BSA (median (90% CI) of geometric mean ratios of $AUC_{0-2week,ss}$ for below the median BSA versus above median: 1.29 (1.19-1.4)). However, none of these covariate effects were considered strong enough to warrant *a priori* dosing adjustment for use of zenocutuzumab in clinical practice.

Overall, the PK profile of zenocutuzumab is consistent with that of other humanized monoclonal antibodies.

The FDA's Assessment:

FDA agrees with the Applicant's position on the PK characteristics of zenocutuzumab. Refer to Section 19.4.1 for detailed assessment of Population PK (popPK) Analysis.

6.2.2 General Dosing and Therapeutic Individualization

6.2.2.1 General Dosing

The Applicant's Position:

Throughout the clinical development program, the dose and dosing frequency of zenocutuzumab were selected based on integrated analysis of available PK, pharmacodynamic, and efficacy and safety data by applying modeling and simulation approaches. The dosing regimen of zenocutuzumab was not selected based on an maximum tolerated dose (MTD) approach.

The recommended dose of 750 mg Q2W for zenocutuzumab achieved concentrations that are shown to be pharmacologically active in preclinical evaluations. The observed trough concentrations after the first dose of 750 mg Q2W was higher than 10 µg/mL in almost all patients. At these concentrations, >99% saturation of HER3 target is expected to be maintained for the entire dosing interval. Also these trough concentrations are higher than the concentrations that provided maximum in vitro cell growth inhibition in a DOC4-NRG1 cell line (30 nM or about 4.5 µg/mL). Lastly, serum steady state peak and trough concentrations achieved with 750 mg Q2W in patients were within the range of concentrations achieved in xenograft mice after administering 25 mg/kg (20.9 to 260 µg/mL), a dose level at which near maximal tumor regression in NRG1+ tumor models was seen.

Additionally, exposure-response analysis for efficacy was conducted on data collected in NRG1+ cancer patients receiving 750 mg Q2W dose and exposure-response analysis for safety was conducted on pooled data from NRG1+ and non-NRG1+ cancer patients across dose levels. Most of the exposure-safety relationships were flat and there were a few with negative trends. None of the exposure metrics had a positive relationship with the occurrence of treatment-related adverse event (TRAE) grade ≥3, TRAE any grade, any AE grade ≥3, Diarrhea and LVEF reduction. With respect to efficacy, a positive trend for exposure-response was observed for most of the evaluated efficacy response variables (ORR, CBR, change in tumor size from baseline) indicating to an increasing (probability of) response with increasing exposure. Additional evaluations showed that exposure-response relationship was also present with individual clearance as a predictor (independent of the individual dosing history). These findings indicated that exposure-response relationships for efficacy were confounded by patient health factors to an unknown extent.

Overall, totality of these data supported that a dose of zenocutuzumab 750 mg Q2W is an adequate dose for clinical use of zenocutuzumab in NRG1+ cancer patients. Exposure-safety relationships were flat. MTD of zenocutuzumab was not reached in the dose range tested in

clinical studies (up to 900 mg Q3W). With respect to efficacy, a positive trend for exposure-response was observed which would indicate to the possibility of achieving higher benefit with higher Q2W exposures, although there were limitations in interpreting these analyses because of potential confounding by patient health factors.

The FDA's Assessment: The nonclinical data/information on receptor occupancy (saturation of HER3 target) provided by the Applicant can only be considered supportive; the nonclinical data would also likely be supportive of the other dosing regimens tested (based on trough concentrations). While the nonclinical data provide supportive information, they do not significantly contribute to distinguishing between the clinically tested doses for optimization. In our assessment, the clinical data serve as the primary basis for dose-selection decisions.

FDA generally agrees with the Applicant's position on PK studies and exposure-response analyses for dose selection. No maximum tolerated dose was achieved up to 900 mg Q3W dose of zenocutuzumab. A positive trend for efficacy-exposure relationship between exposure (Cavg,ss) and response (overall response rate & duration of response) at one dose level at 750 mg was observed; however, the interpretation of the efficacy-exposure relationship should be approached with caution due to potential confounding factors and data limitations, as only one dose level was tested. No positive trend of exposure (Cavg,ss and Cmax,ss) for TEAE Grade ≥ 3, TEAE any grade, diarrhea and LVEF reduction was observed.

The proposed dosage of 750 mg Q2W, through IV infusion (infusion duration 4 hours) is supported by a clinically meaningful overall response rate, duration of response, and no positive trends in ER relationships for safety. See Section 19.4. for detailed assessment of E-R relationships.

6.2.2.2 Therapeutic Individualization

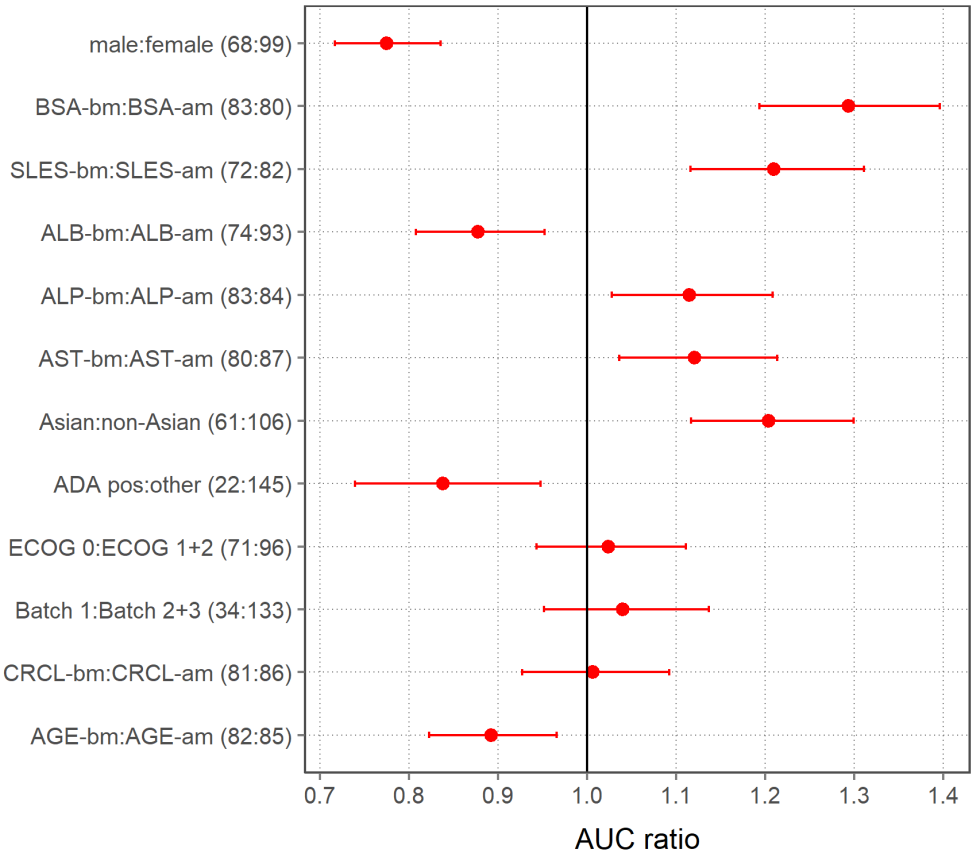
The Applicant's Position:

A range of intrinsic and extrinsic factors at baseline (covariates) were evaluated for impact on PK, including the following: body weight (38-126 kg), body surface area (1.3-2.4 m^2), age (22-88 years), sex (60% female), race [White (N=230), Asian (N=64), Black (N=6)], ECOG performance status, sum of lesions, alanine aminotransferase, hepatic function , renal function, number of previous lines of therapy and drug product batch.

To evaluate the effect of covariates, PK simulations were conducted for each patient in the dataset using the individual estimates of PK parameters. All patients received 750 mg Q2W dosing for 200 weeks. Subjects were assigned into two groups based on a covariate of interest, both for categorical covariates and for continuous covariates. Per dichotomized variable, 10000 replicate trials were generated by sampling the individual $AUC_{0-2week,ss}$ values. For each trial, the geometric

mean of the $AUC_{0-2week,ss}$ values was calculated. Per covariate evaluation, the median, and the 90%CI of the ratios were plotted in a forest plot.

Figure 9. Applicant - Forest plot of geometric mean AUC0−2week,ss ratios for the NRG1+ cancer subpopulation derived from the final population PK model of zenocutuzumab by dichotomized covariate of interest.



Within the NRG1 subpopulation, the magnitude of covariate effects on PK exposures was generally modest. Most of the statistically significant covariates had a minor impact on exposures (≤20% change). Males had 23% lower exposures compared to females (median (90% CI) of geometric mean ratios of $AUC_{0-2week,ss}$ for males versus females: 0.77 (0.72-0.84)) and patients with below median BSA had 29% higher exposure compared to above median BSA (median (90% CI) of geometric mean ratios of $AUC_{0-2week,ss}$ for below the median BSA versus above median: 1.29 (1.19-1.4)). In clinical data, no imbalance in efficacy was observed between male and females for NRG1+ NSCLC and NRG1+ PDAC patients. Also, no imbalance in efficacy was observed in NSCLC NRG1+ cancer patients with below vs. above median body weight. Range of responses in PDAC NRG1+ cancer patients were also overlapping between below vs. above median body weight, although the number of PDAC patients were small (N=29) to reliably

compare the responses by body weight. None of these covariate effects were considered strong enough to warrant a priori dosing adjustment for use of zenocutuzumab in clinical practice.

Given the large molecular mass of zenocutuzumab (145.9 kDa), its clearance is not anticipated to be affected by decreased renal function. Based on population PK analyses, renal function (defined by baseline creatinine clearance) had no statistically significant relevant effect on exposure of zenocutuzumab. Changes in hepatic function are unlikely to have any effect on the elimination of zenocutuzumab as IgG1 molecules such as zenocutuzumab are not metabolized through hepatic pathways. Based on population PK analyses, hepatic function (defined by baseline albumin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin) had no statistically significant or clinically relevant effect on exposure of zenocutuzumab. (b) (4)

The FDA's Assessment:

FDA agrees that based on the PopPK analysis, no clinically significant differences in the PK of zenocutuzumab were observed across the evaluated covariates: age (22 to 88 years), sex, race [White or Asian], body weight (38 to 126 kg), albumin level (20 to 49 g/L), mild or moderate renal impairment (creatinine clearance (CLcr) 30 to 89 mL/min), and mild hepatic impairment (total bilirubin >1 to 1.5 times ULN or AST > ULN). Black patients were excluded from the race group covariate analysis due to an insufficient sample size.

FDA agrees with the Applicant's position that the covariate effects are not considered clinically meaningful, as the expected exposure differences are relatively small. None of these covariate effects were deemed significant enough to warrant dosing adjustments.

6.2.2.3 Outstanding Issues

Data:

Not applicable.

The Applicant's Position:

Not applicable.

The FDA's Assessment:

The following PMC will be issued to request new NAb data generated from an adequately developed and validated NAb assay.

Develop and validate a neutralizing antibody (NAb) assay and submit a full validation report of the developed NAb assay. The assay format should be adequately justified to be suitable for the detection of NAbs. This NAb assay will be used to test available confirmed anti-drug antibody (ADA) positive samples from banked and ongoing clinical studies. Include the updated NAb results analyzed using the validated NAb assay to address the effects of neutralizing antibody on pharmacokinetics (PK), pharmacodynamics (PD), safety, or effectiveness of zenocutuzumab.

6..3 Comprehensive Clinical Pharmacology Review

6.3.1 General Pharmacology and Pharmacokinetic Characteristics

The Applicant's Position:

The clinical pharmacology of zenocutuzumab has been studied in 318 subjects with advanced solid tumors, including subjects with NRG1+ cancer, who received zenocutuzumab by IV infusion at 40-900 mg Q3W, 400 mg Q1W (with 800 mg loading dose) or 750 mg Q2W. Levels of serum zenocutuzumab, cytokines and anti- zenocutuzumab antibodies were measured using either fully validated or qualified for fit-for-purpose methods to evaluate PK, PD and immunogenicity.

Bioanalytical Methods

Blood serum was analyzed for zenocutuzumab levels using a validated electrochemiluminescence immunoassay with LLOQ of 50 ng/mL.

The presence of anti-zenocutuzumab antibodies (ADA) in human serum samples were detected using validated bioanalytical methods employing a classic three tier approach where samples were first screened (screening assay) for anti-zenocutuzumab antibodies. A potentially positive sample from screening assay was then confirmed (confirmatory assay) for the presence of anti-zenocutuzumab antibodies. A confirmed positive sample was then further investigated to obtain the anti-zenocutuzumab antibodies titer (titration assay). Two bioanalytical methods were used during the course of study. First bioanalytical method employed semi-homogenous MSD bridging assay, including an acid dissociation pre-treatment step with a sensitivity of 120 ng/mL and drug tolerance of 5 µg/mL zenocutuzumab at 250 ng/mL ADA. This method was deemed sufficient for the majority of trough levels of zenocutuzumab achieved after administration of 750 Q3W dosing. As higher trough levels were obtained after 400 mg Q1W (with 800 mg loading dose) and 750 mg Q2W dosing the assay drug tolerance was deemed not sufficient anymore. Hence a new method was developed and validated. The new assay was developed on AlphaLISA® platform, a technique by Perkin Elmer. This assay resulted in an assay sensitivity of 7 ng/mL with a drug tolerance of 150 µg/mL zenocutuzumab at 100 ng/mL ADA.

Pharmacokinetics

Frequent blood samples were taken from each patient participating in the MCLA-128-CL01 study to allow assessment of the PK of zenocutuzumab after single and multiple dose. Concentration-time profiles after first dose administration showed a clear increase of half-life with increasing dose. In the 480 to 900 mg Q3W dose range, concentration-time curves run more or less in parallel suggesting linear PK at dose levels of 480 mg and above. This dose-dependent change in half-life is consistent with target mediated drug disposition typically observed for monoclonal antibodies.

The PK of zenocutuzumab was described with a typical two-compartment model with linear and non-linear clearance. The linear part of the clearance changed in a time-dependent manner. There were no clinically relevant differences in clearance, volume of distribution and other PK parameters of zenocutuzumab based on tumor type (NSCLC vs. PDAC vs. others).

PK characteristics of zenocutuzumab based on non-compartmental and population PK analysis and findings from covariate analysis are summarized in sections 6.2.1 and 6.2.2.2. Overall, the PK profile of zenocutuzumab is consistent with that of other humanized monoclonal antibodies.

Exposure-Response analysis

An exposure-response analysis for efficacy was conducted on data collected in NRG1+ cancer patients and exposure-response analysis for safety was conducted on pooled data from NRG1+ and non-NRG1+ cancer patients.

MTD of zenocutuzumab was not reached in the dose range tested in clinical studies (up to 900 mg Q3W). Most of the exposure-safety relationships were flat and there were a few with negative trends. None of the exposure metrics (average and peak steady-state concentrations, Cavg,ss and Cmax,ss) were significant predictors for the occurrence of treatment-related adverse event (TRAE) grade ≥3, TRAE any grade, diarrhea and LVEF reduction. A negative relationship was observed between Cavg,ss and any AE grade ≥3, which may possibly be because of early dropout of patients or enrollment of patients with more advanced disease on Q3W regimen in the dose escalation cohort.

With respect to efficacy, a positive trend for exposure-response was observed which would indicate to the possibility of achieving higher benefit with higher Q2W exposures, although there were limitations in interpreting these analyses because of potential confounding by patient health factors.

Drug Interactions

No formal clinical drug-drug interaction studies were performed, and no interactions with concomitant medications are expected

Pharmacodynamics

A cytokine panel (tumor necrosis factor alpha [TNFα], interferon gamma [IFNγ], interleukin-1β [IL-1β], IL-2, IL-6, IL-8, and IL-10) was assessed in serum samples during the Phase 1 dose escalation part of the MCLA-128-CL01 study and for a significant number of patients of the Phase 2 part. A modest and transient cytokine elevations from baseline were observed 2 hours after the end of the infusion, mainly in IFNγ (0.4-3.4 fold), IL-8 (0.7-8.4 fold) and TNFα (0.8-11.6 fold), which returned to baseline values within 24 hours post-dose. There was no clear correlation between cytokine elevations and dose level of zenocutuzumab.

Immunogenicity

Longitudinal serum samples from 306 patients receiving zenocutuzumab according to the Q1W, Q2W, and Q3W dosing regimens were evaluated for anti-zenocutuzumab antibodies. Across all dose regimens and tumor types there were 20 patients with a treatment-emergent ADA positive status, with an incidence rate of 6.5%. Of the 153 evaluable NRG1+ cancer patients receiving a 750 mg Q2W dose there were 7 patients positive for treatment-emergent anti-zenocutuzumab antibodies, with an incidence rate of 4.6%. There were no identified clinically significant effects of ADA on zenocutuzumab pharmacokinetics. Because of the low occurrence of ADA, the effect of ADA on efficacy and safety of zenocutuzumab cannot be evaluated. These results confirm the low risk of immunogenicity for zenocutuzumab.

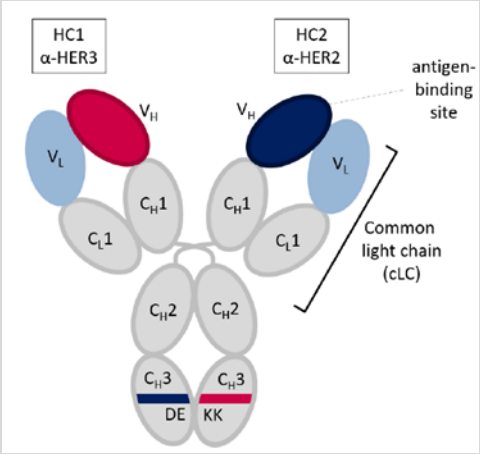
The FDA's Assessment:

FDA generally agrees with the Applicant's assessments on general pharmacology, PK characteristics of zenocutuzumab, and immunogenicity. The effect of ADAs on the PK, PD, safety, and efficacy of zenocutuzumab remains unknown due to i) the low occurrence of ADAs; and ii) the absence of NAb results due to a pending NAb assay validation.

The general overview of ADME and clinical PK information of zenocutuzumab as assessed by FDA are presented in Table 6.2:

Table 6.2: Highlights of Clinical Pharmacology for Zenocutuzumab

Physiochemical properties	
Chemical structure and molecular weight	Zenocutuzumab is a heterodimer composed of HC1+cLC and HC2+cLC. A predicted pictorial structural scheme is shown in Figure 6.3.1 -1. Figure 6.3.1 -1 Predicted antibody structure of zenocutuzumab



C: constant domain; V: variable domain; H: Heavy chain; L: Light chain; D: aspartate; E: glutamate; K: lysine

Molecular mass: 145.9 kDa

Pharmacology	
Mechanism of Action	Zenocutuzumab is a bispecific antibody that binds to the extracellular domains of HER2 and HER3 expressed on the surface of cells, including tumor cells. Zenocutuzumab blocks NRG1 binding to HER3, inhibiting NRG1-induced HER2:HER3 dimerization. Zenocutuzumab decreased cell proliferation and signaling through the phosphoinositide 3-kinase (PI3K)-AKT-mammalian target of rapamycin (mTOR) pathway. In addition, zenocutuzumab mediates antibody-dependent cellular cytotoxicity (ADCC). Zenocutuzumab showed antitumor activity in mouse models of NRG1 fusion-positive lung and pancreatic cancers.
Active Moieties	Zenocutuzumab
QT/QTc Prolongation	No dedicated thorough QT study was performed given zenocutuzumab is a bispecific antibody.
General Information	
Bioanalysis	The serum concentrations of zenocutuzumab were measured using validated assay, i.e., Electrochemiluminescence Immunoassay (ECLIA). Serum concentrations were determined using a lower limit of quantification (LLOQ) of 50 ng/mL. The ADA assay had adequate drug tolerance because the concentrations of zenocutuzumab collected at Ctrough are below the drug tolerance limit of the ADA assay. Thus, the ADA status of these samples is reliable for immunogenicity assessment. Table 6.2.1 summaries the characteristics of ADA assay.

Table 6.2.1: Summary of key ADA assay characteristics related to immunogenicity assessment

Validation report number	LGC313236QB10
Drug tolerance*	150 µg/mL at 100 ng/mL positive control
Positive control type	Polyclonal Ab

	% of Ctrough > drug tolerance (150 µg/mL) | 0% * Drug tolerance at 100 ng/mL of positive control is expected for drug tolerance testing per FDA guidance. NAb were not assessed. The neutralizing antibody assay validation remains inadequate.
Dose Proportionality	Zenocutuzumab-zbco exposure increases proportionally over a dose range from 480 mg (0.6 times the approved recommended dosage) to 900 mg (1.2 times the approved recommended dosage).
Accumulation	The median time to steady state of zenocutuzumab concentrations is 8 weeks and the median accumulation ratio is 1.6-fold at the approved recommended dosage
Immunogenicity	7 of 153 (4.6%) patients developed anti-zenocutuzumab antibodies. Because of the low occurrence of anti-drug antibodies, the effect of these antibodies on the PK, PD, safety, and efficacy of zenocutuzumab is unknown.
Distribution	
Volume of distribution	Zenocutuzumab volume of distribution is 6 L (CV 18%).
Elimination	
Half-life	8 days (SD ±1.3 days)
Clearance	22 mL/h (CV 37%)
Metabolism	
Primary metabolic pathway(s)	Zenocutuzumab is expected to be metabolized via degradation to small peptides and individual amino acids.
DDI potential	No dedicated drug-drug interaction studies were performed with zenocutuzumab and is not anticipated to alter the activity of drug-metabolizing enzymes. Zenocutuzumab showed small transient elevations of cytokines in patients, which are not expected to modulate the activity of cytochrome P450 (CYP450) enzymes and transporters
Excretion	
Primary excretion pathways	No dedicated excretion studies were performed

FDA generally agrees with the Applicant's position regarding the exposure response analysis. Refer to section 6.3.2.1 and 19.4.1 and 19.4.2 for detailed comments on ER analysis.

6.3.2 Clinical Pharmacology Questions

6.3.2.1 Does the clinical pharmacology program provide supportive evidence of effectiveness?

The Applicant's Position:

Exposure-efficacy analysis was conducted to provide supportive evidence of zenocutuzumab effectiveness in NRG1+ cancer patients. These analyses were performed on data collected from 129 NRG1+ cancer patients receiving 750 mg Q2W dose. The following endpoints were evaluated: ORR per central and local assessments, CBR at 24 weeks per central and local assessments, tumor size change from baseline, and DOR per central and local assessments. The limitations of performing exposure-efficacy assessment for monoclonal antibodies with data from a single-dose level were well known. These analyses were performed nonetheless to understand the directionality of relationship between exposure and response.

For all evaluated efficacy response variables, the Cavg,ss was found to be a significant predictor leading to an increasing (probability of) response with increasing exposure. These effects remained significant after accounting for covariate effects in the multivariate models. In these analyses, the response was found to be significantly higher for PDAC patients versus patients with tumor types other than PDAC and NSCLC (based on all evaluated endpoints: ORR central and local, CBR 24w central and local, Sum of lesions nadir central and local), for males (CBR 24w central and local, Sum of lesions nadir local) and for ECOG 0 patients (BIC based model for ORR local). The response was found to be significantly lower for patients with 4 or more prior therapies versus the 2-3 prior therapy reference (based on Sum of lesions nadir central and local), and for patients with increasing number of organs involved (based on AIC based model for CBR 24w local and BIC based model for Sum of lesions nadir central).

Based on a KM analysis, the Cavg,ss was not a significant predictor for the duration of response per central assessment. Per local assessment, the Cavg,ss was found to be a borderline significant predictor for the duration of response: after one year of treatment, more than 50% of the patients in the upper two Cavg,ss quartiles were still responders, while this was lower than 25% for the lower two Cavg,ss quartiles.

Based on additional evaluations for the ORR central endpoint, it was found that the ER relationship is partially driven by early drop out of patients who received only a few doses and thus did not reach their potential Cavg,ss or timepoint of first imaging assessment. Additionally, an ER relationship was also observed with individual clearance (independent of the individual dosing history) as a predictor.

Overall, the positive trends for exposure-efficacy analyses would indicate to the possibility of achieving higher benefit with higher exposures achieved with Q2W dosing, although there were

limitations in interpreting these analyses because of potential confounding by patient health factors. These analyses supported that a fixed dose of 750 mg Q2W is an adequate dose for clinical use of zenocutuzumab in NRG1+ cancer patients.

The FDA's Assessment:

FDA agrees with the Applicant that there are limitations of performing exposure-efficacy assessment for monoclonal antibody like zenocutuzumab with data from a single-dose level. Therefore, the interpretation of the efficacy exposure-response relationship should be approached with caution due to i) limitations inherent in data derived from a single dose level; and ii) due to the potential for confounding factors in this case. Refer to Section 19.4.1 for detailed assessment of E-R analysis.

FDA concluded that the Cavg,ss was not a significant predictor for the duration of response, per central assessment. The Cavg,ss was a borderline significant predictor for the duration of response, per local assessment. The ER relationship for efficacy endpoints may be confounded by interaction between patient health factors, antibody clearance, and response status.

Cavg,ss and Cmax,ss were not the significant predictors for the occurrence of TEAE Grade ≥3, TEAE any grade, diarrhea and left ventricular ejection fraction (LVEF) reduction.

The Cavg,ss was a significant predictor for the occurrence of any AE grade ≥3 whereby the probability of this event decreased with increasing Cavg,ss. The Cavg,ss and the dosing interval were significant predictors for any AE grade ≥3. Within the first year, the most pronounced decrease in the proportion of patients without any AE grade ≥3 was observed among those whose Cavg,ss was below the median of the population.

The Cavg,ss and Cmax,ss quartiles, and the dosing interval were significant predictors for the time to first occurrence of a dose interruption; however, the causal relationship remains unclear. The ER analysis for IRRs following the first dose was not informative.

6.3.2.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The Applicant's Position:

Zenocutuzumab administered as a fixed dose of 750 mg Q2W is an appropriate dose for clinical use in NRG1+ cancer patients.

Zenocutuzumab was generally well tolerated after IV infusion at 40-900 mg Q3W, 400 mg Q1W (with 800 mg loading dose) or 750 mg Q2W. The MTD of zenocutuzumab was not reached in the dose range tested in clinical studies (up to 900 mg Q3W).

The dose and dosing frequency of zenocutuzumab were selected based on integrated

analysis of available PK, pharmacodynamic, and efficacy and safety data by applying modeling and simulation approaches. The observed trough concentrations after the first dose of 750 mg Q2W was higher than 10 µg/mL in almost all patients. At these concentrations, >99% saturation of HER3 target is expected to be maintained for the entire dosing interval. Exposure-response analysis for efficacy and safety also justified adequacy of 750 mg Q2W dose in NRG1+ cancer patients.

PK profile of zenocutuzumab supported fixed-dosing approach. Based on simulations with the final population PK model, zenocutuzumab exposure is expected to be higher for NRG1+ cancer patients below the median BSA versus above, with a median AUC0−2week,ss (90% CI) ratio of 1.29 (1.19-1.4). To investigate this further, efficacy was also analyzed by body weight. In clinical data, no imbalance in efficacy was observed in NSCLC NRG1+ cancer patients with below vs. above median body weight. The range of responses in PDAC NRG1+ cancer patients were also overlapping between below vs. above median body weight, although the number of PDAC patients were small (N=29) to reliably compare the responses by body weight. These analyses supported the adequacy of using fixed-dosing approach.

At zenocutuzumab 750 mg Q2W regimen a favorable therapeutic efficacy was demonstrated with a generally well tolerated safety profile.

The FDA's Assessment:

The nonclinical data provide only supportive information, they do not significantly contribute to distinguishing between the clinically tested doses for optimization. In our assessment, the clinical data serve as the primary basis for dose-selection decisions.

Zenocutuzumab activity in initial dose finding cohorts was only observed in the narrow subgroup of patients with NGR1+ NSCLC and NGR1+ PDAC, and not in broader patient groups with solid tumors. Patients with NRG1+ NSCLC or NGR1+ PDAC are rare patient subgroups, which made extensive dose finding over a broad exposure range challenging.

FDA agrees with the Applicant's position that the proposed dosage of zenocutuzumab 750 mg Q2W is appropriate for the proposed indication based on available efficacy and safety data, PopPK, and E-R analyses. Refer to section 19.4.1 and 19.4.2 for detailed comments on ER analysis.

6.3.2.3 Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors (e.g. race, ethnicity, age, performance status, genetic subpopulations, etc.)?

The Applicant's Position:

Zenocutuzumab administered as a fixed dose of 750 mg Q2W is an appropriate dose for clinical use in the subpopulations analyzed based on intrinsic patient factors.

A comparison of zenocutuzumab steady-state exposure parameters was conducted in specific subpopulations using forest plots, i.e., by presenting the estimated geometric mean ratios and its 90% CI for the exposure metrics of interest and for a given covariate stratum relative to the reference stratum and adjusting for the other covariates based on the final population PK model. Continuous covariates were first categorized as being either below or above the median value across subjects.

Please refer to Section 6.2.2.2. for additional details.

Within the NRG1+ subpopulation, the magnitude of covariate effects on PK exposures was generally modest. Most of the statistically significant covariates had a minor impact on exposures (≤ 20% change). Males had 23% lower exposures compared to females and patients with below median BSA had 29% higher exposure compared to above median BSA. However, none of these covariate effects were considered strong enough to warrant a priori dosing adjustment for use of zenocutuzumab in clinical practice.

No dose adjustment is necessary based on age or race, or in patients with mild to moderately decreased renal function or those with mild hepatic impairment. Given the large molecular mass of zenocutuzumab (145.9 kDa), its clearance is not anticipated to be affected by decreased renal function. Based on population PK analyses, renal function (mild to moderately decreased) had no statistically significant nor clinically relevant effect on exposure of zenocutuzumab. Changes in hepatic function are unlikely to have any effect on the elimination of zenocutuzumab since IgG1 molecules such as zenocutuzumab are not metabolized through hepatic pathways. Based on population PK analyses, hepatic function (mild impairment) had no statistically significant nor clinically relevant effect on exposure of zenocutuzumab.

The FDA's Assessment:

FDA agrees with the Applicant's position that no dosage adjustment is warranted for the evaluated intrinsic (e.g. age, sex, race (White and Asian), and body weight) and extrinsic factors based on PopPK assessment, including for patients with mild to moderately decreased renal function or mild hepatic impairment.

However, given that the PK of zenocutuzumab in patients with moderate to severe hepatic impairment or severe renal impairment is unknown, FDA does not provide specific recommendations on dosage adjustment or safety monitoring for this patient population at this time.

Zenocutuzumab PK was studied and compared in a limited number of cancer types. Therefore, the data are insufficient to support the conclusion that tumor type has no effect on drug exposure.

Antitumor activity by HER2 and HER3 expression status

Although HER2 and HER3 are the targets of zenocutuzumab, HER2 and HER3 tumor expression status at baseline was not required for enrollment of patients in the eNRGy study. A total of 22 patients (29.3%) had known HER2 and/or HER3 status based on local assays in the NSCLC PES. Of these patients, 10 were HER2 negative without assay information provided, 1 patient was HER2 negative by in situ hybridization, 1 patient was HER2 amplified, 1 patient was HER2 +2 by immunohistochemistry (IHC+2), 8 patients were HER3 negative, and 1 patient was HER3 positive. Three patients (4.0%) had known HER2 and HER3 status, all 3 patients were HER2 and HER3 negative without assay information provided. In the PDAC PES, HER2 status was reported for 1 patient as negative, and no patients had known HER3 status (Table 11). There was no apparent trend in response based on HER2 or HER3 status in patients with NSCLC; the data on HER2/HER3 status in patients with PDAC are not interpretable due to limited reporting.

Table 11. FDA – HER2 and HER2 tumor expression status at baseline.

	NSCLC		PDAC	
	N	ORR by BICR, n (%)	N	ORR by BICR, n (%)
Total	75	25 (33.3)	29	12 (41.4)
HER2 status (local)				
Unknown	62	20 (32.3)	28	11 (39.3)
Negative (incl. ISH negative)	11	5 (45.5)	1	1 (100)
Amplified	1	0	0	--
IHC +2	1	0	0	--
HER3 status (local)				
Unknown	66	21 (31.8)	29	12 (41.4)
Negative	8	3 (37.5)	0	--
Positive	1	1 (100)	0	--

Source: Response to FDA information request dated July 10, 2024.

Antitumor activity by *NRG1* fusion partner

Patients were enrolled in the eNRGy trial based on the presence of an *NRG1* fusion in tumor DNA or RNA as detected by local NGS-based assays. A total of 18 patients with *NRG1* fusion-positive tumors were excluded at screening for not meeting other eligibility criteria. All eligible patients classified as *NRG1* fusion-positive were treated with zenocutuzumab. The NSCLC and PDAC PES included two patients with *NRG1* fusion-positive tumors that had been classified as ineligible based on the retrospective *NRG1* fusion functionality assessment by the independent reviewer (1 patient with NSCLC, USUBJID: (b) (6), and 1 patient with PDAC, USUBJID: (b) (6)).

There were 18 *NRG1* fusions with unique partner genes in the combined *NRG1* fusion-positive NSCLC plus PDAC PES, with 8 *NRG1* fusions in the NSCLC PES and 10 in the PDAC PES (Table 6.4). In general, the type and approximate frequency of *NRG1* fusions in the PDAC and NSCLC PESs appear to be consistent with estimates from the literature (PMID: (b) (6), PMID (b) (6)). *NRG1* fusions with *SDC4* and *CDH1* were present in patients from both NSCLC and PDAC PES (*SDC4*: 7 patients with NSCLC [10.9%] and 1 patient with PDAC [3.3%]. *CDH1*: 2 patients with NSCLC [3.1%] and 2 patients with PDAC [6.7%]). There were no apparent trends in antitumor activity by type of *NRG1* fusion partner in evaluable subgroups in the previously-treated NSCLC and PDAC PES (Table 12). These results support a broad indication for the treatment of patients with NSCLC and PDAC harboring *NRG1* fusions.

Table 12. Efficacy by *NRG1* gene fusion partner in patients with NSCLC and PDAC.

	NSCLC N = 64				**PDAC N = 30**				
***NRG1* partner**	**N**	**ORR N (%)**	**95% CI**	**DOR Range (Months)**	***NRG1* partner**	**N**	**ORR N (%)**	**95% CI**	**DOR Range (Months)**
CD74	37	12 (32)	(18, 50)	1.8+; 20.3+	*ATP1B1*	14	7 (50)	(23, 77)	3.7, 16.6
SLC3A2	14	5 (36)	(13, 65)	3.6; 20.8+	*CD44*	3	0	(0, 71)	NA
SDC4	7	2 (29)	(3.7, 71)	7.4; 16.6	*NOTCH2*	3	1 (33)	(0.8, 91)	7.4+
CDH1	2	1 (50)	(1.3, 99)	1.9+	*SLC4A4*	3	2 (67)	(9, 99)	7.5+, 15.2+
FUT10	1	PD	NA	NA	*AGRN*	1	PR	NA	9.1+
PVALB	1	PD	NA	NA	*APP*	1	PR	NA	3.7
ST14	1	PD	NA	NA	*CDH1*	2	SD, SD	NA	NA
VAMP2	1	PR	NA	5.6	*SDC4*	1	SD	NA	NA
					THBS1	1	PD	NA	NA
					VTCN1	1	SD	NA	NA

ORR: overall response rate; DOR: duration of response; PR: partial response; PD: progressive disease; NA: not applicable; "+" indicates ongoing response.
Source: FDA analysis

6.3.2.4 Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

The Applicant's Position:

Zenocutuzumab is intended for IV administration; therefore, food-drug interactions are not expected. As an IgG1 antibody, renal excretion and hepatic enzyme mediated metabolism of intact zenocutuzumab are unlikely to represent major elimination routes, nor are drug-metabolizing enzymes expected to affect the elimination of zenocutuzumab. As zenocutuzumab binds to the extracellular domains of HER2 and HER3 with high specificity, it is not anticipated to alter the activity of drug-metabolizing enzymes. Hence, no drug-drug interactions with concomitant medications are expected.

The FDA's Assessment:

FDA concurs with the Applicant's position.

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7 Sources of Clinical Data

7.1. Table of Clinical Studies

Data:

Table 13. Applicant - Listing of Clinical Studies Relevant to this BLA

Trial Identity & NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients treated	Study Population	No. of Centers and Countries
Primary Study to Support Efficacy and Safety							
eNRGy study NCT02912949 Active, recruiting	Phase 1/2, open-label, multicenter, multinational study, with a dose escalation phase followed by a single-arm, multiple-indication expansion group assignment phase. Patients were enrolled in Group F (NRG1+ non-small cell lung cancer [NSCLC]), Group G (NRG1+ pancreatic ductal adenocarcinoma [PDAC], or Group H (other NRG1+ solid tumors).	**Part 2 Expansion:** Zenocutuzumab 750 mg IV Q2W	**Primary/key secondary:** ORR/DOR per RECIST 1.1 and local investigator assessment	Treatment until progression, unacceptable toxicity, or other listed reasons, an End of Treatment (EOT) visit within 7 days after the final zenocutuzumab dose, a Final Study Visit 30 days (+7 days) after the final zenocutuzumab dose, and follow-up for disease progression	**Total 175 patients** (99 NRG1+ NSCLC, 39 NRG1+ PDAC, 37 other NRG1+ solid tumor types)	Patients with NRG1+ NSCLC, NRG1+ PDAC and other NRG1+ solid tumors	49 centers, 12 countries

Trial Identity & NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients treated	Study Population	No. of Centers and Countries
				and/or survival status every 3 months for up to 2 years after completing the Final Study Visit or until the initiation of new anticancer treatment.			
Studies to Support Efficacy and Safety							
Early Access Program (EAP) in NRG1+ cancer Active	Non-randomized, open-label expanded access program for patients with an advanced NRG1+ solid tumor on a single patient/ named patient basis Patients must have a documented predicted functional NRG1 fusion detected by a molecular assay	Zenocutuzumab 750 mg IV Q2W	No formal objectives in the setting of an EAP. Efficacy and safety endpoints were aligned with the eNRGy study.	Patients are to remain on treatment until unacceptable toxicity, patient withdrawal of consent, or investigator decision to withdraw the patient from treatment (e.g., disease progression).	**Total 15 patients**	Individual patients with advanced/metastatic cancer with a documented NRG1 gene fusion are enrolled in the EAP on a single patient/named access basis if they could not be enrolled in the Merus sponsored eNRGy study	France, Germany, Spain, USA, UK

Trial Identity & NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients treated	Study Population	No. of Centers and Countries
Studies to Support Safety							
MCLA-128-CL01 (non-NRG1+) NCT02912949 Completed	**Part 1 Dose Escalation** Open label, Phase 1/2, first in human, multicenter, multinational, single arm, dose escalation and dose expansion study of zenocutuzumab monotherapy in solid tumors	Zenocutuzumab 40 to 900 mg IV Q3W	**Primary:** Evaluation of AEs and dose-limiting toxicities	Treatment was to be administered until the occurrence of DLT (for patients in the dose escalation only), disease progression, unacceptable toxicity, or 1 of the other specified events.	**Dose escalation:** 28 patients	Selected advanced/metastatic solid tumors that were not prospectively tested for NRG1 status	9 centers for dose escalation, 6 countries Spain, The Netherlands, France, Italy, Korea, Singapore
	Part 2 Expansion Open label, Phase 1/2, multicenter, multinational, single arm, dose escalation and dose expansion study of zenocutuzumab monotherapy in solid tumors	Zenocutuzumab 750 mg IV Q3W or Q1W	**Primary safety:** Frequency and nature of AEs **Primary efficacy:** ORR, DOR, CBR per RECIST 1.1 and local investigator assessment	Treatment was to be administered until the occurrence of DLT (for patients in the dose escalation only), disease progression, unacceptable toxicity, or 1 of the other	**Total 127 patients** - Q3W (non-NRG1+ cancer): 101 patients - Q1W (non-NRG1+ cancer): 23 patients	Selected advanced/metastatic solid tumors that were not prospectively tested for NRG1 status	12 centers for dose expansion, 6 countries Spain, The Netherlands, France, Italy, Korea, Singapore

Trial Identity & NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients treated	Study Population	No. of Centers and Countries
				specified events.	- Q1W (NRG1+ cancer): 3 patients for safety only)		
EAP in non-NRG1+ cancer patients	Expanded access program for patients with an advanced nonNRG1+ *HER3* mutant solid tumor on a single patient/ named patient basis	Zenocutuzumab 750 mg IV Q2W	No formal objectives in the setting of an EAP. No formal analyses or CSR planned. Narratives prepared for each patient.	Patients are to remain on treatment until unacceptable toxicity, patient withdrawal of consent, or investigator decision to withdraw the patient from treatment (e.g., disease progression).	**Total 8 patients**	Non-NRG1+ *HER3* mutant cancer patients	France, USA
Supportive Safety in Combination Setting							
MCLA-128-CL02 NCT03321981	Phase 2, open-label, multicenter international study to evaluate the efficacy of zenocutuzumab-based combinations in 2 metastatic breast cancer populations, HER2-positive/amplified (Cohort 1) and estrogen	Zenocutuzumab (750 mg IV Q3W) combined with trastuzumab ± vinorelbine[1],	**Primary:** CBR at 24 weeks by RECIST 1.1 and investigator assessment	Study treatment was administered until disease progression, unacceptable toxicity, treatment	**Total 104 patients**; Cohort 1: 54 patients (15 doublet, 39 triplet), Cohort 2: 50 patients	Women with histologically or cytologically confirmed breast cancer with evidence of metastatic or locally advanced	24 centers enrolled patients, 7 countries Belgium, France, the Netherlands, Portugal,

Trial Identity & NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients treated	Study Population	No. of Centers and Countries
	receptor-positive/low-HER2 expression (Cohort 2). Three combination treatments were evaluated, 2 in Cohort 1 and 1 in Cohort 2. Study activities have been completed.	Q3W (Cohort 1) Zenocutuzumab (750 mg IV Q3W) combined with endocrine therapy[1] (Cohort 2)	**Secondary:** Cohort 1: CBR at 24 weeks per central review, and ORR, PFS, and DOR per investigator and central review. **Cohort 2:** CBR at 24 weeks per central review, and PFS per investigator and central review.	interruption >6 consecutive weeks, withdrawal of any of the study drugs, withdrawal of consent, patient non-compliance, or investigator decision.		disease not amenable to any local therapy with curative intent	Spain, UK, and the USA

1 Trastuzumab was administered as 8 mg/kg IV loading dose then 6 mg/kg for subsequent cycles. Vinorelbine 25 mg/m2 IV was administered on Days 1 and 8 of each cycle. Endocrine therapy was administered at the same dose and regimen of the last prior endocrine therapy on which the patient progressed prior to study entry.
AEs: Adverse events, BICR: Blinded independent central review, BOR: best overall response, CBR: clinical benefit rate, DCR: disease control rate, DLTs: dose limiting toxicities, DOR: duration of response, EAP: expanded access program, NRG1: neuregulin 1, NSCLC: non-small cell lung cancer, ORR: Overall response rate, OS: overall survival, PFS: progression-free survival, PDAC: pancreatic ductal adenocarcinoma, RECIST 1.1: Response Evaluation Criteria in Solid Tumors version 1.1,SAEs: Serious adverse events, TTR: time to response

The Applicant's Position:

The overview of efficacy and safety for this submission focuses on the response rate and durability of response, and overall safety from the pivotal eNRGy study for the proposed population and dose/regimen. The EAP study provides supportive efficacy and safety data for the proposed population at the indicated dose and regimen.

The EAP (*HER3* mutant patients) data are provided for safety review at the proposed dose/regimen in a non-NRG1+ patient population. The MCLA-128-CL01 (non-NRG1+ patients) CSR1 provides safety analyses data by dose level for all dose levels across the zenocutuzumab single agent development program. The MCLA-128-CL02 (zenocutuzumab in combination in breast cancer patients) data are provided in this BLA to support the safety review of zenocutuzumab.

The FDA's Assessment:

FDA agrees with the Applicant's position.

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

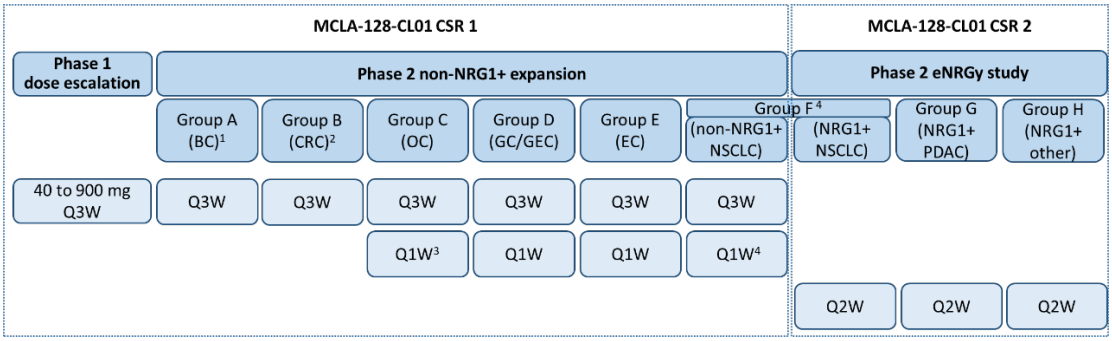
8.1.1. eNRGy Study

Trial Design

The Applicant's Description:

Basic study design: This is 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. It was initially designed to establish the RP2D of monotherapy zenocutuzumab, and to explore this RP2D in the Phase 2 part to assess the safety, tolerability, PK, pharmacodynamics, immunogenicity, and antitumor activity of zenocutuzumab monotherapy in patients with selected advanced/metastatic solid tumors. At that time, NRG1 gene fusion testing was not performed prospectively, and these patients are referred to as non NRG1+ cancer patients. The dose escalation part has been completed and enrollment into all non NRG1+ expansion Groups A to F has been closed. As of Protocol Amendment 5.0, the Phase 2 part of the study focused exclusively on patients with advanced unresectable or metastatic cancer harboring a documented NRG1 gene fusion, and the MCLA-128-CL01 study was thereafter named the "eNRGy study". The eNRGy study was designed to assess the magnitude and durability of the antitumor activity of zenocutuzumab 750 mg Q2W in patients with NRG1+ cancer and was ongoing at the data cutoff date. The overall study design is presented in Figure 10. An overview of the eNRGy study design is presented in Figure 11.

Figure 10. Applicant – Analysis of the MCLA-128-CL01 study, by group, treatment regimen, and CSR

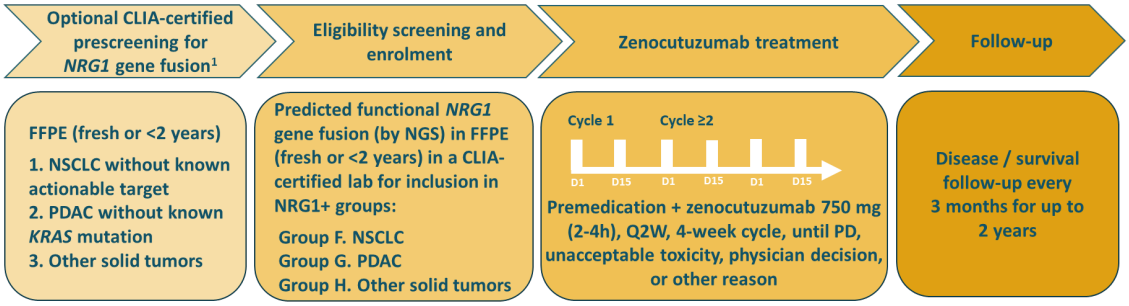


Note: Q3W = zenocutuzumab 750 mg every 3 weeks; Q1W = zenocutuzumab 800 mg loading dose on Cycle 1 Day 1, followed by a flat dose of 400 mg weekly for the first 2 cycles, and thereafter 400 mg weekly for 3 weeks, followed by 1 week off; Q2W = zenocutuzumab 750 mg every 2 weeks.

1. *Premature termination of Group A due to adequate proof of concept.*
2. *Premature termination of Group B as it was anticipated that this population was less likely to benefit from zenocutuzumab.*
3. *No patients in Group C were treated with the Q1W regimen due to enrollment reaching completion at the time the amendment introducing this regimen was implemented in centers actively recruiting OC patients.*
4. *Group F includes non-NRG1+ NSCLC and NRG1+ NSCLC patients; 3 NRG1+ NSCLC patients were treated with the Q1W regimen and were analyzed in CSR 1 for safety (i.e., according to the treatment regimen received) and in an addendum to CSR 1 for efficacy. All other NRG1+ NSCLC patients in Group F were treated with the Q2W regimen and were analyzed in CSR 2 for safety and efficacy.*

BC = breast cancer; EC = endometrial cancer; GC/GEC = gastric cancer/gastroesophageal carcinoma; OC = ovarian cancer; other = other solid tumor types.
Source: eNRGy CSR Figure 1

Figure 11. Applicant - eNRGy study design



1. *Suspended as of Amendment 7.0.*

CLIA = Clinical Laboratory Improvement Amendments; FFPE = formalin-fixed paraffin-embedded; NGS = next-generation sequencing; PD = progressive disease; Q2W = every 2 weeks.
Source: eNRGy CSR Figure 2

Trial Location: The 175 NRG1+ cancer patients were treated with zenocutuzumab 750 mg Q2W at 49 centers, in 12 countries across Europe, Asia, and North America between 25 Sep 2019 and the data cutoff date of 31 Jul 2023.

Choice of control group: Not applicable as this was a single-arm study.

Diagnostic criteria: A fresh recently acquired FFPE tumor sample (preferred) or an archival tumor sample (preferably collected within 2 years of starting study treatment) was required for assessment of the NRG1 fusion. For patients who had received afatinib or other HER-targeting agents, a biopsy after the last line of treatment was strongly preferred to assess for mechanisms of acquired resistance. A baseline biopsy for screening was still required even if a prescreening biopsy sample was provided for central prescreening.

Key Inclusion/Exclusion criteria: The eligibility criteria for the study are appropriate for the population under investigation.

Key inclusion criteria: Age 18 years or older with ≥1 measurable lesion according to RECIST 1.1 and histologic or cytologic diagnosis of locally advanced, unresectable or metastatic solid tumor malignancy with a documented NRG1 gene fusion identified through molecular assays such as next-generation sequencing (NGS)-based assays (DNA or RNA), as routinely performed at Clinical Laboratory Improvement Amendments (CLIA) or other similarly certified laboratories; received prior standard therapy appropriate for their tumor type and stage of disease, or in the opinion of the investigator, would be unlikely to tolerate or derive clinically meaningful benefit from appropriate standard-of-care therapy or no satisfactory alternative treatment options were available; Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 to 2; adequate organ function; negative pregnancy test results and appropriate birth control; written informed consent prior to any study-specific screening procedures.

Key exclusion criteria: Pregnant or lactating; presence of an active and uncontrolled infection; known hypersensitivity to any of the components of zenocutuzumab or history of severe hypersensitivity reactions to human or humanized monoclonal antibodies, including therapeutic antibodies; known human immunodeficiency virus, active hepatitis B infection or positive for hepatitis C virus RNA; known symptomatic or unstable brain metastases; leptomeningeal metastases; previous or concurrent malignancy unless previously treated and did not affect safety and efficacy assessment of study drug; left ventricular ejection fraction (LVEF) <50%, history or presence of significant cardiovascular disease including unstable angina or myocardial infarction, congestive heart failure, or ventricular arrhythmia requiring medication.

Dose selection: The recommended phase 2 dose chosen for zenocutuzumab monotherapy in the eNRGy study was 750 mg IV Q2W.

Study treatments: Zenocutuzumab was administered intravenously (IV) over 2 hours (h), with a 4-week cycle. Premedication (antipyretics, antihistamines, and corticosteroids) was administered prior to each infusion. For the first infusion (i.e., Cycle 1 Day 1), the infusion duration was 4 h and was reduced to 2 h for subsequent treatment administrations in the absence of Grade ≥2 infusion-related reactions (IRRs) with the first infusion. The infusion duration could be extended to approximately 4 h to avoid or reduce the incidence or severity of IRRs; corticosteroids were used per investigator discretion after first infusion.

Assignment to treatment: N/A. This was an open-label, single arm study.

Blinding: N/A. This was an open-label, single-arm study.

Dose modification, dose discontinuation: Specific rules for dose modifications and discontinuations are outlined in the study protocol.

- For the first infusion (Cycle 1 Day 1), the infusion duration was 4 h to mitigate the incidence and severity of IRRs. The infusion duration could be reduced to 2 h for subsequent treatment administrations in the absence of Grade ≥2 IRRs with the first infusion. The infusion duration could be extended back up to approximately 4 h when considered appropriate to avoid or reduce the incidence or severity of IRRs.
- If more than 2 consecutive doses of study medication need to be skipped due to toxicity assessed as related to zenocutuzumab, the patient will be withdrawn from the study.
- In the event of severe IRR (CTCAE Grade 4, life-threatening) zenocutuzumab treatment should be discontinued and no additional zenocutuzumab should be administered.
- No dose reduction will be allowed.

Administrative structure: The study was sponsored by Merus N.V. (the sponsor) and conducted by investigators contracted by and under the direction of the sponsor. Study centers were monitored by the CRO.

In addition to the investigator assessment, scans were centrally collected for independent determination of response (using RECIST v1.1 criteria) by BICR, utilizing a 2-reader with adjudication paradigm.

Procedures and schedule: A table of trial schedule of events are included in Table 11.

Concurrent medications: Any medication considered necessary for the patient's safety and wellbeing could be given at the discretion of the investigator(s). However, other anticancer medications and other IMPs (except COVID-19 vaccinations) were prohibited. Systemic corticosteroids were permitted and were part of the mandatory premedication regimen prior to each zenocutuzumab administration. In the event of hypersensitivity or IRRs, corticosteroids could be used as clinically indicated. Patients who were receiving treatment with corticosteroids due to chronic diseases at the time of study enrollment could continue to receive this treatment if the dose remained stable at the pre-enrollment level.

In cases of anemia requiring blood transfusion, transfusions with packed red blood cells could be administered. Concurrent radiation treatment was permitted during the study for symptom control.

Dietary restrictions/instructions: N/A. No dietary restrictions.

Treatment compliance: Treatment was administered in a hospital setting and compliance was recorded by qualified personnel under the supervision of the investigator or a designee in terms of the infusion administration.

Rescue medication: N/A.

Subject completion, discontinuation, or withdrawal: Subjects were considered to have completed study after completion of the Final Study Visit. The investigator could withdraw a participating patient from the study and discontinue study treatment and assessments at any time for the following reasons: disease progression, clinical signs/symptoms suggesting congestive heart failure, LVEF decrease, unacceptable toxicity, protocol non-compliance, pregnancy, patient withdrawal of consent. The Sponsor reserved the right to request the withdrawal of a patient due to protocol violation or other significant reason. After the Final Study Visit, patients were followed up every 3 months ±2 weeks for up to approximately 2 years for disease and/or survival status.

APPEARS THIS WAY ON ORIGINAL

Table 14. Applicant – Schedule of Assessments: Groups F, G, H bi-weekly dose (4-week cycle)

Assessment	Pre-screening (optional for lung & pancreatic adenocarcinoma, & selected Group H pts only)	Screening	Cycles 1 & 2		Cycles 3 & 4		Cycles ≥5		End of Treatment Visit[13]	Final Study Visit[14]	Long-Term Follow-Up
			Day		Day		Day				
	Any time prior to screening	-28 to 0	1	15	1	15	1	15			
Pre-screening Informed consent	X										
Molecular Profiling	X										
Informed consent		X									
Demographics		X									
Medical history		X									
Inclusion/exclusion		X									
Adverse events			Continuous assessment								
ECOG PS		X	X		X		X		X	X	
Physical examination[1]		X	X		X		X		X	X	
Vital signs[2]		X	X	X	X	X	X	X	X	X	
ECG (resting 12-lead)[3]		X	X		X		X		X	X	
LVEF assessment[4]		X	LVEF assessment to be performed at Cycle 5 Day 1							X	
Clinical chemistry		X	X	X	X	X	X	X	X	X	
Hematology		X	X	X	X	X	X	X	X	X	
Coagulation		X	X		X		X		X	X	
Urinalysis		X	X		X		X		X	X	

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

Assessment	Pre-screening (optional for lung & pancreatic adenocarcinoma, & selected Group H pts only)	Screening	Cycles 1 & 2		Cycles 3 & 4		Cycles ≥5		End of Treatment Visit[13]	Final Study Visit[14]	Long-Term Follow-Up
			Day		Day		Day				
	Any time prior to screening	-28 to 0	1	15	1	15	1	15			
Pregnancy test [6]		serum	urine		urine		urine		serum		
Immunogenicity assessment [16, 17]			X		X		X				
Pharmacokinetics [8, 17]			X	X [8]	X [8]	X [8]	X [8]				
Tumor assessment (radiological) [9]		X	Tumor assessments will be performed every 8 weeks until end of treatment Where available, PET/CT to be performed at baseline, 8 weeks and 16 weeks after first treatment							X	X[9]
Tumor assessment (serum marker) [10]		X	Elevated serum markers at screening will be monitored at the end of every cycle (pre-dose Day 1 Cycle 2, Cycle 3, etc.)						X	X	X
Biomarker/PD assessment (biopsy) [11]		X	Tumor sample to be optionally provided on Cycle 5 Day 1						X		
Biomarker/PD assessment (blood sample) [12]			To be performed pre-dose at Cycle 1 Day 1 Cycle 2 D1 and every 2 cycles thereafter (Day 1 Cycle 4, Day 1 Cycle 6, etc.)						X		
MCLA-128 administration			X	X	X	X	X	X			
Concomitant medication		X	Continuous assessment								
Survival follow-up [15]											X

Footnotes: general and assessment-specific

- Assessments made on Day 1 of each cycle are to be conducted prior to MCLA-128 administration, unless specified otherwise. Assessments scheduled for end-of-cycle are intended to be obtained prior to initiation of the subsequent cycle.
- Additional assessments may be conducted as clinically indicated.

- A window of +/-2 days will be permitted for all study visits and a window of -2 days for all assessments relative to the study visit, unless critical for valid assessment, e.g., PK sampling, or otherwise specified in assessment-specific footnotes.
- See APPENDIX I of Protocol Amendment 7 for COVID-19 guidance for the Schedule of Assessments.

1. Patient's height will be recorded at Screening. A physical examination is required at Screening and prior to dosing on Day 1 of each cycle. Weight will be recorded at Screening and on Day 1 of each cycle.

2. On each MCLA-128 administration day, vital signs (heart rate, BP, body temperature and respiration rate) will be assessed pre-dose and at least 1 hour from EOI. Patient status will be monitored during MCLA-128 administration and repeat vital signs taken if needed. Vital signs will also be repeated at End of Treatment and the Final Study visit.

3. On Cycle 1, Day 1 a resting 12-lead ECG will be conducted pre-dose and 60 mins (+/- 15 mins) after end of MCLA-128 administration. On Day 1 of all other cycles, a resting 12-lead ECG will be conducted pre-dose and when needed afterwards based on study nurse and or Investigator's judgment.

4. LVEF will be assessed by echocardiogram. MUGA scan as an alternate method of assessment will be accepted as per investigational site's standard practice. Assessments will be performed at Screening, end of Cycle 4, Final Study Visit, and at any time during study treatment as clinically indicated, based on Investigator's judgment (see APPENDIX G of Protocol Amendment 7).

5. Not applicable.

6. A pregnancy test is to be performed on all female patients of child-bearing potential. Where urine pregnancy testing is performed and is positive, a serum test must be carried out to confirm the result. No need to repeat Cycle 1, Day 1 assessment required if Screening assessment within 7 days of Cycle 1, Day 1.

7. Not applicable.

8. Patients will have PK blood sampling conducted at the following sample times. The DRC may advise on adjusted time points. The maximum number of PK samples to be collected during any Cycle 1 dose schedule will not exceed 10. The actual time for each blood draw must be accurately recorded. Sampling time points for the biweekly schedule: In Cycle 1, blood samples will be collected for PK analysis on Day 1 at pre-dose, EOI, 2, 4, 24 hours post EOI, and pre-dose and EOI on Day 15. In Cycles 2 and 3, a pre-dose and EOI blood sample will be collected on Day 1 and a pre-dose on Day 15. In Cycles 4, 6 and 8 a pre-dose blood sample will be collected on Day 1.

   Windows for pharmacokinetics assessment sampling:
   Pre-dose sampling can be as early as 2 hours before start of infusion and up to 5 minutes prior to start of infusion. EOI sampling can be up to 15 minutes post EOI.

Sampling on Cycle 1 Day 1 can be taken as per the following time windows:

- 2h EOI: **+/-** 15 minutes
- 4h EOI: +/- 30 minutes
- 24h EOI: +/- 2 hours

9. Radiological tumor assessment (CT and/or MRI) will be performed at Screening and every 8 weeks from the start of study treatment until end of treatment. A standard, full assessment for lesions should be conducted at baseline, including CT/MRI scans of chest, abdomen, and pelvis. A brain MRI or CT scan should be performed at baseline in order to assess CNS disease. Contrast enhanced brain MRI is preferred, however, if MRI contrast is contraindicated, then brain MRI without contrast or brain CT with/without contrast is acceptable. Brain MRI or CT scans should be performed at the same frequency of CT/MRI of chest, abdomen and pelvis, only if brain metastases were detected on the baseline scan. Additional imaging of anatomical sites (e.g., head, neck) should be performed as applicable for the participant's tumor type. Note that where there is a rationale for assessment of bone lesions, these assessments will be performed as part of the CT or MRI assessment and will not require additional radiological bone scan assessment. Additional scans may be performed to confirm a response as appropriate. Any requirement for confirmatory scans will typically be performed at the next protocolled assessment time point or at Follow-Up Visit. Tumor assessments may be adjusted to align with delays in study treatment. Only for the first tumor assessment a window of +3 days is allowed. Thereafter a +/- 3-day window is permitted but should precede initiation of the next treatment cycle. Upon completion of the study (i.e., after completing the Final Study Visit), those patients who do not have disease progression and who have not withdrawn consent will have their disease status assessed every 3 months, if possible or as per local standard, for a maximum of 2 years as part of the Long-Term Follow-Up.
   Where available, PET/CT should be conducted at baseline and for those patients with FDG avid disease 2 post baseline assessments using PET/CT should be performed 8 and 16 weeks after initiation of treatment.

10. When applicable based on patient's cancer type a blood sampling for monitoring of tumor status will be collected at Screening. When serum markers are elevated at screening they will be monitored prior to beginning the next cycle (or predose C2, C3, etc.) until end of treatment. Tumor serum markers should be assessed when there is an approved test and required by institutional protocols for management of specific type of patient's cancer or upon Investigator's discretion. For example, for patients with ovarian cancer or pancreatic adenocarcinoma who at screening show elevated CA-125 and CA 19-9, respectively; monitoring will be done at every cycle. Serum markers will be evaluated in patients who do not have disease progression at the Final Study Visit and every 3 months (only for any indication where there is a serum tumor marker that is evaluable for follow-up), if possible or as per local standard, as part of the long-term follow up, until eventual disease progression or next anti-cancer treatment has commenced.

11. At baseline the patient will be requested to provide a mandatory tumor sample, if safe/feasible, preferably a block, which could be from fresh (recently acquired FFPE biopsy) or archival tissue without age restriction. The Sponsor indicates the preference for fresh FFPE tissue or archival tissue collected no more than two years prior to treatment with MCLA-128. For patients that received afatinib or any other HER inhibitor a fresh biopsy is strongly preferred after discontinuation of this treatment and prior to entering the study. In addition, the patient will be requested optionally to provide a biopsy at the end of Cycle 4 (or at Cycle 5 Day 1) and optionally at the End of Treatment Visit. Imaging techniques may be used to facilitate this process. Full details of biopsy sampling and associated informed consents can be found in Section 5.4.6 and APPENDIX F in Protocol Amendment 7.

12. Collection of blood samples for PD and biomarker purposes (liquid biopsy) is mandatory pre-dose at Cycle 1, Day 1, and then at Cycle 2 Day 1 and at the end of every 2 Cycles (Cycle 4 Day 1, Cycle 6 Day 1, etc.), and the End of Treatment Visit. PD assessments will consist of circulating tumor DNA analysis and Fc-gamma receptor polymorphism (the latter on Cycle 1, Day 1 only).

13. The End of Treatment Visit should be performed up to 1 week after decision is made to discontinue treatment.

14. The Final Study Visit should be performed 30 days (+ 7-day window) after the last dose of MCLA-128 to enable a final safety assessment.

15. Patients who stop study treatment and proceed to their Final Study Visit, but who do not withdraw their consent, will be followed up every 3 months (±2 weeks) by telephone for a maximum of 2 years to check their survival status.

16. Immunogenicity assessments will be performed on Day 1 pre-dose for Cycles 1, 2, 3, 4, and 8 with a window of -3 days prior to the MCLA-128 administration (Days 25-28).

17. Remnant serum samples from the immunogenicity and/or PK analysis will be used for exploratory research based on emerging literature on serum tumor biomarkers such as shed HER2.

The FDA's Assessment:

FDA agrees with the Applicant's description of the eNRGy study design. In a single arm trial, FDA does not use any inferential procedures to evaluate the trial results. Instead an efficacy decision will be based the exclusion of a clinically relevant rate by the lower limit of a 95% confidence interval of the response rate, with adequate duration of response and a positive benefit:risk assessment.

Eligibility Criteria

The Applicant's Description:

See Key Inclusion/Exclusion criteria above.

The FDA's Assessment:

FDA generally agrees with the Applicant's description of the key inclusion and exclusion criteria for the eNRGy trial. FDA notes that the following changes were made to the eligibility criteria with protocol Amendment 7:

- The threshold for platelets was lowered from ≥100 x 10^9/L to 75 x 10^9/L. The Applicant's rationale for this change was that experience with zenocutuzumab until that time indicated a low risk of thrombocytopenia.
- A statement was added to the inclusion criteria for liver function, that isolated elevation of AST or ALT >3x ULN in the absence of underlying liver disease may be considered for enrollment upon Sponsor review and approval.

Patients with a remote history of myocardial infarction and unstable angina (longer than 12 months prior to enrollment) would be permitted to enroll based on the Applicant's assessment that zenocutuzumab had demonstrated a favorable cardiac safety profile to date.

The eNRGy trial protocol specified that eligible patients must have a documented *NRG1* gene fusion which was predicted to be functional. Predicted functionality was assessed by the presence of an EGF-like domain, the in-frame status for both the fusion partner and *NRG1*, 3' direction of *NRG1*, and the identification of the fusion partner in the nucleic acid sequence. For equivocal cases, the Applicant manually reviewed the genomic results and could request collateral testing if necessary. A translational scientist reviewed each patient's pathology report for the *NRG1* gene fusion and completed a Review Form which was then reviewed by an NRG1+ review team at the (b) (4). This review team assessed functionality and confirmed whether the patient could be enrolled in the study. In a response to an information request from the review team, the Applicant stated that the interpretation of *NRG1* fusion functionality by the NRG1+ review team at (b) (4) was fully

concordant (100%, 175/175) with the Applicant's translational scientists based on assessment of the local test reports.

Study Endpoints

The Applicant's Description:

A brief summary and description of the primary and secondary endpoints are provided in Table 12. Detailed methodology for summary and statistical analyses are provided in the MCLA-128-CL01 SAP, including full definitions and censoring rules.

The primary endpoint of ORR in conjunction with DOR (key secondary endpoint) per RECIST 1.1 and investigator assessment, that are of sufficient magnitude, constitute meaningful surrogate endpoints likely to predict clinical benefit in a rare cancer with a high unmet medical need. ORR and DOR per RECIST 1.1 based on blinded independent central review (BICR) are secondary endpoints that further support the validity of ORR as a surrogate endpoint. The secondary endpoint CBR at 24 weeks, defined as the proportion of patients with CR, PR, or SD lasting ≥24 weeks, may reflect meaningful durable antitumor activity in an advanced metastatic setting. Use of PERCIST allows for evaluation of antitumor activity in patients in Group H without measurable disease.

Tumor response rate (ORR) and DOR are standard efficacy endpoints in clinical investigations of new NSCLC therapies. Moreover, the primary endpoint of ORR (per RECIST), in conjunction with the DOR endpoint, has been recognized by the FDA as acceptable endpoints reasonably likely to predict clinical benefit in single-arm studies in settings of unmet medical need in support of accelerated approval. The ORR, together with DOR, allow for evaluation of anti-tumor activity and enable assessment of the potential clinical benefit of zenocutuzumab in the NRG1+ NSCLC population.

Although drug approvals for locally advanced or metastatic PDAC have almost exclusively been based on OS as the endpoint, overall response rate (ORR) has been a common surrogate endpoint used to support accelerated approvals of cancer drugs and biologics (Blumenthal and Pazdur, 2016; FDA Clinical Trial Endpoints, 2018). In the setting of metastatic and refractory malignancies, ORR can reliably correspond with treatment effect in single-arm studies, and durable ORR has been used to support traditional approval after comprehensive assessment of the overall context and evidence, including specific malignancy, magnitude of treatment effect, drug toxicity, and suitable alternative therapies (i.e., unmet medical need).

The rationale for the use of durable ORR as a regulatory endpoint in the context of NRG1+ PDAC was discussed with FDA. Salient points include:

- In a sensitivity analysis, high ORR with zenocutuzumab in patients with previously treated NRG1+ PDAC is consistent between the total population and i) the population after excluding pancreatic target lesions (TLs), and ii) the population after excluding patients with pancreatic TLs;
- ORR has previously been used as an approval endpoint for molecularly targeted therapies in tissue agnostic indications, including PDAC;

- A strong positive association between ORR and OS in eight previously reported first-line and second-line randomized studies of PDAC;
- Durability of responses observed with zenocutuzumab treatment in NRG1+ PDAC.

Agreement was obtained from FDA in applying ORR as a regulatory endpoint in a single-arm study setting: "*ORR may be considered acceptable in this rare population depending on the magnitude of response and depending on the characterization of duration of response with a sufficient number of responding patients being followed for at least six months from onset of response*".

As discussed with the FDA, BICR assessment of ORR and DOR are presented for regulatory review (i.e., marketing application review) in the Summaries of Clinical Efficacy.

Table 15. Applicant – eNRGy Study Primary and Secondary Endpoints

Primary Endpoint
Overall response rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and local investigator assessment.
Key Secondary Endpoint
Duration of response (DOR) per RECIST 1.1 and local investigator assessment.
Secondary Endpoints
ORR per RECIST 1.1 and central review.
CBR (defined as the proportion of patients with a complete response [CR] or partial response [PR], or stable disease [SD] of a minimum duration of 24 weeks) per RECIST 1.1 and local investigator assessment.
CBR per RECIST 1.1 and central review.
DOR per RECIST 1.1 and central review.
Time to response (TTR) per RECIST 1.1. and local investigator assessment.
TTR per RECIST 1.1 and central review.
Frequency and nature of adverse events (AE).
Assessment of PK variables, including total exposure, C_{max}, V, V_{ss}, $t_{1/2}$, AUC_{0-t}, AUC_{0-t}, t_{max}.
Population PK analysis.
Incidence and serum titers of antidrug antibodies against zenocutuzumab.
Time from start of treatment until progression or death, whichever occurs first.
Time from start of treatment until death.

The FDA's Assessment:

In general, FDA agrees with the Applicant's description of the endpoints. FDA considers ORR per RECIST 1.1. by BICR an appropriate efficacy endpoint to support accelerated approval where ORR is of sufficient magnitude and duration with a corresponding 95% confidence interval excluding clinically irrelevant response rates for the proposed dose. The endpoint CBR, which includes stable disease, may reflect the natural history of disease and is not typically considered when assessing the antitumor activity of a drug and evaluating clinical benefit. Additionally, time to event endpoints such as "time from start of treatment until progression or death, whichever occurs first" and "time from start of treatment until death" are not interpretable in a single arm study due to lack of comparator, and will be considered exploratory only.

Statistical Analysis Plan and Amendments

The Applicant's Description:

The initial MCLA-128-CL01 SAP was finalized 08 Jan 2020. It was amended to reflect changes in protocol amendments and add additional details to the analysis. The modifications to the original SAP are not considered to have had an impact on the integrity of the trial or the interpretation of the results.

The Statistical Analysis Plan (SAP) Amendment 4.0 for the MCLA-128-CL01 (eNRGy) Study was finalized and submitted to FDA prior to the interim database lock, and is included in the BLA. Based on the agreements made with the FDA, the SAP was amended with the following changes:

1) Removed "had at least one post-baseline response assessment or early discontinuation due to disease progression (including death due to underlying disease)" from the criteria for allocation to the Primary Efficacy Set (PES).
2) Added "toxicity" to "at least one post-baseline response assessment or early discontinuation due to toxicity or disease progression (including death due to underlying disease)" for the Secondary Efficacy Set (SES).
3) Added "Analysis of safety subgroups" (i.e. additional summaries may be presented for safety subsets, e.g. previously treated NSCLC, platinum pretreated NSCLC)

The BLA includes efficacy and safety results for the primary and supportive populations with a data cutoff date of 31 Jul 2023. The statistical methods described in the SAP 4.0 apply to NRG1+ cancer patients included in Groups F, G, and H treated with zenocutuzumab 750 mg Q2W. The SAP outlines protocol violation criteria and specific analysis population definitions.

The primary analysis per tumor type in the eNRGy study is planned when all enrolled evaluable NRG1+ cancer patients have completed ≥24 weeks or discontinued to allow sufficient follow-up to estimate DOR. The study is ongoing and the maximum enrollment of total NRG1+ cancer patients is limited to 300 patients.

Safety Analysis Set (SAF): comprises all NRG1+ cancer patients who received ≥1 infusion of study treatment at 750 mg Q2W.

Subsets of the SAF include NRG1+ NSCLC SAF, previously treated NRG1+ NSCLC SAF, platinum-pretreated NRG1+ NSCLC SAF, platinum/immunotherapy-pretreated NRG1+ NSCLC SAF, treatment-naïve NRG1+ NSCLC SAF, and NRG1+ PDAC SAF.

Primary Efficacy Set (PES): comprises all NRG1+ cancer patients who received ≥1 infusion of study treatment at 750 mg Q2W, had a documented functional NRG1 fusion based on a NGS test, had the opportunity for ≥24 weeks follow-up (i.e., received the first dose of study treatment ≥24 weeks prior to the data cutoff date), absence of other known driver mutations, and had not been exposed to anti-HER3 targeting antibodies.

Subsets of the PES include NRG1+ NSCLC PES, previously treated NRG1+ NSCLC PES, platinum-pretreated NRG1+ NSCLC PES, platinum/immunotherapy-pretreated NRG1+ NSCLC PES, treatment-naïve NRG1+ NSCLC PES, and NRG1+ PDAC PES.

Supportive Efficacy Set (SES): comprises all NRG1+ cancer patients who received ≥1 infusion of study treatment at 750 mg Q2W, had a documented functional NRG1 fusion based on an NGS test, absence of other known driver mutations, had not been exposed to anti-HER3 targeting antibodies, and had ≥1 post-baseline tumor assessment or early discontinuation due to disease progression (including death due to underlying disease) or toxicity.

Pharmacokinetic Analysis Set (PKAS): comprises all patients who provided ≥1 evaluable PK concentration. For a concentration to be evaluable, patients were required to receive ≥1 dose of study treatment prior to sampling with an available assessment of concentration (either quantitative or qualitative).

NSCLC Analysis Population Subsets

1) **Previously treated NRG1+ NSCLC:** NRG1+ NSCLC patients treated with any prior systemic anticancer therapy in any setting.
2) **Platinum-pretreated NRG1+ NSCLC:** NRG1+ NSCLC patients treated with, and previously progressed on or after, any platinum-based chemotherapy in the metastatic setting, or NRG1+ NSCLC patients who progressed within 6 months of the last dose of platinum-based chemotherapy in the (neo)adjuvant setting.
3) **Platinum-based chemotherapy/immunotherapy pretreated NRG1+ NSCLC:** NRG1+ NSCLC patients i) treated with, and previously progressed on or after, any platinum-based chemotherapy in the metastatic setting, or who progressed within 6 months of the last dose of platinum-based chemotherapy in the (neo)adjuvant setting; and ii) treated with immunotherapy. Note: Platinum-based chemotherapy and immunotherapy could be administered concurrently or sequentially.
    a. A patient who received a platinum-based chemotherapy agent in the metastatic setting belongs to this set irrespective of duration of or outcome of this therapy, the time since the last dose, or the date of documented progression relative to platinum-based chemotherapy.
    b. A patient who received platinum-based chemotherapy in the (neo)adjuvant setting must have a date of progression within 6 months of the last dose; a patient without documented progression or without a date that enables calculation of the 6 months definition, was excluded.
4) **Treatment-naïve NRG1+ NSCLC:** NRG1+ NSCLC patients with no prior systemic anticancer therapy in any setting.

The SAP v4.0 (20 Sep 2023) defines the analysis populations and details all data handling rules, including the management of missing data.

The FDA's Assessment:

In general, FDA agrees with the Applicant's description of the statistical analysis plan. The efficacy population should include the Primary Efficacy Set as defined by the Applicant, as well as the patients who were screened but ineligible based on assessment by the independent reviewer who made the final decision about functionality for the data analyses by retrospective assessment. Patient USUBJID (b) (6) was included for efficacy evaluation in patients with PDAC.

Protocol Amendments

The Applicant's Description:
The original protocol for the MCLA-128-CL01 study dated 30 Oct 2014 was amended 6 times. At the time of the 31 July 2023 data cutoff, the MCLA-128-CL01 (eNRGy) study protocol version 7.0 (dated 26 May 2023) was in place globally. The Applicant does not believe that any of the amendments impacted the integrity of the trial.

A summary of key changes to the MCLA-128-CL01 Protocol versions are listed in Table 13 below. Please note that the eNRGy study and eNRGy CSR only include data as of protocol amendment version 5.0 (05 Jun 2019).

Table 16. Applicant – Key Changes Implemented in the MCLA-128-CL01 (eNRGy) Study Protocol Amendments

Protocol Version, Date	Description & Rationale for Amendment
Version 2.0 14 Jul 2016	• Additional groups added to the protocol in exploratory design, also affecting the total number of patients that can potentially participate • Changes to the inclusion criteria added for the additional groups • Update to the statistical analysis for the change in design from Simon 2-stage to exploratory design • Addition of recommended dose for part 2 and premedications to be used
Version 3.0 19 Jan 2017	• Updates and clarifications of the eligibility criteria • Added text describing the most frequent treatment emergent adverse events • Modification of the schedule of assessments and preventive measures

Protocol Version, Date	Description & Rationale for Amendment
	• Modification to the biomarker requirements at study entry and their assessment during the study
Version 4.0 07 Nov 2017	• Restriction of the Part 2 Cohort F composed of non-small cell cancer (NSCLC) patients, to include NSCLC patients with invasive mucinous adenocarcinoma (IMA) or with documented NRG1 fusion, from sites in Asia • Evaluation of a weekly recommended dose schedule of zenocutuzumab treatment in Part 2 • Removal of the Part 2 breast cancer group
Version 5.0 05 Jun 2019	• Changes in this amendment were designed to restrict the study to NRG1+ cancer patients and to facilitate patient recruitment of this rare entity • Addition of a zenocutuzumab Q2W regimen specific to NRG1+ patients • Removal of the Q3W and Q1W regimens • Addition of a new primary efficacy endpoint and a new key secondary efficacy endpoint specific to the evaluation of efficacy in the 3 NRG1+ cancer groups • Clarification of the role of the DRC up to the Q1W regimen, with no planned role for the DRC from Protocol Amendment 5.0. • Addition of a new exploratory endpoint of antitumor activity of zenocutuzumab using PET response criteria • Addition of a PK sampling schedule for the new zenocutuzumab Q2W regimen
Version 6.0 23 Feb 2021	• Addition of 'eNRGy' to the protocol title • Clarification of primary and key secondary efficacy objectives and endpoints as investigator-assessed and per RECIST 1.1, to allow for the addition of central independent review, and clarification of secondary efficacy objectives/endpoints, in support of the use of this study in a potential future registration. • Modification from PET response criteria to PERCIST which is more widely used • Modification of the mandatory premedication • Addition of guidance on managing COVID-19-related issues
Version 7.0 26 May 2023	• Removal of molecular NRG1 fusion central prescreening • Clarification that central NRG1 fusion confirmation is planned in patients with NRG1+ fusions identified during prescreening • Clarification that patients are followed up for survival for up to 2 years (irrespective of whether they receive other anticancer treatment) • Clarification that infusion duration could be reduced to 2 h if no Grade ≥2 IRRs were seen in the first infusion (previously stated in the first cycle)

Protocol Version, Date	Description & Rationale for Amendment
	• Modification of the statistical analyses from group to tumor type

The FDA's Assessment:

FDA generally agrees with the applicant's description of the protocol amendments and includes the following additional information:

- In Version 3.0, the number of study visits after Cycle 2 was decreased based on the safety data collected during the dose escalation.
- In Version 3.0, a regimen for prophylaxis of infusion related reactions became mandatory before each infusion of zenocutuzumab, after a fatal suspected allergic reaction was reported during Part 2 of the study.
- In Version 5.0, language was added to specify that the duration of the first zenocutuzumab infusion (C1D1) will be 4 hours to mitigate the incidence and severity of IRRs, and that the duration of the infusion can be reduced to 2 hours for subsequent treatment administrations if there are no IRRs ≥Grade 2 in the first cycle.
- In Version 6.0, a baseline brain MRI or CT scan was added to the screening assessments.
- In Version 6.0, inclusion criteria were modified to allow patients with a performance status of ECOG 2 to enroll (previous versions specified ECOG 0 or 1) to facilitate recruitment.

In Version 7.0, inclusion criteria for platelets and AST/ALT were modified (see FDA response to eligibility criteria above).

8.1.2. Study Results

Compliance with Good Clinical Practices

Data:

The eNRGy study was conducted under the US IND in accordance with 21 CFR 312. For this global study, it was conducted in conformance with the ethical principles of the Declaration of Helsinki (1964), this study was conducted in accordance with the International Council for Harmonisation (ICH)-Good Clinical Practice (GCP), the European Union (EU) Clinical Trials Regulation (Regulation (EU) No 536/2014), the GCP Directive 2005/28/EC, applicable local and national regulatory requirements and laws, and the Standard Operating Procedures of the Sponsor and/or the contract research organization (CRO).

The Applicant's Position:

The eNRGy Study was conducted in accordance with US FDA regulations and was GCP compliant.

The FDA's Assessment:

FDA acknowledges the Applicant's statement of compliance with GCP requirements as per the ICH GCP Guidance.

Financial Disclosure

Data:

All the principal investigators and subinvestigators participating in the eNRGy study were assessed for financial disclosures as defined in 21 CFR Part 54, and none had disclosable financial interests.

The Applicant's Position:

The Applicant has adequately assessed clinical investigators for any financial interest/ arrangements and no disclosable financial interests were found.

The FDA's Assessment:

In accordance with 21 CFR Part 54, the Applicant submitted Form FDA 3454 (Financial Interests and Arrangements of Clinical Investigators) certifying that as the sponsor of the submitted studies, they did not enter into any financial arrangement with the listed clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study. All investigators were assessed for equity interest, significant payments of other sorts, and other compensation by the sponsor or proprietary interest. The Applicant certified that none of the financial interests or arrangements described in 21 CFR Part 54 existed for any of the investigators who participated in the eNRGy study. In Module 1.3.4 of the BLA, the Applicant provided a list of all investigators for the eNRGy study who disclosed that they have no financial interests in the study drug (see Section 19.2).

FDA reviewed the financial disclosure information provided by the Applicant and agree that integrity of the eNRGy trial data was not affected by the financial interest of the Investigators.

Patient Disposition

Data:

Table 17. Applicant – eNRGy study: Patient disposition (Primary Efficacy Set)

	NRG1+ NSCLC					NRG1+ PDAC (N=29)	All NRG1+ Tumor Types (N=129)
	All NSCLC (N=75)	Previously treated (N=64)	Platinum pretreated (N=55)	Platinum/IO pretreated (N=36)	Treatment naive (N=11)		
Patients treated, n (%)	75 (100)	64 (100)	55 (100)	36 (100)	11 (100)	29 (100)	129 (100)
Study treatment disposition, n (%)							
Discontinued study treatment	55 (73.3)	47 (73.4)	40 (72.7)	29 (80.6)	8 (72.7)	23 (79.3)	100 (77.5)
Treatment ongoing	20 (26.7)	17 (26.6)	15 (27.3)	7 (19.4)	3 (27.3)	6 (20.7)	29 (22.5)
Reason for discontinuation of study treatment, n (%)[1]							
Disease progression	46 (83.6)	39 (83.0)	32 (80.0)	21 (72.4)	7 (87.5)	16 (69.6)	81 (81.0)
Investigator decision[2]	4 (7.3)	4 (8.5)	4 (10.0)	4 (13.8)	0	3 (13.0)	9 (9.0)
Death[3]	2 (3.6)	2 (4.3)	2 (5.0)	2 (6.9)	0	2 (8.7)	5 (5.0)
Adverse event[4]	2 (3.6)	1 (2.1)	1 (2.5)	1 (3.4)	1 (12.5)	0	2 (2.0)
Patient withdrawal of consent[5]	1 (1.8)	1 (2.1)	1 (2.5)	1 (3.4)	0	1 (4.3)	2 (2.0)
Other[6]	0	0	0	0	0	1 (4.3)	1 (1.0)
Study disposition, n (%)							
Discontinued from study	55 (73.3)	47 (73.4)	40 (72.7)	29 (80.6)	8 (72.7)	21 (72.4)	98 (76.0)
Ongoing	20 (26.7)	17 (26.6)	15 (27.3)	7 (19.4)	3 (27.3)	8 (27.6)	31 (24.0)
Duration of study follow-up (months)[7]							
Mean (SD)	9.30 (7.70)	9.41 (7.74)	9.62 (7.96)	8.93 (7.50)	8.66 (7.83)	9.98 (6.51)	9.11 (7.24)
Median	8.02	8.13	8.25	7.49	6.74	9.86	8.38
Min ; Max	0.3 ; 36.2	0.3 ; 36.2	0.3 ; 36.2	0.3 ; 25.9	1.2 ; 25.9	1.0 ; 34.3	0.3 ; 36.2
Duration of overall survival follow-up (months)[8]							

	NRG1+ NSCLC					NRG1+ PDAC (N=29)	All NRG1+ Tumor Types (N=129)
	All NSCLC (N=75)	Previously treated (N=64)	Platinum pretreated (N=55)	Platinum/IO pretreated (N=36)	Treatment naive (N=11)		
Mean (SD)	11.29 (8.72)	11.38 (8.73)	11.72 (8.92)	10.34 (7.27)	10.75 (9.09)	12.88 (8.32)	11.52 (8.66)
Median	9.23	9.64	9.66	8.94	8.87	11.40	9.63
Min ; Max	0.3 ; 36.2	0.3 ; 36.2	0.3 ; 36.2	0.3 ; 26.9	1.6 ; 30.0	1.0 ; 34.3	0.3 ; 36.2

[1] *Denominator is the number of patients who discontinued study drug.*
[2] *Investigator decisions are all due to clinical progression (4 NRG1+ NSCLC, 3 NRG1+ PDAC, 2 other NRG1+ tumor types).*
[3] *Death due to clinical progression (2 NRG1+ NSCLC, 1 NRG1+ PDAC, 1 other NRG1+ tumor type), and COVID-19 (1 NRG1+ PDAC).*
[4] *Adverse events were Grade 3 dyspnea (not treatment-related; previously treated NRG1+ NSCLC), Grade 2 pneumonitis (treatment-related; treatment-naïve NRG1+ NSCLC).*
[5] *Withdrawal of consent: starting another treatment (1 NRG1+ NSCLC); withdrew from all protocol activities (1 NRG1+ PDAC).*
[6] *Other: Patient decision to look for other treatment options (NRG1+ PDAC).*
[7] *Study follow-up is defined as start of study treatment to end of study (Final Study Visit), and excludes survival follow-up after end of study.*
[8] *Survival follow-up is defined as start of study treatment to last contact with the patient or date of death, whichever is earlier.*

IO = immunotherapy
Source: Tables 14.1.1.3, 14.1.1.3.1, Listings 16.2.1.1, 14.3.1.1, 16.2.3.1

The Applicant's Position:

Patient disposition in the PES is summarized in Table 14. At the data cutoff date, approximately one-quarter of the patients with all NRG1+ tumor types in the PES (29 patients [22.5%]) were continuing zenocutuzumab therapy. Among the 100 patients who had discontinued zenocutuzumab, the main reason for discontinuation was disease progression (94 patients [94.0%], including 9 patients with symptomatic clinical progression [investigator decision] and 4 patients with fatal disease progression).

- Among the 75 NRG1+ NSCLC patients, 20 patients (26.7%) were continuing treatment with zenocutuzumab. Of the 55 patients who had discontinued zenocutuzumab, the main reason for discontinuation was disease progression (52 patients [94.5%], including 4 patients with symptomatic clinical progression [investigator decision], and 2 patients with fatal disease progression). Two patients discontinued due to AEs, 1 for Grade 3 dyspnea (not treatment-related), and 1 for Grade 2 pneumonitis (treatment-related).
- Among the 29 NRG1+ PDAC patients, 6 patients (20.7%) were continuing treatment with zenocutuzumab. Of the 23 patients who had discontinued zenocutuzumab, the main reason for discontinuation was disease progression (20 patients [87.0%], including 3

patients with symptomatic clinical progression [investigator decision], and 1 patient with fatal disease progression). One patient discontinued due to fatal COVID-19, and no patients discontinued due to non-fatal AEs.

The FDA's Assessment:

In general, FDA agrees with the Applicant's description of patient disposition. The primary efficacy analysis was limited to previously-treated NSCLC (N = 64) and PDAC patient populations (N = 30), respectively. In alignment with the efficacy population described in the Section entitled "*Statistical Analysis Plan and Amendments,*" one patient with PDAC (USUBJID (b) (6)) who was screened but deemed ineligible was also included in the analyses of patient disposition (ineligibility based on assessment by the independent reviewer who made the final decision about functionality for the data analyses by retrospective assessment). The updated patient disposition analysis is shown in Table 18.

Table 18. eNRGy study: FDA Analysis on Patient disposition in PDAC population

	NRG1+ PDAC (N=30)
Patients treated, n (%)	30
Study treatment disposition, n (%)	
Discontinued study treatment	24 (80)
Treatment ongoing	6 (20)
Reason for discontinuation of study treatment, n (%)[1]	
Disease progression	16 (67)
Investigator decision	4 (17)
Death	2 (8)
Adverse event	0
Patient withdrawal of consent	1 (4.3)
Other	1 (4.3)

Source: FDA-generated based on dataset adsl.xpt.
[1] Denominator is the number of patients who discontinued study drug.

Protocol Violations/Deviations

Data:

Table 19. Applicant – eNRGy study: Protocol deviations (Safety Analysis Set

Category	NRG1+ NSCLC (N=99)	NRG1+ PDAC (N=39)	All NRG1+ Tumor Types (N=175)
Patients with ≥1 protocol deviation	**88 (88.9)**	**36 (92.3)**	**158 (90.3)**
Study conduct/procedures[1]	88 (88.9)	36 (92.3)	158 (90.3)
Informed consent	8 (8.1)	3 (7.7)	13 (7.4)
Investigational product	3 (3.0)	3 (7.7)	6 (3.4)
Safety	1 (1.0)	1 (2.6)	4 (2.3)
Trial procedures[2]	1 (1.0)	1 (2.6)	3 (1.7)
Inclusion / exclusion[1]	0	1 (2.6)	1 (0.6)
Other	0	0	3 (1.7)
Patients with ≥1 important protocol deviation	**58 (58.6)**	**25 (64.1)**	**104 (59.4)**
Study conduct/procedures[1]	57 (57.6)	24 (61.5)	101 (57.7)
Informed consent	5 (5.1)	1 (2.6)	7 (4.0)
Safety	1 (1.0)	1 (2.6)	4 (2.3)
Trial procedures[2]	1 (1.0)	1 (2.6)	3 (1.7)
Inclusion / exclusion[1]	0	1 (2.6)	1 (0.6)
Investigational product	1 (1.0)	0	1 (0.6)
Other	0	0	1 (0.6)

[1] *Inclusion/exclusion criteria protocol deviations were categorized either under the category 'inclusion/ exclusion' or under the category 'study conduct/procedures' with a subcategory 'inclusion/exclusion criteria'.*

[2] *All patients who had a protocol deviation under the category 'trial procedures' also experienced a protocol deviation under the category 'study conduct/procedures'.*

Source: Tables 14.1.2.1, 14.1.2.2, Listing 16.2.2.1

All 158 patients (90.3%) with ≥1 protocol deviation (Table 15), had a deviation categorized as a study conduct/protocol procedural deviation. Other deviation categories included the informed consent procedure (13 patients [7.4%]) and investigational product (6 patients [3.4%]). All other deviations were reported in ≤4 patients (2.3%).

Important protocol deviations were reported in 104 patients (59.4%). The most common important deviations were those categorized as a study conduct/protocol procedural deviation (101 patients [57.7%]). In addition, 7 patients (4.0%) had an important deviation involving the informed consent procedure, and 4 patients (2.3%) had important safety deviations. Important deviations related to informed consent included incorrect date, incomplete completion (biopsy page and associated signatures), incorrect version of ICF (not site-specific)/not reconsenting to applicable ICF version, missing documentation of corrections). Important safety deviations included late/absent SAE reporting, and troponin I and T assessment not performed at screening.

The Applicant's Position:

All major deviations are described in the eNRGy CSR. The major protocol deviations observed in the eNRGy study were not expected to impact the primary endpoint, patient safety or the interpretation of the study results.

The FDA's Assessment:

FDA agrees with the Applicant's position.

Table of Demographic Characteristics

Data:

Table 20. Applicant – eNRGy study: Demographics and baseline patient characteristics (Primary Efficacy Set)

	NRG1+ NSCLC			NRG1+ PDAC (N=29)	All NRG1+ Tumor Types (N=129)
	All NSCLC (N=75)	Previously treated (N=64)	Treatment naive (N=11)		
Age (years)					
Mean (SD)	64.1 (13.1)	62.7 (12.3)	72.0 (15.1)	48.4 (14.7)	58.9 (15.0)
Median	65.0	63.5	78.0	49.0	61.0
Min ; Max	32 ; 88	32 ; 86	39 ; 88	21 ; 72	21 ; 88
Age categories, n (%)					
<65 years	37 (49.3)	34 (53.1)	3 (27.3)	26 (89.7)	82 (63.6)
≥65 years	38 (50.7)	30 (46.9)	8 (72.7)	3 (10.3)	47 (36.4)
Sex, n (%)					
Female	48 (64.0)	41 (64.1)	7 (63.6)	13 (44.8)	77 (59.7)
Male	27 (36.0)	23 (35.9)	4 (36.4)	16 (55.2)	52 (40.3)
Race, n (%)					
White	27 (36.0)	21 (32.8)	6 (54.5)	25 (86.2)	69 (53.5)
Asian	41 (54.7)	36 (56.3)	5 (45.5)	2 (6.9)	47 (36.4)
Black or African American	0	0	0	1 (3.4)	2 (1.6)
Other	2 (2.7)	2 (3.1)	0	0	4 (3.1)
Not reported	5 (6.7)	5 (7.8)	0	1 (3.4)	7 (5.4)
Ethnicity, n (%)					
Not Hispanic or Latino	65 (86.7)	56 (87.5)	9 (81.8)	27 (93.1)	110 (85.3)
Hispanic or Latino	1 (1.3)	0	1 (9.1)	1 (3.4)	3 (2.3)
Unknown	4 (5.3)	3 (4.7)	1 (9.1)	0	6 (4.7)
Not reported	5 (6.7)	5 (7.8)	0	1 (3.4)	10 (7.8)

	NRG1+ NSCLC			NRG1+ PDAC (N=29)	All NRG1+ Tumor Types (N=129)
	All NSCLC (N=75)	Previously treated (N=64)	Treatment naive (N=11)		
BMI (kg/m²)					
n (missing)	71 (4)	61 (3)	10 (1)	29 (0)	125 (4)
Mean (SD)	24.23 (4.57)	24.43 (4.64)	22.97 (4.11)	23.82 (3.58)	24.17 (4.69)
Median	23.60	23.80	23.20	23.30	23.60
Min ; Max	16.5 ; 37.7	16.5 ; 37.7	17.8 ; 30.8	17.8 ; 31.6	14.5 ; 40.9
ECOG performance status, n (%)					
0	23 (30.7)	20 (31.3)	3 (27.3)	16 (55.2)	56 (43.4)
1	48 (64.0)	42 (65.6)	6 (54.5)	13 (44.8)	67 (51.9)
2	4 (5.3)	2 (3.1)	2 (18.2)	0	6 (4.7)

BMI = body mass index; IO = immunotherapy.
Source: Tables 14.1.3.2, 14.1.3.3

The Applicant's Position:

Median age across all NRG1+ cancer patients was 61.0 years (range 21-88) (Table 16). Patients with NRG1+ NSCLC had a median age of 65.0 years (range 32-88), with approximately half of the patients (37 patients [49.3%]) under 65 years of age. Patients with NRG1+ PDAC had a median age of 49.0 years (range 21-72) and most (26 patients [89.7%]) were under 65 years of age.

In the overall NRG1+ cancer population, 77 patients (59.7%) were female; in the NRG1+ NSCLC population, 48 patients (64.0%) were female, and 13 NRG1+ PDAC patients (44.8%) were female.

Most patients were White (69 patients [53.5%]) or Asian (47 patients [36.4%]); more than half of the NRG1+ NSCLC population was Asian (41 patients [54.7%]).

Almost all patients were in good to fair general physical condition at baseline, with an ECOG PS of 0 in 56 patients (43.4%) and ECOG PS of 1 in 67 patients (51.9%).

Demographics were generally consistent across the NRG1+ NSCLC prior treatment subgroups, although the 11 treatment-naïve NRG1+ NSCLC patients had a median age of 78.0 years (range 39-88) with 3 patients (27.3%) under 65 years of age, compared to a median age of 63.5 years (range 32-86) and 34 patients (53.1%) under 65 years of age for previously-treated patients.

The FDA's Assessment:

In general, FDA agrees with the Applicant's description of baseline disease characteristics. As described earlier, the primary efficacy analysis was limited to previously-treated NSCLC (N = 64) and PDAC patient population (N = 30), respectively. Although demographics are not well-characterized by subtype for patients with NRG1 fusions given the rarity, the percentage of female patients in eNRGy was higher than would be expected based on NSCLC demographics in

the United States, as NSCLC is more common in males. Compared to the expected racial demographics for NSCLC in the U.S. population, the percentage of Black patients was lower (Primm et al, 2022). Compared to the expected demographics for (unselected) PDAC in the United States, patients in eNRGy were younger, and Black patients were underrepresented (SEER). The updated demographics and baseline disease characteristic table for PDAC patient population is shown below (Table 19).

Table 21. FDA Analysis on Demographics for PDAC Patient Population in eNRGy study

	NRG1+ PDAC (N=30)
Age (years)	
Mean (SD)	48 (5)
Median	48.5
Min; Max	21; 72
Age categories, n (%)	
<65 years	27 (90)
≥65 years	3 (10)
Sex, n (%)	
Female	13 (43)
Male	17 (57)
Race, n (%)	
White	26 (87)
Asian	2 (7)
Black or African American	1 (3.3)
Not reported	1 (3.3)
Ethnicity, n (%)	
Not Hispanic or Latino	1 (3.3)
Hispanic or Latino	28 (93)
Not reported	1 (3.3)
ECOG performance status, n (%)	
0	16 (53)
1	14 (47)
2	0

Source: FDA-generated based on datasets adsl.xpt and adbs.xpt.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Data:

Table 22. Applicant – eNRGy study: Cancer history (NRG1+ NSCLC Primary Efficacy Set)

	Previously-treated (N=64)	Treatment-naïve (N=11)	All NRG1+ NSCLC Patients (N=75)
Histologic diagnosis, n (%)			
Adenocarcinoma	52 (81.3)	10 (90.9)	62 (82.7)
Invasive mucinous adenocarcinoma	11 (17.2)	0	11 (14.7)
Squamous cell carcinoma	1 (1.6)	0	1 (1.3)
Other[1]	0	1 (9.1)	1 (1.3)
Time since initial diagnosis (months)			
Median (min, max)	12.5 (3, 149)	1.9 (1, 15)	11.8 (1, 149)
Stage at initial diagnosis, n (%)			
n (missing)	56 (8)	11 (0)	67 (8)
IA	1 (1.6)	0	1 (1.3)
IB	1 (1.6)	0	1 (1.3)
IIA	2 (3.1)	0	2 (2.7)
IIB	2 (3.1)	0	2 (2.7)
IIIA	10 (15.6)	0	10 (13.3)
IIIB	8 (12.5)	0	8 (10.7)
IV	32 (50.0)	11 (100)	43 (57.3)
Stage at screening, n (%)			
IIIA	1 (1.6)	0	1 (1.3)
IIIB	2 (3.1)	0	2 (2.7)
IV	61 (95.3)	11 (100)	72 (96.0)
Metastatic disease sites at baseline			
Yes	63 (98.4)[2]	11 (100)	74 (98.7)
Number of metastatic disease sites at baseline			
n (missing)	63 (1)	11 (0)	74 (1)
Median (min, max)	2.0 (1, 8)	4.0 (1, 5)	2.0 (1, 8)

Notes: Summary statistics for number of metastatic disease sites are based on patients with at least 1 metastatic site at baseline. Time since initial diagnosis: time from initial diagnosis of cancer to date of screening visit. Time since metastatic disease: time from diagnosis of metastatic disease to date of screening visit.

[1] Other histology: poorly differentiated carcinoma (1 treatment-naïve patient).

[2] Two of 3 patients with locally advanced disease at screening had lung, and lung plus lymph nodes, reported as metastatic disease sites.

Source: eNRGy CSR Table 14.1.3.5.1 and eNRGy CSR Section 11.4.2.2

Table 23. Applicant – eNRGy study: Cancer history (NRG1+ PDAC Primary Efficacy Set)

	NRG1+ PDAC (N=29)
Histologic diagnosis, n (%)	
Adenocarcinoma[1]	29 (100)
Time since initial diagnosis (months)	
Median (min; max)	21.7 (8; 151)
Stage at initial diagnosis, n (%)	
n (missing)	25 (4)
IA/B-IIA/B	2 (6.9)
IIIA/B/C	0
IV	23 (79.3)
Stage at screening, n (%)	
IV	29 (100)
Metastatic disease sites at baseline, n (%)	
Yes	29 (100)
Number of metastatic disease sites at baseline	
Median (min; max)	2.0 (1; 8)
Time since diagnosis of metastatic disease (months)	
Median (min; max)	19.40 (1.7; 82.7)

Notes: Summary statistics for number of metastatic disease sites are based on patients with at least 1 metastatic site at baseline. Time since initial diagnosis: time from initial diagnosis of cancer to date of screening visit. Time since metastatic disease: time from diagnosis of metastatic disease to date of screening visit.

[1] Includes 1 patient with histology reported as 'other: ductal adenocarcinoma'.

Source: eNRGy CSR Table 23

The Applicant's Position:

For NRG1+ NSCLC patients, all but 2 patients (97.3%) had adenocarcinoma histology, including 11 patients (14.7%) with IMA. Most patients had advanced/metastatic disease at diagnosis (61 patients [81.3%]), with a median time since diagnosis of 11.8 months (range 1-149). Metastatic disease at baseline was reported in 72 patients (96.0%), and 3 patients had locally advanced disease.

Most NRG1+ PDAC patients had advanced/metastatic disease at diagnosis (23 patients [79.3%]), with a median time since diagnosis of 21.7 months (range 8-151). All 29 patients (100%) had metastatic disease at baseline (stage IV).

Overall, the baseline disease characteristics were as expected for the subject population enrolled per protocol for the eNRGy study. The baseline disease characteristics were generally representative for patients with advanced/metastatic NSCLC or advanced/metastatic PDAC populations with no alternative treatment options.

Table 24. Applicant – eNRGy study: Prior systemic anticancer therapy (NRG1+ NSCLC Primary Efficacy Set)

	Previously-treated (N=64)	All NRG1+ NSCLC Patients (N=75)
Prior systemic therapy, n (%)	64 (100)	64 (85.3)
Number of regimens of prior systemic therapy		
Median (min, max)	2.0 (1, 6)	1.0 (0, 6)
Agent type, n (%)		
Chemotherapy	61 (95.3)	61 (81.3)
Immunotherapy[1]	41 (64.1)	41 (54.7)
Targeted therapy	17 (26.6)	17 (22.7)
Anti-VEGF therapy	10 (15.6)	10 (13.3)
Afatinib	7 (10.9)	7 (9.3)
Other targeted therapy[2]	2 (3.1)	2 (2.7)
Other therapy – investigational agent	6 (9.4)	6 (8.0)
Number of regimens in metastatic setting		
Median (min, max)	1.0 (0, 4)	1.0 (0, 4)
Setting at last treatment, n (%)		
Metastatic	58 (90.6)	58 (77.3)
Adjuvant	6 (9.4)	6 (8.0)
Best response at last treatment, n (%)		
Complete response	2 (3.1)	2 (2.7)
Partial response	16 (25.0)	16 (21.3)
Stable disease	14 (21.9)	14 (18.7)
Progressive disease	21 (32.8)	21 (28.0)
Not evaluable	2 (3.1)	2 (2.7)
Not applicable	1 (1.6)	1 (1.3)
Unknown	8 (12.5)	8 (10.7)
Reason for discontinuation of last treatment, n (%)		
Relapse/progressive disease	45 (70.3)	45 (60.0)
Completed scheduled cycles of treatment	21 (32.8)	21 (28.0)
Toxicity	7 (10.9)	7 (9.3)
Unknown	3 (4.7)	3 (4.0)
Other	3 (4.7)	3 (4.0)

Notes: A patient could be counted in more than 1 category of reason for discontinuation of last treatment.
[1] *All but 1 patient received an anti-PD-(L)1 inhibitor.*
[2] *Other targeted therapies include 2 patients who received a tyrosine kinase inhibitor.*
Source: eNRGy CSR Table 14.1.3.9.1, Listing 16.2.4.7, and Section 11.4.2.3

Table 25. Applicant – eNRGy study: Prior systemic anticancer therapy (NRG1+ PDAC Primary Efficacy Set)

	NRG1+ PDAC (N=29)
Prior systemic therapy, n (%)	28 (96.6)
Number of regimens of prior systemic therapy	
Median (min; max)	2.0 (0; 5)
Number of regimens, n (%)	
0	1 (3.4)[1]
1	7 (24.1)
2	10 (34.5)
3	6 (20.7)
4	4 (13.8)
5	1 (3.4)
Treatment type, n (%)	
Chemotherapy	28 (96.6)
Immunotherapy	3 (10.3)
Targeted therapy	4 (13.8)
Afatinib	1 (3.4)
Other targeted therapy[2]	4 (13.8)
Other therapy – investigational agent	6 (20.7)
Number of regimens in metastatic setting	
Median (min; max)	2.0 (0; 5)
Number of regimens in metastatic setting, n (%)	
0	3 (10.3)
1	7 (24.1)
2	10 (34.5)
3	4 (13.8)
4	4 (13.8)
5	1 (3.4)

[1] *One 28-year-old patient diagnosed with stage IB disease, with metastatic disease reported 20.3 months prior to study entry, was treatment-naïve.*
[2] *Tyrosine kinase inhibitor (1 patient), PARP inhibitor (2 patients) and ADC (1 patient).*
Source: eNRGy CSR Table 25

The Applicant's Position:

Of the 75 NRG1+ NSCLC patients in the PES, 64 (85.3%) had received prior systemic therapy, 6 of whom only received therapy in the adjuvant or neoadjuvant setting. Patients had received a median of 1.0 line (range 0-6) of prior systemic therapy. A total of 58 patients (77.3%) had prior therapy in the metastatic setting, with a median of 1.0 line (range 0-4), and 21 patients (28.0%) had received ≥2 prior lines in the metastatic setting.

Of the 29 NRG1+ PDAC patients in the PES, 28 (96.6%) had received prior systemic therapy, 2 of whom only received therapy in the adjuvant or neoadjuvant setting. One patient was treatment-naïve. Patients had received a median of 2.0 lines (range 0-5) of prior systemic therapy. Twenty-six patients (89.7%) had received prior therapy in the metastatic setting, with a median of 2.0 lines (range 0-5), and 19 patients (65.5%) had received ≥2 prior lines in the metastatic setting.

The FDA's Assessment:

FDA concurs with the Applicant's analysis. Per FDA analysis of the primary efficacy dataset, 36 (56%) of previously-treated patients with NRG1+ NSCLC received both prior chemotherapy and immunotherapy; 95% received prior platinum-based chemotherapy and 64% received prior immunotherapy 29/30 patients with NRG1+ PDAC received prior therapy; 22/29 patients (76%) received prior gemcitabine and taxane-based therapy, 24/29 patients (83%) received prior FOLFIRINOX and 17/29 patients (59%) received prior therapy with both FOLFIRINOX and gemcitabine+taxane. One patient (MCLA-128-CL01 (b) (6)) did not receive any prior chemotherapy. The updated cancer history table for PDAC patient population is shown below (Table 24).

Table 26. FDA Analysis on Cancer History for PDAC Patient Population in eNRGy study.

	NRG1+ PDAC (N=30)
Histologic diagnosis, n (%)	
Adenocarcinoma	29 (97)
Other	1 (3.3)
Prior systemic therapy, n (%)	29 (97)
Number of regimens of prior systemic therapy	
Median (min; max)	2.0 (0; 5)
Treatment type, n (%)	
Chemotherapy	29 (97)
Immunotherapy	3 (10)
Targeted therapy	4 (13)
Other therapy – investigational agent	6 (20)

Source: FDA-generated table based on data sets adbs.xpt, adrs.xpt and adtte.xpt.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data and Applicant's Position:

Treatment Compliance: Treatment was administered as an IV infusion in a hospital setting and compliance was recorded by qualified personnel under the supervision of the investigator or a

designee in terms of the infusion administration. Subjects in the primary efficacy population were dosed consistent with the intended RP2D regimen: 750 mg IV Q2W.

At the data cutoff date, median duration of exposure in NRG1+ NSCLC patients was 5.75 months (range 0.1-36.2), with 47 patients (47.5%) receiving >6 months of treatment. Median duration of exposure in NRG1+ PDAC patients was 7.16 months (range 0.5-34.3) which was higher than for the overall population, with 20 patients (51.3%) receiving >6 months of treatment. Median relative dose intensity for NRG1+ NSCLC and NRG1+ PDAC populations was equivalent to that of the all NRG1+ tumor types population.

Concomitant Medications: Any medication considered necessary for the patient's safety and wellbeing could be given at the discretion of the investigator(s). However, other anticancer medications and other IMPs (except COVID-19 vaccinations) were prohibited.

Systemic corticosteroids were permitted and were part of the mandatory premedication regimen prior to each zenocutuzumab administration. In the event of hypersensitivity or IRRs, corticosteroids could be used as clinically indicated. Patients who were receiving treatment with corticosteroids due to chronic diseases at the time of study enrollment could continue to receive this treatment if the dose remained stable at the pre-enrollment level.

In cases of anemia requiring blood transfusion, transfusions with packed red blood cells could be administered. Concurrent radiation treatment was permitted during the study for symptom control.

In the eNRGy study safety analysis set of 175 patients, most patients received premedication (98.3%). The most frequently reported therapeutic classes of medications were analgesics (96%), antihistamines for systemic use (95.4%), and corticosteroids for systemic use (90.9%).

Rescue Medication Use: Not applicable.

The FDA's Assessment:

FDA agrees with the Applicant's description of treatment compliance, concomitant medications, and rescue medication use. The review team notes that corticosteroids were only mandatory prior to Day 1 Cycle 1 for patients receiving the bi-weekly regimen, and could be used for subsequent injections per the investigator's discretion.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:

The primary objective and key secondary objective of the eNRGy study were assessment of ORR and DOR by investigator, respectively, per protocol and SAP. As discussed with the FDA at the, BICR assessment of ORR and DOR are presented for regulatory review (i.e., marketing application review) and presented below.

Efficacy data are presented using the data cutoff date of 31 Jul 2023 for the following patient populations and documented in the study SAP prior to database lock: NRG1+ NSCLC, NRG1+ PDAC, and data for NRG1+ NSCLC patients are presented in prior therapy subsets.

All efficacy analyses were performed in the Primary Efficacy Set (PES) composed of 129 patients (73.7% of treated patients), which excluded 46 patients (26.3%) from the Safety Analysis Set (24 NRG1+ NSCLC and 10 NRG1+ PDAC); 32 of the 46 were excluded due to receiving the first dose of study treatment <24 weeks prior to the data cutoff date, which was considered the primary reason for exclusion from the PES.

NRG1 Fusion-Positive NSCLC

All 75 patients in the NSCLC PES were assessed for response by BICR and the ORR was 33.3% (95% CI: 22.9, 45.2). The ORR was comparable for the 64 previously-treated patients (32.8%; 95% CI: 21.6, 45.7) and the 11 treatment-naïve patients (36.4%; 95% CI: 10.9, 69.2). One previously-treated patient (1.3%) of the 75 patients with NRG1+ NSCLC in the NSCLC PES had a confirmed CR. Confirmed PR was achieved by 24 of 75 patients (32.0%) including 20 previously-treated and 4 treatment-naïve patients. The posterior probability of the true ORR to exceed 20% was above 97.5%, qualifying for the protocol predefined success criteria of outstanding activity, in both previously treated NRG1+ NSCLC and all NRG1+ NSCLC patients (Table 21).

Table 27. Applicant – eNRGy study: Overall response rate per RECIST 1.1 by BICR (NSCLC Primary Efficacy Set)

	Previously-treated (N=64)	Treatment-naive (N=11)	All NRG1+ NSCLC patients (N=75)
Patients with measurable disease at baseline, n (%)	62 (96.9)	11 (100)	73 (97.3)
Patients with non-measurable disease at baseline[1], n (%)	2 (3.1)	0	2 (2.7)
Number of patients assessed for response by BICR	64	11	75
Overall response rate (CR or PR)[2], n (%)	**21 (32.8)**	**4 (36.4)**	**25 (33.3)**
95% CI	21.6; 45.7	10.9; 69.2	22.9; 45.2
Best overall response[2], n (%)			
Complete response (CR)	1 (1.6)	0	1 (1.3)
Partial response (PR)	20 (31.3)	4 (36.4)	24 (32.0)
Stable disease (SD)	27 (42.2)	4 (36.4)	31 (41.3)
Non-CR/non-PD	1 (1.6)	0	1 (1.3)
Progressive disease (PD)	11 (17.2)	1 (9.1)	12 (16.0)
Not evaluable (NE)	4 (6.3)	2 (18.2)	6 (8.0)

CR: at least 2 determinations of CR at least 4 weeks apart before progression. PR: at least 2 determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR). SD: at least 1 SD assessment (or better) >6 weeks after start of treatment (and not qualifying for CR or PR). PD: progression after start of treatment (and not qualifying for CR, PR, or SD). NE: all other cases, also including early disease progression.
CBR: proportion of patients in whom a CR or PR is observed, or SD of a minimum duration of 24 weeks. Confidence intervals are calculated using the exact (Clopper-Pearson) formula.

[1] *Percentages are based on number of patients assessed for response (patients were excluded from the assessment for response if they had non-measurable disease by investigator as well as BICR). Overall, no patient was assessed as non-measurable by both investigator and BICR. No patients were excluded from BICR ORR analysis based on measurability.*

[2] *Percentages are based on number of patients assessed for response.*

Source: Module 2.7.3 Table 8

The median DOR for the 25 NRG1+ NSCLC patients with a confirmed response was 9.2 months (95% CI: 5.5, not calculable), ranging from 1.8 to 24.0 months. The Kaplan-Meier estimate of DOR at 6 months was 66.6% (95% CI: 42.2, 82.6) and at 12 months was 41.5% (95% CI: 18.9, 62.9) (Table 24).

The median DOR for the 21 previously-treated NRG1+ NSCLC patients with a confirmed response was 7.4 months (95% CI: 4.0, 16.6), ranging from 1.8 to 20.8 months. The Kaplan-Meier estimate of DOR at 6 months was 60.0% (95% CI: 33.7, 78.7) and at 12 months was 30.0% (95% CI: 9.8, 53.6) (Table 24).

Median DOR for the 4 treatment-naïve NRG1+ NSCLC patients with a confirmed response was not reached, ranging from 3.7 to 24.0 months. The Kaplan-Meier estimate of DOR at 6 and 12 months was 100% (Table 24).

Table 28. Applicant – eNRGy study: Duration of response per BICR (NSCLC Primary Efficacy Set)

	Previously-treated (N=64)	Treatment-naive (N=11)	All NRG1+ NSCLC patients (N=75)
Number of patients with a BOR of confirmed CR or PR[1]	21	4	25
Duration of response (months)			
Event, n (%)	12 (57.1)	1 (25.0)	13 (52.0)
Censored, n (%)	9 (42.9)	3 (75.0)	12 (48.0)
Kaplan-Meier estimates (months)			
Median (95% CI)	7.4 (4.0; 16.6)	NC (13.4; NC)	9.2 (5.5; NC)
Min; Max	1.8; 20.8	3.7; 24.0	1.8; 24.0
Kaplan-Meier probability estimates (95% CI)			
6 months	60.0 (33.7; 78.7)	100.0 (100.0; 100.0)	66.6 (42.2; 82.6)
12 months	30.0 (9.8; 53.6)	100.0 (100.0; 100.0)	41.5 (18.9; 62.9)

[1] *Percentages are based on number of patients with BOR of confirmed CR or PR.*

Note: Duration of response is the time from the date of the first documented response (CR or PR) to the date of first documented progression, or death due to study indication.

NC = not calculable

Source: eNRGy CSR Table 14.2.2.27

All 29 patients in the PDAC PES were assessed for response per BICR and the ORR was 41.4% (95% CI: 23.5, 61.1). One patient (3.4%) had a confirmed CR and 11 patients (37.9%) had a confirmed PR. The posterior probability of the true ORR exceeding 20% was above 97.5%, qualifying for outstanding activity in NRG1+ PDAC patients (Table 23).

Table 29. Applicant – eNRGy study: Overall response rate per RECIST 1.1 by BICR (PDAC Primary Efficacy Set)

	NRG1+ PDAC N=29
Patients with measurable disease at baseline, n (%)	29 (100)
Overall response rate (CR or PR), n (%)[1,2]	12 (41.4)
95% CI	23.5; 61.1
Best overall response, n (%)[1,2]	
Complete response	1 (3.4)
Partial response	11 (37.9)
Stable disease	11 (37.9)
Non-CR/non-PD	0
Progressive disease	5 (17.2)
Not evaluable	1 (3.4)

Note: Confidence intervals were calculated using the exact (Clopper-Pearson) formula.

[1] For investigator assessment, percentages are based on number of patients with measurable disease at baseline by investigator. For BICR, percentages are based on number of patients assessed for response (patients were excluded from the assessment for response if they had non-measurable disease by investigator as well as central assessment).

[2] BOR and ORR are summarized for patients with confirmed CR or PR.

Source: Module 2.7.3 Table 8

The median DOR in the 12 NRG1+ PDAC patients with a confirmed response was 16.6 months (95% CI: 3.7, not calculable [NC]), ranging from 3.7 to 16.6 months. The Kaplan-Meier estimate of DOR at 6 months was 74.1% (95% CI: 39.1, 90.9) and at 12 months was 50.8% (95% CI: 17.8, 76.6) (Table 24).

Table 30. Applicant – eNRGy study: Duration of response per BICR (PDAC Primary Efficacy Set)

	NRG1+ PDAC N=29
Number of patients with a BOR of confirmed CR or PR	12
Duration of response[1] (months)	
Event, n (%)	6 (50.0)

	NRG1+ PDAC N=29
Censored, n (%)	6 (50.0)
Kaplan-Meier estimates (months)	
Median (95% CI)	16.6 (3.7; NC)
Min; Max	3.7; 16.6
Kaplan-Meier probability estimates (95% CI)	
6 months	74.1 (39.1; 90.9)
12 months	50.8 (17.8; 76.6)

Note: Duration of response is the time from the date of the first documented response (CR or PR) to the date of first documented progression, or death due to study indication.
[1] Calculations are based on number of patients with BOR of confirmed CR or PR.
NC = not calculable
Source: Module 2.7.3 Table 9

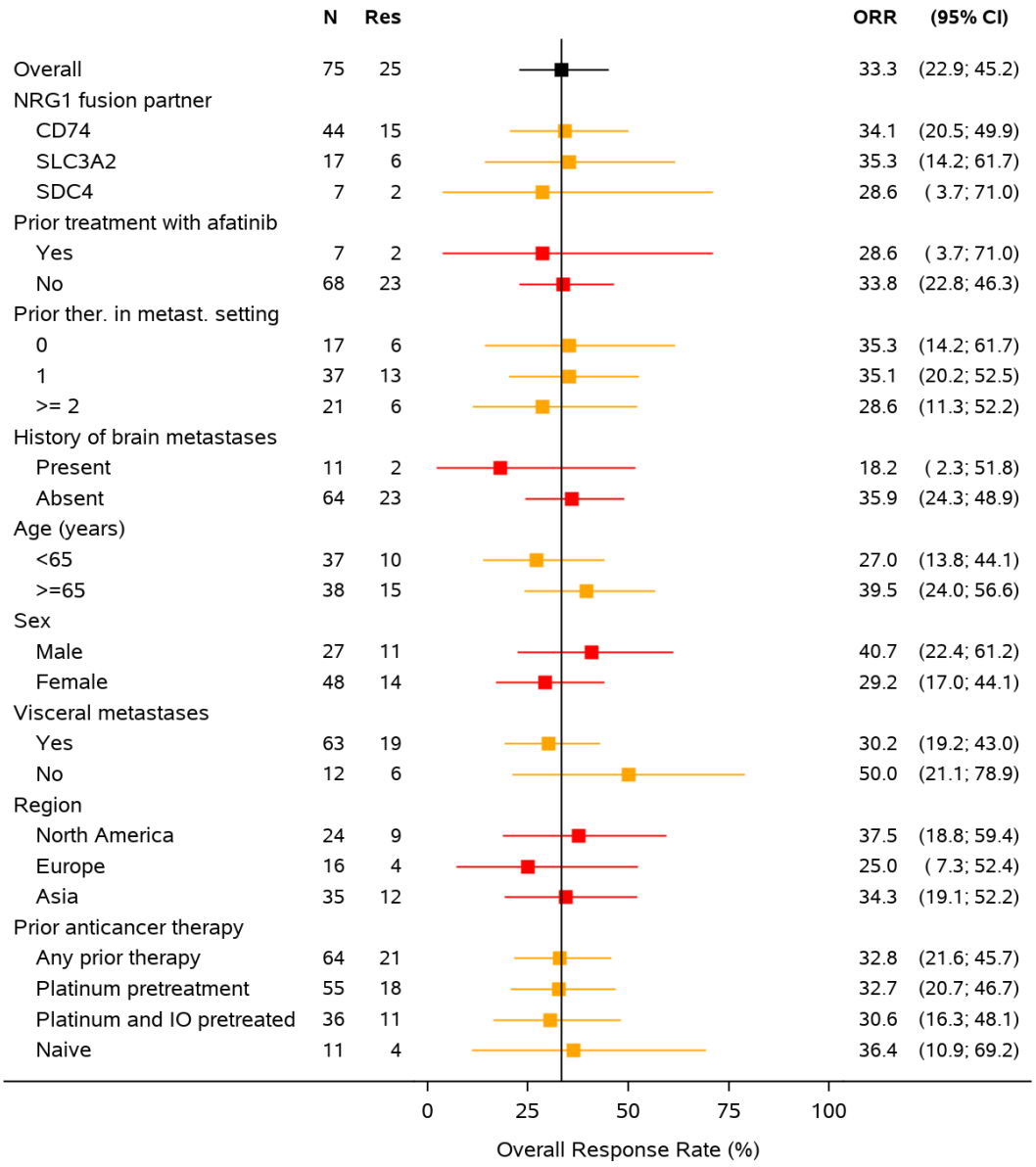
Effects in Subpopulations:

Analyses of ORR were performed for predefined subgroups of interest in the eNRGy study, as defined in the eNRGy SAP v4.0, 20 Sep 2023.

***NRG1* Fusion-Positive NSCLC**

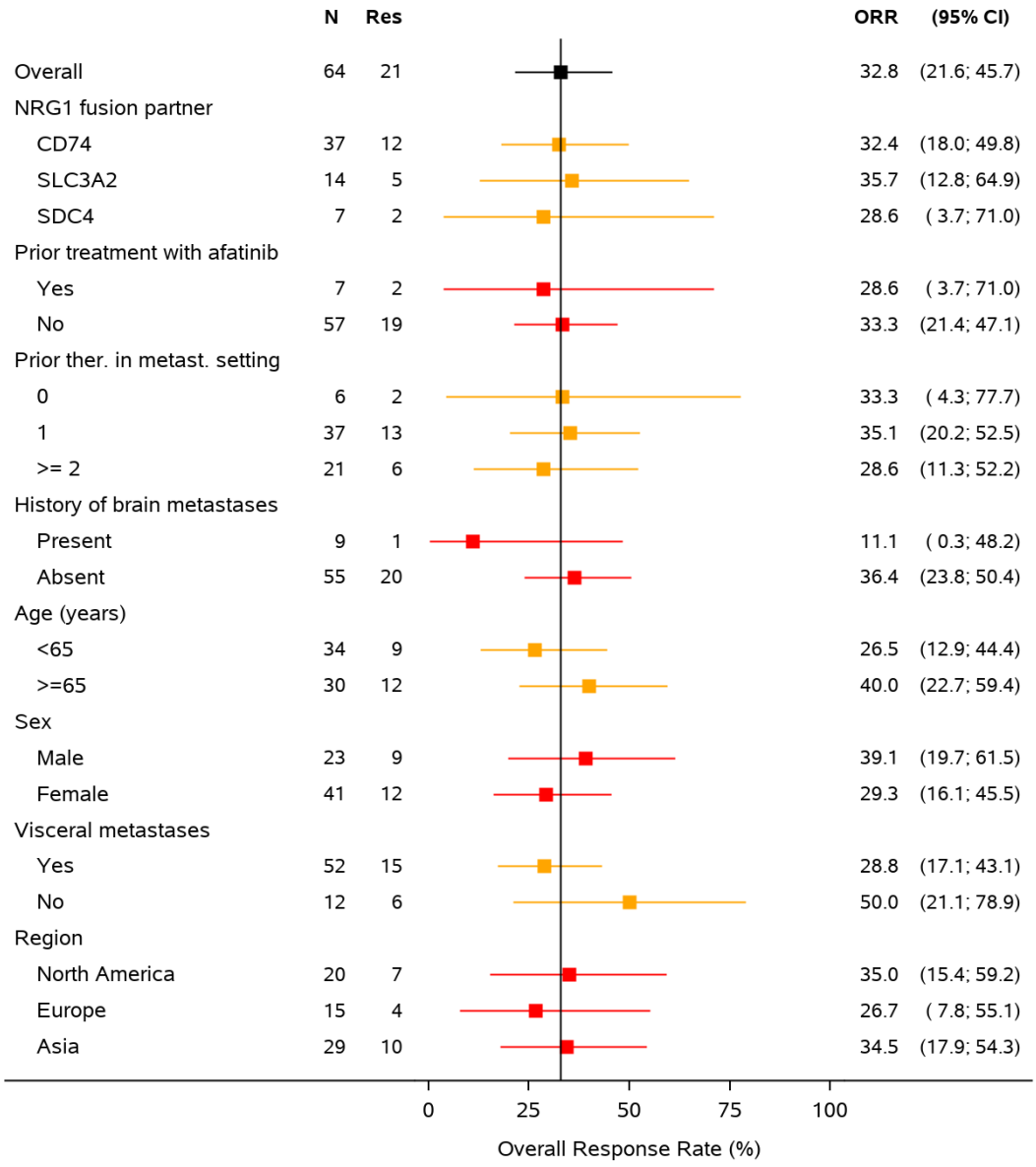
Forest plots showing ORR in subgroups of interest are provided in Figure 12 and Figure 13 in the NSCLC PES and the previously-treated NSCLC PES, respectively.

Figure 12. Applicant – eNRGy study: Forest plot of subgroup analysis of overall response rate per RECIST 1.1 by BICR (NSCLC Primary Efficacy Set)



Note 1: N =Number of patients with measurable disease at baseline; Res = Number of responders.
Note 2: Only fusion partners identified in ≥5 patients in the NSCLC PES were analyzed.
IO = immunotherapy; Ther = therapy.
Source: eNRGy CSR Figure 14.2.2.6

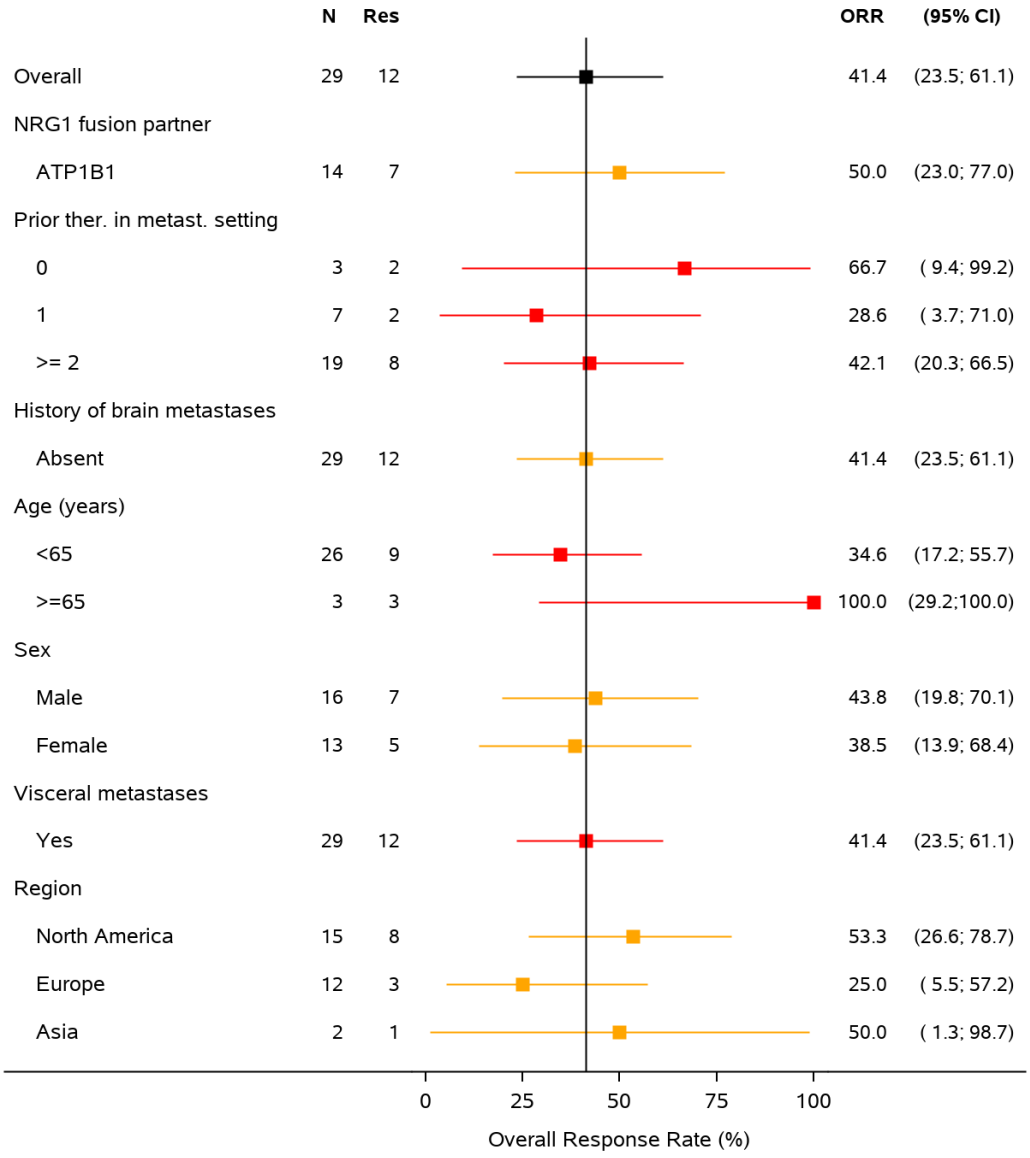
Figure 13. Applicant – eNRGy study: Forest plot of subgroup analysis of overall response rate per RECIST 1.1 by BICR (Previously-treated NSCLC Primary Efficacy Set)



Note 1: N =Number of patients with measurable disease at baseline; Res = Number of responders.
Note 2: Only fusion partners identified in ≥5 patients in the NSCLC PES were analyzed.
Ther = therapy.
Source: eNRGy CSR Figure 14.2.2.6.1

Results of the predefined subgroup analyses of ORR per RECIST 1.1 in NRG1+ PDAC patients per BICR in the PES are presented in Figure 14; all 3 patients ≥65 years of age responded and the ORR in the 19 patients with ≥2 lines of prior therapy in the metastatic setting was 42.1% (95% CI: 20.3, 66.5).

Figure 14. Applicant - eNRGy study: Forest plot of subgroup analysis of overall response rate per RECIST 1.1 by BICR (PDAC Primary Efficacy Set)



Note 1: N =Number of patients with measurable disease at baseline; Res = Number of responders.
Note 2: Only fusion partners identified in ≥5 patients in the PDAC PES were analyzed.
Ther = therapy.
Source: eNRGy Figure 14.2.2.7

The Applicant's Position:

Zenocutuzumab is the first NRG1-directed therapy to demonstrate robust antitumor activity in patients with NRG1+ NSCLC and NRG1+ PDAC. High response rates with durability have been observed, substantially exceeding standard-of-care in a population with significant unmet medical need.

In the eNRGy study, 2 patients with NRG1+ NSCLC demonstrated extended DORs. One previously-treated patient, who achieved CR, had a DOR of 20.8 months, and was censored at the data cutoff date. Another patient who previously received both prior platinum and prior immunotherapy, who achieved PR, had a DOR of 20.3 months and was also censored for the analysis (eNRGy CSR Listing 16.2.6.4). Two patients with NRG1+ PDAC demonstrated extended DORs. One patient who achieved PR had a DOR of 16.6 months. Another patient who achieved CR had a DOR of 15.2 months and was censored at the data cutoff date (eNRGy CSR Listing 16.2.6.4).

Efficacy is consistent across multiple subsets of NSCLC, including patients who have received prior systemic therapy (mainly platinum-based chemotherapy with or without immunotherapy) and patients who are treatment-naïve. These results demonstrate the high clinical efficacy of zenocutuzumab in NRG1+ NSCLC.

Considering the rarity of the patient population and the biological plausibility of NRG1+ cancer as a unique disease entity with an actionable genetic alteration, the totality of efficacy results, including ORR and DOR from the NRG1+ NSCLC population, would be adequate to support the efficacy review of zenocutuzumab in patients with NGR1+ PDAC. These results demonstrate the high clinical efficacy of zenocutuzumab in NRG1+ PDAC.

The FDA's Assessment:

As described earlier, the primary efficacy analysis was limited to previously treated NSCLC (N = 64) and PDAC patient population (N = 30), respectively.

NSCLC

In general, FDA agrees with the Applicant's analyses of ORR by BICR for the previously treated NSCLC population. FDA does not agree with the Kaplan-Meier based estimate to summarize the proportion of responders with at least 6 months of DOR as it is unstable. Based on the observed DOR, the proportion of responders with at least 6 months of DOR in previously treated NSCLC is 43%.

FDA notes that the observed ORR in the 11 patients with NSCLC who had not received prior anti-cancer therapy was 36% (95% CI: 11%, 69%), similar to the ORR of 33% (95% CI: 22%, 46%) in the 64 previously-treated NSCLC patients. Given the small number of treatment-naïve patients with NSCLC, the point estimate of the ORR is associated with considerable uncertainty and should be interpreted with caution. Furthermore, both the point estimate of ORR and the lower bound of the 95% confidence interval (11%) is substantially lower than response rates reported with available first-line therapies for NSCLC, which range from 48-58% (Pembrolizumab USPI).

FDA also evaluated subgroup analyses by histology (Table 29) and types of prior treatment (Table 30). The results of ORR in different subgroups are consistent with the primary analysis result of ORR in the previously-treated NSCLS patient population.

Table 31. Subgroup Analyses by Histology in Previously-treated NSCLC (N = 64) in eNRGy study

BICR-Assessed	**Adenocarcinoma (N=52)**	**Non-Adenocarcinoma* (N=12)**
Best overall response, n (%)		
CR	1 (1.9)	0
PR	14 (27)	6 (50)
ORR (CR + PR), n (%)	15 (29)	6 (50)
95% CI	17, 43	21, 79
Duration of response (months)	**N = 15**	**N = 6**
Median (95% CI)	7.4 (3.7, NE)	5.6 (3.7, NE)
Min, Max	1.9^{+}, 24.0^{+}	1.8^{+}, 16.6

Source: FDA-generated table based on data sets adbs.xpt, adrs.xpt and adtte.xpt.
CI: confidence interval, NE: not evaluable, +: censored
* Non-adenocarcinoma histology includes invasive mucinous adenocarcinoma (n=11), squamous cell carcinoma (n=1)

Table 32. Subgroup Analyses by Prior Therapy Type in Previously-treated NSCLC (N = 64) in eNRGy Study

BICR-Assessed	Chemotherapy (N=61)*	Immunotherapy (N=41)	Chemotherapy and Immunotherapy (n=39)	Treatments excluding Immunotherapy (N=23)	Target therapy (N=17)	Treatments excluding target therapy (N=47)
Best overall response, n (%)						
CR	1 (1.6)	0	0	1 (4.3)	0	1 (2.1)
PR	19 (31)	13 (32)	12 (31)	7 (30)	4 (24)	16 (34)
ORR (CR + PR), n (%)	20 (33)	13 (32)	12 (31)	8 (35)	4 (24)	17 (36)
95% CI	21, 46	18, 48	17, 48	16, 57	7, 50	23, 51
Duration of response (months)	**N = 20**	**N = 13**	**N = 12**	**N = 8**	**N = 4**	**N = 17**
Median (95% CI)	7.4 (4.0, 16.6)	5.6 (3.7, 16.6)	7.4 (3.7, 16.6)	7.4 (5.5, NE)	4.0 (3.7, NE)	7.4 (3.7, 16.6)
Min, Max	1.8^{+}, 20.8^{+}	1.9^{+}, 20.3^{+}	1.9^{+}, 20.3^{+}	1.8^{+}, 20.8^{+}	1.8^{+}, 5.5^{+}	1.9^{+}, 20.8^{+}

Source: FDA-generated table based on data sets adbs.xpt, adrs.xpt and adtte.xpt.
CI: confidence interval, NE: not evaluable, +: censored
* Three patients had prior systemic anticancer therapy other than chemotherapy, and thus the subgroup analysis in these 3 patients are not presented.

The efficacy analysis by NRG1 Gene Fusion Partner in previously-treated NSCLC patients are summarized in Table 31.

Table 33. Efficacy Results by NRG1 Gene Fusion Partner in NRG1 Fusion-Positive NSCLC Patients the eNRGy Study.

NRG1 Partner1	BIZENGRI (n = 64)	ORR		DOR
		n (%)	95% CI	Range (Months)
CD74	37	12 (32)	(18, 50)	1.8+; 20.3+
SLC3A2	14	5 (36)	(13, 65)	3.6; 20.8+
SDC4	7	2 (29)	(3.7, 71)	7.4; 16.6
CDH1	2	1 (50)	(1.3, 99)	1.9+
FUT10	1	PD	NA	NA
PVALB	1	PD	NA	NA

ST14	1	PD	NA	NA
VAMP2	1	PR	NA	5.6

Source: FDA-generated table based on data sets adbs.xpt, adrs.xpt and adtte.xpt.
[1]Fusion partners identified in this primary analysis set (n=64) may not represent all potential fusion partners.
PR=partial response; PD=progressive disease; NA=not applicable; "+" indicates ongoing response.

PDAC

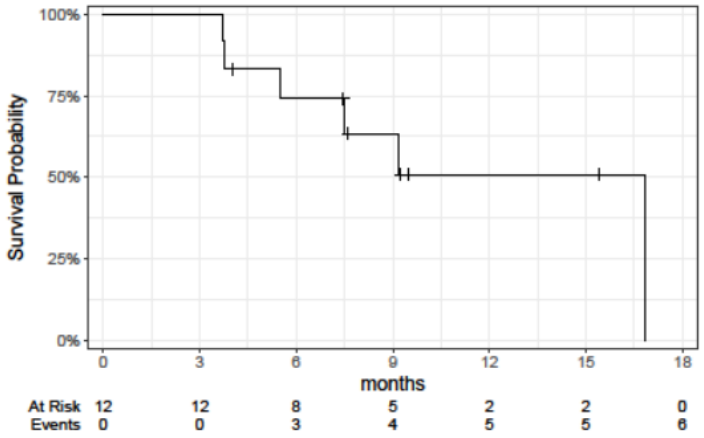
As described in the Section titled "Statistical Analysis Plan and Amendments", one patient was added to the PDAC primary efficacy set, which introduced minor numerical differences between the Applicant's analysis and FDA analysis on ORR and corresponding 95% CI. In addition, FDA does not agree with the estimated median DOR. The median follow-up time for DOR is 9.1 months (95% CI: 3.9, NE) and the estimated median DOR is 16.6 months (95% CI: 3.7, NE), which is driven by one responder with a prolonged observed DOR out of 12 responders (Figure 15). The estimated median DOR may not be accurate, and is thus not reported in the label. Since 29 (97%) patients with PDAC received prior chemotherapy and 29 (97%) had adenocarcinoma histology, subgroup analyses based on types of prior anti-cancer therapy and histology were not conducted. The FDA analysis of ORR and DOR are summarized in Table 34.

Table 34. Efficacy Results for Advanced Unresectable or Metastatic NRG1 Fusion-Positive PDAC population in the eNRGy Study

Efficacy Parameter	BIZENGRI (N = 30)
Overall response rate[1] (95% CI)	40% (23%, 59%)
Complete response rate	3.3%
Partial response rate	37%
Duration of response	N = 12
Range (months)	3.7, 16.6
Patients with DOR ≥6 months[2]	67%

Source: FDA-generated table based on data sets adrs.xpt and adtte.xpt
[1] Confirmed overall response rate assessed by BICR.
[2] Based on observed duration of response

Figure 15. The Estimated Duration of Response for PDAC Patients



Source: FDA-generated figure based on adtte.xpt data set.

FDA's efficacy analyses by NRG1 Gene Fusion Partner in previously treated patients with PDAC are summarized in Table 33.

Table 35. Efficacy Results by NRG1 Gene Fusion Partner in NRG1 Fusion-Positive PDAC Patients the eNRGy Study

***NRG1* Partner**[1]	BIZENGRI (n = 30)	ORR		DOR
		n (%)	95% CI	Range (Months)
ATP1B1	14	7 (50)	(23, 77)	3.7, 16.6
CD44	3	0	(0, 71)	NA
NOTCH2	3	1 (33)	(0.8, 91)	7.4+
SLC4A4	3	2 (67)	(9, 99)	7.5+, 15.2+
AGRN	1	PR	NA	9.1+
APP	1	PR	NA	3.7
CDH1	2	SD, SD	NA	NA
SDC4	1	SD	NA	NA
THBS1	1	PD	NA	NA
VTCN1	1	SD	NA	NA

Source: FDA-generated table based on data sets adbs.xpt, adrs.xpt and adtte.xpt.

[1] Fusion partners identified in this primary analysis set (n=30) may not represent all potential fusion partners.

PR=partial response; PD=progressive disease; SD=stable disease; NA=not applicable; NC=not calculable;"+" indicates ongoing response

Data Quality and Integrity

Data:

There were no issues related to data quality and integrity. The study was performed following GCP and all local regulations, see also Section 8.1.2 Compliance with GCP.

An assigned study site monitor reviewed the progress of the study according to the study Monitoring Plan, to ensure the collection of accurate, reliable and complete data. All CRF data for the eNRGy study were collected using an electronic CRF within a fully validated and Code of Federal Regulations (CFR) 21 Part 11 compliant EDC system, and entered into the CRF by the designated and appropriately trained site staff. Data were source data verified and reviewed by the study site monitor(s) before data cleaning by data management. All queries were raised and resolved within the EDC system.

Predefined project-level quality tolerance limits (QTLs) were established to identify systematic issues that may impact subject safety or integrity of trial results and evaluate any deviations from these limits to determine if action is needed. QTLs were defined in conjunction with the Baseline Risk Assessment and the Critical Data Definition and Critical Process Definition. The QTLs defined for this study are documented in Appendix A of the Risk Management Plan, which is available in the study TMF.

Quality assurance audits were conducted for sites that treated patients in the eNRGy study. Audits were conducted of vendors providing services for the MCLA-128-CL01 study.

The Applicant's Position:

It is the Applicant's position that there are no issues related to data quality and integrity.

The FDA's Assessment:

FDA did not identify quality or integrity issues in the data. The data submitted was organized and adequate to perform a complete review of the efficacy of zenocutuzumab.

Efficacy Results – Secondary and other relevant endpoints

Response analyses by BICR was a secondary endpoint per study protocol and SAP, but presented above as primary efficacy endpoint for regulatory review. This section presents the secondary endpoints of CBR, DCR, TTR, OS, PFS by BICR. Investigator responses are provided within the BLA.

Data:

***NRG1* Fusion-Positive NSCLC**

In the 75 NRG1+ NSCLC patient assessed for response, the CBR at 24 weeks was 58.7% (95% CI: 46.7, 69.9), and the DCR was 76.0% (95% CI: 64.7, 85.1). The CBR and DCR for previously-treated and treatment-naïve patients were similar to those for all NRG1+ NSCLC patients.

Responses occurred early in the treatment course, with a median time to onset of response (TTR) of 1.84 months (range 1.5-9.2) for all NRG1+ NSCLC patients, 1.87 months for previously-treated patients, and 1.79 months for treatment-naïve patients

Median duration of OS follow-up in the PES was 9.63 months (range 0.3-36.2) for all NRG1+ tumor types, 9.23 months (range 0.3-36.2) for NRG1+ NSCLC patients, and 11.40 months (range 1.0-34.3) for NRG1+ PDAC patients.

Analysis of PFS per RECIST 1.1 was performed for the NRG1+ NSCLC prior therapy subsets in the NSCLC PES. Per BICR, median PFS was consistent across the overall NRG1+ NSCLC population (7.3 months [95% CI: 5.5, 9.2]), the platinum pretreated subset (7.2 months [95% CI: 5.5, 9.2]) and the treatment-naïve subset (8.9 months [95% CI: 1.2, not calculable]), and lower in the previously-treated NRG1+ NSCLC (5.7 months [95% CI: 5.5, 9.2]) and the prior platinum/immunotherapy (5.5 months [95% CI: 3.0, 9.2]) subsets (eNRGy CSR Section 11.5.1.4.1).

Analysis of OS was performed for the NRG1+ NSCLC prior therapy subsets of the NSCLC PES. Median OS was not reached for any of the prior therapy subsets other than treatment-naïve patients who had a median OS of 9.2 months (95% CI: 2.5, not calculable).

***NRG1* Fusion-Positive PDAC**

In the 29 NRG1+ PDAC patients assessed for response, the CBR at 24 weeks was 65.5% (95% CI: 45.7, 82.1), and the DCR was 79.3% (95% CI: 60.3, 92.0). All 12 responders had received prior FOLFIRINOX and/or gemcitabine/taxed-based therapy, including 6 patients who had received both regimens.

Responses occurred early in the treatment course, with a median TTR of 1.84 months (range 1.6 7.1) in the NRG1+ PDAC patients.

Per BICR, the median PFS was 7.4 months (95% CI: 3.7, 11.0) for NRG1+ PDAC patients. The Kaplan-Meier estimate of PFS at 6 months was 55.2% (95% CI: 35.6, 71.0).

At the data cutoff date, 11 of the 29 NRG1+ PDAC patients (37.9%) in the PDAC PES had died and the median OS was 20.5 months (95% CI: 13.0, not calculable). The Kaplan-Meier estimate of OS at 6 months was 93.1% (95% CI: 75.1, 98.2), at 12 months was 79.7% (95% CI: 57.3, 91.1), and at 24 months was 37.9% (95% CI: 12.1, 64.1).

The Applicant's Position:

Secondary efficacy endpoints included CBR, TTR, PFS and OS per investigator and BICR (presented above for BICR). The clinical activity demonstrated by a CBR at 24 weeks of 58.7% for the NRG1+ NSCLC patients, and a CBR at 24 weeks of 65.5% for the NRG1+ PDAC patients, contributed to the median PFS of 7.3 months (BICR) for the NRG1+ NSCLC, and a median PFS of 7.4 months (BICR) for the NRG1+ PDAC patients respectively. This corroborates the clinical

relevance of zenocutuzumab as an effective treatment option in this rare patient population for which limited viable therapies are available.

The FDA's Assessment:
FDA does not consider analyses for time-to-event endpoints to be interpretable in a single arm study. These analyses were considered descriptive in nature and were not verified by FDA.

Dose/Dose Response

The Applicant's Position:

The RP2D for zenocutuzumab was established based on the totality of PK, PD, safety, and efficacy data obtained in the dose escalation (Part 1) and dose expansion (part 2) phases of the MCLA-128-CL01 study. Pharmacokinetic and PD data, including population PK, exposure responses and exposure-efficacy analyses are described and summarized in Sections 6.2.1, 6.2.2.1, 6.3.1 and 6.3.2.1.

The FDA's Assessment:

FDA agrees with the Applicant's position. See Section 6 for FDA's assessment of clinical pharmacology related analyses.

Durability of Response

Data:

The duration of response data are presented as primary endpoint in Section 8.1.2 Efficacy Results.

The Applicant's Position:

See Applicant's Position presented in Section 8.1.2 Efficacy Results.

The FDA's Assessment:

See Section 8.1.2 for FDA's assessments on duration of response.

Persistence of Effect

The Applicant's Position:

As with the use of other anticancer therapies for advanced or metastatic solid tumors, zenocutuzumab monotherapy was administered to patients enrolled in the eNRGy study until

clinical or radiographic disease progression was observed. The zenocutuzumab monotherapy data currently available do not allow meaningful analysis of persistence of effect after drug discontinuation.

The FDA's Assessment:

FDA agrees with the Applicant's position.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Data and Applicant's Position:

No patient reported outcome data was collected.

The FDA's Assessment:

FDA agrees with the Applicant's position.

Additional Analyses Conducted on the Individual Trial

Data and The Applicant's Position:

Supportive Efficacy Analyses

Supportive Efficacy Set (SES): all NRG1+ cancer patients who received ≥1 infusion of study treatment at 750 mg Q2W, had a documented functional NRG1 fusion based on an NGS test, absence of other known driver mutations, had not been exposed to anti-HER3 targeting antibodies, and had ≥1 post-baseline tumor assessment or early discontinuation due to disease progression (including death due to underlying disease) or toxicity.

All 149 patients with NRG1+ cancer in the SES underwent BICR. Patients with non-measurable disease per BICR and per investigator assessment were excluded from the antitumor assessment; 1 patient was assessed as having non-measurable disease by both BICR and per investigator, and 148 patients were thus included in the analysis of antitumor response per BICR.

Per BICR, ORR for the 148 patients with all NRG1+ tumor types in the SES who were evaluated was 29.1% (95% CI: 21.9, 37.1), and 3 patients (2.0%) had a confirmed CR and 40 patients (27.0%) had a confirmed PR. The CBR at 24 weeks was 50.0% (95% CI: 41.7, 58.3), and the DCR was 73.0% (95% CI: 65.1, 79.9). Median DOR in the 43 patients with a confirmed response was 11.1 months (95% CI: 7.3, 16.6). The ORR in the 87 NRG1+ NSCLC patients in the SES was 29.9% (95% CI: 20.5, 40.6) and was 39.4% (95% CI: 22.9, 57.9) in the 33 NRG1+ PDAC patients.

Exploratory Efficacy Analyses

The metabolic ORR according to PERCIST 1.0 in the 61 NRG1+ all tumor types patients with FDG-positive disease at baseline was 45.9% (95% CI: 33.1, 59.2), and was 40.6% (95% CI: 23.7,

59.4) in the 32 NRG1+ NSCLC patients, and was 76.5% (95% CI: 50.1, 93.2) in the 17 NRG1+ PDAC patients.

Nine of the 27 NRG1+ NSCLC patients (33.3%) in the PES evaluable for changes in carcinoembryonic antigen levels on-treatment had a decrease of ≥50% relative to baseline. Decreases were consistently observed within 2 months after treatment start and were durable.

Nineteen of the 24 NRG1+ PDAC patients (79.2%) in the PES evaluable for changes in carbohydrate antigen 19-9 levels on-treatment had a decrease of ≥50% relative to baseline. Decreases were consistently observed within 2 months after treatment start and were durable.

The FDA's Assessment:

FDA considered the results of the Supportive Efficacy Set (SES) and results per PERCIST 1.0 presented in this section to be exploratory, and therefore did not independently verify the results.

8.1.3. Integrated Review of Effectiveness

The FDA's Assessment:

The efficacy evaluation for this BLA is based on Study MCLA-128-CL01 (eNRGy) investigating zenocutuzumab in patients with NSCLC, PDAC, and other solid tumors harboring an *NRG1* fusion with disease progression on or after prior systemic therapy or who do not have satisfactory alternative treatment options. The primary efficacy population consisted of 64 patients with previously treated NSCLC and 30 patients with PDAC. The confirmed BICR-assessed ORR in the previously-treated NSCLC population (N = 64) was 33% (95% CI: 22, 46) with a median DOR of 7.4 months (95% CI: 4.0, 16.6) for the 21 responders; 43% of responders had a DOR ≥6 months. The confirmed BICR-assessed ORR in the PDAC population was 40% (95% CI: 23, 59). The percentage of responders with a DOR of ≥6 months was 67%, and the percentage of responders with a DOR of ≥12 months was 17%.

Data was also provided for 11 patients with treatment-naïve NSCLC who were not considered part of the primary efficacy population. The ORR in these patients was 36% (95% CI: 11, 70); the median DOR for the 4 responders was not reached (95% CI: 13.4, NE) and the percentage of responders with DOR ≥6 months was 75%.

Overall, FDA review team determined that the results of the eNRGy study support accelerated approval in patients with previously-treated NSCLC and PDAC harboring an *NRG1* fusion. However, given the small number of patients with NSCLC who were treatment-naïve, the point estimate for ORR of 36% with a lower limit of the 95% confidence interval of 11% compared to that observed with currently available therapies for metastatic NSCLC (e.g., platinum-based chemotherapy and a PD-(L)1 inhibitor), the

currently available data does not demonstrate a therapeutic benefit over existing treatments in treatment-naïve patients with NSCLC. (b) (4)

8.1.4. Assessment of Efficacy Across Trials

The Applicant's Position:

Efficacy was assessed based on data from the single, pivotal clinical eNRGy trial presented in Section 8.1.2 of this Assessment Aid. Additional supportive efficacy data from an Early Access Program (EAP) is included in the application.

The FDA's Assessment:

FDA generally agrees with the Applicant's assessment of results in the eNRGy study. The primary endpoint ORR and secondary endpoint DOR demonstrated a clinically meaningful treatment effect in patients with advanced unresectable or metastatic previously-treated NSCLC and PDAC harboring a NRG1 gene fusion. FDA did not independently verify the supportive efficacy results in EAP.

8.1.5. Integrated Assessment of Effectiveness

The Applicant's Position:

As discussed and agreed with the FDA, an integrated analysis of efficacy is not applicable in this application. The primary efficacy data supporting the indication at the proposed dose is based on a single data source: eNRGy study.

The FDA's Assessment:

Refer to Section 8.1.3 Integrated Review of Effectiveness.

8.2. Review of Safety

The Applicant's Position:

The primary data to support the safety of zenocutuzumab in the proposed indications are from the eNRGy study including a total of 175 patients with NRG1+ cancer (all tumor types) who received at least 1 dose of zenocutuzumab 750 mg Q2W, including 99 patients with NRG1+ NSCLC and 39 patients with NRG1+ PDAC (Safety Analysis Set).

Supportive safety results from patients with NRG1+ cancer (all tumor types) enrolled in the EAP (N=15) and treated with zenocutuzumab 750 mg Q2W are likewise summarized in the Application, including results in NRG1+ NSCLC (N=7) and NRG1+ PDAC patients (N=5).

Additional sources of safety data for zenocutuzumab (not in the proposed indications or at the proposed monotherapy dose [i.e., including combination therapy]) are provided in the Application from the following studies:

- Adverse events (AEs) observed at monotherapy doses other than 750 mg Q2W, which were evaluated in non-NRG1+ cancer patients in the MCLA-128-CL01 study, including 28 patients treated across 9 zenocutuzumab dose levels (40 to 900 mg Q3W), 101 patients treated with zenocutuzumab 750 mg Q3W, and 26 patients treated with the Q1W regimen (MCLA-128-CL01 CSR1), are summarized by dose level and regimen.
- Eight non-NRG1+ cancer patients with a HER3 mutation were treated with zenocutuzumab 750 mg Q2W monotherapy in a non-NRG1+ EAP.
- Safety of zenocutuzumab administered in combination with other anticancer treatments is summarized based on results from the MCLA-128-CL02 study, which evaluated zenocutuzumab 750 mg Q3W combined with trastuzumab ± vinorelbine or combined with endocrine therapy in non-NRG1+ metastatic breast cancer patients with HER2 overexpression or estrogen receptor (ER) positive/low HER2 expression, respectively.

Data from the eNRGy study and EAP were not pooled and an integrated safety analysis is not required for this BLA, as the primary safety data for the proposed dose in the target patient populations are from a single study (eNRGy).

As agreed with the FDA, the safety profile of zenocutuzumab 750 mg IV Q2W in the NRG1+ NSCLC and NRG1+ PDAC populations is consistent with that of all NRG1+ cancer patients (all tumor types) with respect to the type, frequency, and severity of AEs, SAEs, and AEs leading to dose modification or treatment discontinuation. No indication-specific safety signals were apparent across NRG1+ cancer populations. As discussed and agreed with FDA, the overall safety data from all NRG1+ cancer patients (all tumor types) who received zenocutuzumab 750 mg Q2W are included in this Assessment Aid to provide a comprehensive review of zenocutuzumab safety in this initial application.

The FDA's Assessment:

FDA agrees that the safety data for this BLA was derived from patients from the eNRGy study (N=175) with NRG1+ cancer (all tumor types) who received at least 1 dose of zenocutuzumab

750 mg Q2W. FDA also agrees with not pooling safety data from the eNRGy study and EAP because methods for collecting and characterizing data from each of these studies are not similar enough to pool (e.g. different schedules for collection, different rules for reporting etc.). The FDA's analyses and assessment of safety for the eNRGy study are based on the data from the July 31, 2023, data cutoff. Additional information from FDA's review of the 90-day safety update with data cutoff date January 31, 2024, is included in relevant sections.

FDA does not agree that no indication-specific safety signals were apparent across NRG1+ cancer populations. Several adverse events were identified that could potentially be specific to underlying histology of NSCLC or PDAC as described in Section 8.2.2.; for this reason, the USPI contains adverse event tables specific to each population (NSCLC and PDAC). Insufficient number of patients with histologies other than NSCLC and PDAC have been evaluated to adequately assess the safety of zenocutuzumab in these populations.

8.2.1 Safety Review Approach

The Applicant's Position:

The safety evaluation included review of the exposure to zenocutuzumab treatment, AEs of all grades, AEs grade 3-4, SAEs, fatal AEs, AEs leading to treatment discontinuation, dose adjustments, and infusion interruptions.

To optimize the monitoring of AEs and better characterize the zenocutuzumab safety profile, AESIs that are or may potentially be associated with zenocutuzumab treatment were identified, based on the known effects of other HER2 inhibitors. Three AESIs were evaluated: 1) IRRs, 2) decreased cardiac ejection fraction, and 3) diarrhea.

The Safety Analysis Set comprises all NRG1+ cancer patients (all tumor types) who received at least one infusion of zenocutuzumab 750 mg Q2W. Safety subsets of the Safety Analysis Set include:

- NRG1+ NSCLC Safety Analysis Set
    - Previously treated NRG1+ NSCLC Safety Analysis Set
        - NRG1+ NSCLC platinum pretreated Safety Analysis Set
        - NRG1+ NSCLC platinum/immunotherapy pretreated Safety Analysis Set
    - Naïve NRG1+ NSCLC Safety Analysis Set
- NRG1+ PDAC Safety Analysis Set

In addition to the main analyses, assessments of AEs from the eNRGy study were performed in the following subpopulations using the Safety Analysis Set:

- Age (<65 years old, ≥65 years old)
- Sex (male, female)
- Race (White, Asian, Other)
- Geographic region (North America, Europe, Asia)

Additional safety assessments included evaluation of laboratory parameters, vital signs, electrocardiogram (ECG) and other clinical evaluations, including LVEF evaluated by multigated acquisition (MUGA) scan or echocardiogram (ECHO).

The FDA's Assessment:

FDA agrees with the Applicant's description of the safety review approach.

8.2.2 Review of the Safety Database

Overall Exposure

Data:

Table 36. Applicant - Exposure to study treatment in NRG1+ cancer patients treated with zenocutuzumab 750 mg Q2W in the eNRGy study (Safety Analysis Set)

	NRG1+ NSCLC (N=99)	NRG1+ PDAC (N=39)	All NRG1+ Tumor Types[1] (N=175)
Exposure duration[2] (months)			
Mean (SD)	7.91 (7.60)	7.74 (6.56)	7.37 (7.07)
Median (min, max)	5.75 (0.1, 36.2)	7.16 (0.5, 34.3)	5.26 (0.1, 36.2)
Exposure duration[2] (categories), n (%)			
≤1 month	8 (8.1)	3 (7.7)	13 (7.4)
>1-≤3 months	22 (22.2)	8 (20.5)	46 (26.3)
>3-≤6 months	22 (22.2)	8 (20.5)	38 (21.7)
>6-≤12 months	30 (30.3)	15 (38.5)	51 (29.1)
>12-≤18 months	4 (4.0)	2 (5.1)	9 (5.1)
>18 months	13 (13.1)	3 (7.7)	18 (10.3)
Relative dose intensity[3]			
Mean (SD)	0.974 (0.060)	0.984 (0.029)	0.975 (0.056)
Median (min, max)	1.00 (0.65, 1.08)	1.00 (0.89, 1.04)	1.00 (0.65, 1.08)
Relative dose intensity[3] (categories), n (%)			
>0.5 to ≤0.75	1 (1.0)	0	2 (1.1)
>0.75 to ≤0.9	9 (9.1)	1 (2.6)	15 (8.6)
>0.9 to ≤1	81 (81.8)	31 (79.5)	140 (80.0)

	NRG1+ NSCLC (N=99)	NRG1+ PDAC (N=39)	All NRG1+ Tumor Types[1] (N=175)
>1	8 (8.1)	7 (17.9)	18 (10.3)

max=maximum; min=minimum; SD=standard deviation.

[1] *Thirty-seven of the 175 patients had other NRG1+ tumor types, including 12 patients with cholangiocarcinoma, 9 patients with breast cancer, 9 patients with colorectal cancer, 2 patients with carcinoma of unknown primary, and endometrial, gastric, ovarian, pancreatic neuroendocrine, and renal cell cancer in 1 patient each.*

[2] *Exposure duration=time from the date of first administration of study treatment to the date of last exposure (the earliest of data cutoff date, death date, or date of last administration, +13 days).*

[3] *Relative dose intensity=dose intensity / planned dose intensity [planned cumulative dose / exposure duration]. Dose intensity=actual cumulative dose / exposure duration.*

Source: eNRGy CSR Table 14.1.4.1

The Applicant's Position:

The FDA did not object to the proposed safety database.

At the time of the data cutoff (31 Jul 2023), median exposure duration was 5.3 months (range 0.1-36.2) in patients with all NRG1+ tumor types, with 78 patients (44.6%) receiving >6 months of treatment and 27 patients (15.4%) receiving >12 months of treatment. Median relative dose intensity was 100% (range 65-108) with relative dose intensity >90% in 158 patients (90.3%).

Zenocutuzumab exposure in NRG1+ NSCLC and NRG1+ PDAC patients was generally consistent with the all NRG1+ tumor types population. Median exposure duration in patients with NRG1+ NSCLC was 5.8 months (range 0.1-36.2), with 47 patients (47.5%) receiving >6 months of treatment. Median exposure duration in patients with NRG1+ PDAC was 7.2 months (range 0.5-34.3), which was higher than the all NRG1+ tumor types population, with 20 patients (51.3%) receiving >6 months of treatment.

Infusion interruptions were reported in a total of 21 patients (12.0%) in the all NRG1+ tumor types population, including 8 NRG1+ NSCLC (8.1%) and 7 NRG1+ PDAC (17.9%) patients.

The FDA's Assessment:

FDA generally agrees with the Applicant's position. Refer to Section 6 and 19.4 (Clinical Pharmacology and OCP Appendices) for more detail on exposure analyses. FDA assessed temporary infusion interruptions due to IRRs separately from dosage interruptions or delays due to other TEAEs. Refer to Dose Interruptions/Reductions due to Adverse Events and Significant Adverse Events (8.2.2) for more details.

Relevant characteristics of the safety population:

Data:

Table 37. Applicant - Demographics and baseline characteristics of patients in the eNRGy study (Safety Analysis Set)

	NRG1+ NSCLC (N=99)	NRG1+ PDAC (N=39)	All NRG1+ Tumor Types (N=175)
Age (years)			
Mean (SD)	64.2 (13.2)	51.2 (15.6)	60.0 (14.7)
Median (min, max)	66.0 (27, 88)	51.0 (21, 74)	62.0 (21, 88)
Age categories, n (%)			
<65 years	46 (46.5)	30 (76.9)	100 (57.1)
≥65 years	53 (53.5)	9 (23.1)	75 (42.9)
Sex, n (%)			
Male	38 (38.4)	20 (51.3)	71 (40.6)
Female	61 (61.6)	19 (48.7)	104 (59.4)
Race, n (%)			
White	37 (37.4)	32 (82.1)	94 (53.7)
Black or African American	2 (2.0)	1 (2.6)	4 (2.3)
Asian	52 (52.5)	5 (12.8)	63 (36.0)
Other	2 (2.0)	0	5 (2.9)
Not Reported	6 (6.1)	1 (2.6)	9 (5.1)
ECOG performance status[1], n (%)			
0	30 (30.3)	21 (53.8)	73 (41.7)
1	64 (64.6)	18 (46.2)	94 (53.7)
2	5 (5.1)	0	8 (4.6)

max=maximum; min=minimum; SD=standard deviation

[1] *ECOG performance status: 0=Fully active, able to carry on all pre-disease performance without restriction; 1=Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature; 2=Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.*

Source: eNRGy CSR Table 14.1.3.1

Table 38. Applicant - Cancer history and diagnosis of patients in the eNRGy study (Safety Analysis Set)

	NRG1+ NSCLC (N=99)	NRG1+ PDAC (N=39)	All NRG1+ Tumor Types (N=175)
Primary tumor type, n (%)			
NSCLC	99 (100)	0	99 (56.6)
PDAC	0	39 (100)	39 (22.3)
Other:	0	0	37 (21.1)
Cholangiocarcinoma	0	0	12 (6.9)
Breast cancer	0	0	9 (5.1)

	NRG1+ NSCLC (N=99)	NRG1+ PDAC (N=39)	All NRG1+ Tumor Types (N=175)
Colorectal cancer	0	0	9 (5.1)
Carcinoma of unknown primary	0	0	2 (1.1)
Endometrial cancer	0	0	1 (0.6)
Gastric cancer	0	0	1 (0.6)
Ovarian cancer	0	0	1 (0.6)
Pancreatic neuroendocrine cancer	0	0	1 (0.6)
Renal cell carcinoma	0	0	1 (0.6)
Time since initial diagnosis (months)[1]			
Median (min, max)	12.2 (1, 149)	21.2 (6, 151)	16.6 (1, 344)
Time since diagnosis of metastatic disease (months)[2]			
n (missing)	94 (5)	38 (1)	167 (8)
Median (min, max)	8.65 (1.1, 74.7)	18.90 (1.7, 82.7)	11.60 (0.8, 107.9)

max=maximum; min=minimum
[1] Time since initial diagnosis: time from initial diagnosis of cancer to start date of study treatment.
[2] Time since metastatic disease: time from diagnosis of metastatic disease to start date of study treatment.
Source: eNRGy CSR Table 14.1.3.4

Table 39. Applicant – Prior anticancer therapy in patients in the eNRGy study (Safety Analysis Set)

	NRG1+ NSCLC (N=99)	NRG1+ PDAC (N=39)	All NRG1+ Tumor Types (N=175)
Any prior systemic therapy, n (%)	87 (87.9)	38 (97.4)	161 (92.0)
Number of prior systemic therapy regimens, n (%)			
0	12 (12.1)	1 (2.6)	14 (8.0)
1	44 (44.4)	8 (20.5)	59 (33.7)
2	30 (30.3)	14 (35.9)	55 (31.4)
3	6 (6.1)	8 (20.5)	19 (10.9)
4	5 (5.1)	6 (15.4)	18 (10.3)
≥5	2 (2.0)	2 (5.1)	10 (5.7)
Median (min, max)	1.0 (0, 6)	2.0 (0, 5)	2.0 (0, 10)
Agent type, n (%)			
Chemotherapy	84 (84.8)	38 (97.4)	156 (89.1)
Immunotherapy	54 (54.5)	4 (10.3)	64 (36.6)
Targeted therapy	24 (24.2)	9 (23.1)	54 (30.9)
Anti-VEGF therapy	10 (10.1)	0	20 (11.4)
Afatinib	8 (8.1)	2 (5.1)	12 (6.9)
CDK4/6 inhibitor therapy	0	0	7 (4.0)
Other anti-EGFR therapy	2 (2.0)	1 (2.6)	7 (4.0)
Anti-HER3 therapy	3 (3.0)	1 (2.6)	5 (2.9)
Other targeted therapy[1]	3 (3.0)	6 (15.4)	13 (7.4)
Hormonal therapy	0	0	8 (4.6)
Other therapy	8 (8.1)	7 (17.9)	17 (9.7)

	NRG1+ NSCLC (N=99)	NRG1+ PDAC (N=39)	All NRG1+ Tumor Types (N=175)
Investigational agents	8 (8.1)	7 (17.9)	15 (8.6)
Number of regimens in metastatic setting, n (%)			
0	23 (23.2)	3 (7.7)	28 (16.0)
1	47 (47.5)	8 (20.5)	64 (36.6)
2	18 (18.2)	14 (35.9)	45 (25.7)
3	6 (6.1)	7 (17.9)	17 (9.7)
4	5 (5.1)	5 (12.8)	14 (8.0)
≥5	0	2 (5.1)	7 (4.0)
Median (min, max)	1.0 (0, 4)	2.0 (0, 5)	1.0 (0, 9)
Prior radiotherapy, n (%)	43 (43.4)	3 (7.7)	55 (31.4)
Prior surgery, n (%)	39 (39.4)	14 (35.9)	75 (42.9)

ADC=Antibody-drug conjugate; ADP=adenosine diphosphate; CDK=cyclin-dependent kinase; EGFR=epidermal growth factor receptor; max=maximum; min=minimum; mTOR= mechanistic target of rapamycin; PARP=poly (ADP-ribose) polymerase; TKI=tyrosine kinase inhibitor; VEGF=vascular endothelial growth factor.

[1] *Other targeted therapies include TKI (nintedanib 2 NRG1+ NSCLC; lenvatinib 1 NRG1+ PDAC; tarloxotinib 1 NRG1+ PDAC), PARP inhibitor (olaparib; 3 NRG1+ PDAC), ADC (zolbetuximab; 1 NRG1+ PDAC), mTOR inhibitor (everolimus 3 NRG1+ breast cancer), protein kinase inhibitor (savolitinib; 1 NRG1+ RCC).*

Source: eNRGy CSR Table 14.1.3.8, Table 14.1.3.13, Table 14.1.3.15

The Applicant's Position:

The median age in patients with all NRG1+ tumor types was 62 years (range 21-88), and 104 patients (59.4%) were female. Most patients were White (94 patients [53.7%]) or Asian (63 patients [36.0%]). Patients had Eastern Cooperative Oncology Group (ECOG) performance status (PS) scores of 0 in 73 patients (41.7%) and ECOG PS 1 in 94 patients (53.7%).

In the NRG1+ NSCLC population most patients were Asian (52.5%) or White (37.4%), and 61.6% of patients were female. Patients in the NRG1+ PDAC population were younger compared with the all NRG1+ tumor types population, with a median age of 51 years (range 21-74) and 76.9% of PDAC patients were less than 65-years-old. The majority of patients were White (82.1%) and 48.7% of patients were female.

Of the 175 patients with all NRG1+ tumor types, 161 patients (92.0%) received prior systemic anticancer therapy with a median of 2.0 prior lines (range 0-10). A total of 14 patients (8.0%) were treatment-naïve, including 12 patients (12.1%) with NRG1+ NSCLC and 1 patient (2.6%) with NRG1+ PDAC. Prior therapy in the metastatic setting was administered in 147 patients (84%). Fourteen of the 28 patients who did not receive metastatic therapy received systemic therapy in the adjuvant or neoadjuvant setting.

The FDA's Assessment:

FDA agrees with the Applicant's description of the safety population. Although demographics are not well-characterized by subtype for patients with NRG1 fusions given their rarity, the percentage of female patients in eNRGy was higher than would be expected based on NSCLC

demographics in the United States, as NSCLC is more common in males. Compared to the expected racial demographics for NSCLC in the U.S. population, the percentage of Asian patients was higher, while the percentage of Black patients was lower (Primm et al, 2022). Compared to the expected demographics for (unselected) PDAC in the United States, patients in eNRGy were younger, and Black patients were underrepresented (SEER). In eNRGy, 64 (37%) patients were treated at sites in North America, while 55 (31%) and 51 (29%) patients were treated at Asian and European sites, respectively. The rarity of *NRG1* fusions justifies the inclusion of foreign data in this application.

Adequacy of the safety database:

Data and The Applicant's Position:

The safety database of all subjects treated with zenocutuzumab monotherapy or in combination, at any dose (N= 458 patients) as of the data cutoff of 31 July 2023 (see Table 10), which includes:

- the primary data to support the safety of zenocutuzumab in the proposed indications from the eNRGy study with NRG1+ cancer who received at least 1 dose of zenocutuzumab 750 mg Q2W (N = 175 patients)
- supportive safety data from patients with NRG1+ cancer enrolled in the EAP who received at least 1 dose of zenocutuzumab 750 mg Q2W (N = 15 patients)
- supportive safety data observed at monotherapy doses other than 750 mg Q2W which evaluated non-NRG1+ cancer patients in the MCLA-128-CL01 study (N= 155 patients)
- supportive safety data from non-NRG1+ cancer patients with a HER3 mutation treated with zenocutuzumab 750 mg Q2W monotherapy in a non-NRG1+ EAP (N= 8 patients)
- supportive safety data of zenocutuzumab administered in combination with other anticancer treatments from the MCLA-128-CL02 study (N= 104 patients)

This safety database is considered by the Applicant to be adequate to assess the safety of zenocutuzumab monotherapy in the treatment of subjects with NRG1+ NSCLC and NRG1+ PDAC, to provide guidance regarding management of toxicities, and for an assessment of the benefit-risk profile of zenocutuzumab in the target population.

The FDA's Assessment:

FDA agrees with the Applicant's position.

8.2.1. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The Applicant's Position:

There were no data integrity issues identified.

This BLA submission contains all required components of the electronic Common Technical Document (eCTD). Analysis-ready, efficacy and safety datasets, which support the efficacy and safety of zenocutuzumab, are provided.

The FDA's Assessment:
FDA agrees with the Applicant's position. The data submitted were organized and adequate to perform a complete review of the safety of zenocutuzumab in patients with NRG1+ NSCLC and PDAC, particularly considering the rarity of NRG fusions in these malignancies. FDA issued information requests during the review cycle to obtain clarification and additional information regarding data included in the initial BLA and all requests were addressed appropriately.

Categorization of Adverse Event

The Applicant's Position:

Adverse events were analyzed by incidence, severity, and relatedness. AEs were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.03 and coded using Medical Dictionary for Regulatory Activities (MedDRA) v26.0 terminology. Laboratory abnormalities were programmatically calculated using CTCAE grading or low/normal/high based on normal ranges.

Summaries of AEs include all AEs occurring during the on-treatment period. AEs were summarized by number and percentage of patients having ≥1 AE, having ≥1 AE in each primary system organ class and for each PT using MedDRA v26.0 coding. A patient with multiple occurrences of an AE was counted only once in the respective AE category. A patient with multiple CTCAE grades for the same PT was summarized under the maximum CTCAE grade recorded for the event. AEs with a missing CTCAE grade were included in the 'All grades' column of the summary tables. All grades and Grades 3-4 were summarized. In AE summaries, the primary system organ class was presented alphabetically and PTs were sorted within the primary system organ class in descending frequency, based on their frequency in the total column.

Summaries of AEs were prepared as follows: an overview of AEs and deaths (number and percentage of patients who died, who had ≥1 AE, ≥1 SAE, ≥1 AE leading to dosing interruption, ≥1 AE leading to treatment discontinuation), and ≥1 IRR. In addition, AEs by system organ class and PT were summarized by relationship (all AEs, treatment-emergent AEs [TEAEs] and AEs related to study treatment), seriousness (SAEs and non-SAEs), leading to treatment discontinuation, leading to dosing interruption, requiring additional therapy, and leading to a fatal outcome, and IRRs.

All fatal AEs were tabulated in fatal AE summaries, summary of on-study death and causes within the 30 days of last study drug infusion were summarized.

Adverse events leading to dosing interruption (i.e., delay) were defined as AEs that had action taken with study drug of 'Dose Interrupted', 'Dose Delayed' or 'Other Action Taken' with the IRR tick box 'off'. AEs leading to infusion interruption were defined as AEs that had action taken with study drug of 'Dose Interrupted' or 'Other Action Taken' with the IRR tick box 'on'.

Summaries of IRRs were tabulated for patients having ≥1 AE by primary system organ class and each PT. The following variables were summarized using pooled data: was the infusion completed; was infusion interrupted; use of premedication; infusion number at first occurrence; how many IRRs/patient in patients with IRR; outcome; did the IRR led to withdrawal; was the IRR serious. Infusion-related reactions were analyzed as a composite term defined as an AE that developed within 24 h of study drug administration reported as a sign or symptom of an IRR, as judged by the investigator.

For each specified AESI, the number and percentage of patients with ≥1 event of the AESI occurring during the on-treatment period was summarized by AESI, system organ class and PT using the pooled data. Three AEs of special interest (AESIs) identified for zenocutuzumab were analyzed: IRRs (according to the composite term per investigator judgement), diarrhea, and decreased cardiac ejection fraction (according to a case retrieval strategy).

All AEs collected on the AE CRF page were listed along with relevant information, e.g., AE relationship to study drug, AE outcome, etc. AEs with a start date outside of the on-treatment period were flagged in the listings.

The FDA's Assessment:
FDA agrees with the Applicant's position. FDA considers TEAEs to be inclusive of AEs after the first dose of zenocutuzumab through 30 days after receipt of the last dose of study drug. FDA assessed dosing interruptions and delays as described by the Applicant; dosing interruptions and delays were characterized separately from temporary infusion interruptions due to IRRs.

Routine Clinical Tests

The Applicant's Position:

For hematology, biochemistry, and coagulation laboratory data, the number and percentage of patients with abnormalities on treatment were analyzed for selected laboratory parameters with shift tables using CTCAE grades to compare baseline to the worst on-treatment value. Laboratory parameters without defined CTCAE grades were analyzed using shift tables with low/normal/high (low and high) classification to compare baseline to the worst on-treatment value. Liver function parameters were analyzed for the number and percentage of patients with notable abnormalities on treatment. Parameters analyzed were total bilirubin (TBL), ALT, AST, and ALP. Potential Hy's law events were defined as those patients with concurrent occurrence of AST or ALT >3 x ULN and TBL >2 x ULN and ALP <2 x ULN in the same assessment sample during the on-treatment

period. Further medical review was conducted to assess potential confounding factors such as liver metastases, liver function at baseline, etc.

Cardiac function was analyzed using ECG and LVEF measurements.

- For ECG assessments, the number and percentage of patients with notable values were summarized for QT, corrected QT interval (QTc) by Fridericia (QTcF), corrected QT interval by Bazett (QTcB; as calculated from QT and RR), and Q-, R-, S wave (QRS).
- For LVEF assessments, the number and percentage of patients with abnormalities on treatment were summarized as shift tables with baseline vs worse post-baseline value according to CTCAE grade.

The number and percentage of patients with notable vital sign values (high/low) were summarized. Parameters analyzed were height (cm), weight (kg), body temperature (°C), heart rate (beats per minute [bpm]), systolic BP (SBP) and diastolic BP (DBP) (mmHg) and respiration rate (breaths/min).

The number and percentage of patients in each ECOG PS score category were summarized by visit.

The schedule of assessments for these safety measures are presented in Table 11.

The FDA's Assessment:
FDA agrees with the Applicant's position. The study protocol for eNRGy included adequate safety monitoring for known class effects of HER2 inhibitors.

8.2.2 Safety Results

Deaths

Data:

In the Safety Analysis Set of the eNRGy study, twelve patients (6.9%), including 6 NRG1+ NSCLC patients and 3 NRG1+ PDAC patients, died within 30 days of the last study drug infusion; all but 1 of these deaths were due to progression of the underlying disease. This included 8 patients (4.6%) who had AEs with a fatal outcome within 30 days of the last study drug infusion (Table 29): respiratory failure (3 patients including 1 acute case), respiratory disorder, NSCLC, cardiac failure, dysphagia, and COVID-19. None of the fatal AEs were treatment-related. Note that the protocol specified that progression of the disease under study would not be captured as an AE (Section 7.2 of the protocol). Nonetheless for 7 of these 8 patients, the primary cause of death was the underlying disease (i.e., excluding the AE of COVID-19).

Table 40. Applicant - Fatal adverse events in patients treated with zenocutuzumab 750 mg Q2W in the eNRGy study (Safety Analysis Set)

System Organ Class Preferred Term	NRG1+ NSCLC (N=99) n (%)	NRG1+ PDAC (N=39) n (%)	All NRG1+ Tumor Types (N=175) n (%)
Patients with ≥1 fatal AE	5 (5.1)	2 (5.1)	8 (4.6)
Cardiac disorders	**1 (1.0)**	**0**	**1 (0.6)**
Cardiac failure	1 (1.0)	0	1 (0.6)
Gastrointestinal disorders	**1 (1.0)**	**0**	**1 (0.6)**
Dysphagia	1 (1.0)	0	1 (0.6)
Infections and infestations	**0**	**1 (2.6)**	**1 (0.6)**
COVID-19	0	1 (2.6)	1 (0.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1 (1.0)**	**0**	**1 (0.6)**
Non-small cell lung cancer	1 (1.0)	0	1 (0.6)
Respiratory, thoracic and mediastinal disorders	**2 (2.0)**	**1 (2.6)**	**4 (2.3)**
Respiratory failure	1 (1.0)	0	2 (1.1)
Acute respiratory failure	1 (1.0)	0	1 (0.6)
Respiratory disorder	0	1 (2.6)	1 (0.6)

Source: eNRGy CSR Table 14.3.1.12

Among the 15 patients with all NRG1+ tumor types treated with zenocutuzumab 750 mg Q2W in the EAP, at least 1 SAE was reported in 5 patients (33.3%), including 1 patient (6.7%) with a fatal outcome (NRG1+ PDAC patient). No treatment-related fatal AEs or SAEs were observed.

Among the 28 patients treated in the MCLA-128-CL01 dose escalation, three deaths (80 mg, 600 mg, and 750 mg cohorts) up to 30 days after the last study drug infusion were reported during dose escalation (2 due to disease progression, 1 with an unknown cause). There were no deaths due to AEs.

Among the 127 patients treated in the MCLA-128-CL01 dose expansion at Q1W and Q3W, a total of 9 deaths were reported up to 30 days after the last study drug infusion. Four patients died due to disease progression and the remaining 5 experienced Grade 5 SAEs (2 treated with the Q3W and 3 treated with the Q1W regimen). The Grade 5 SAEs in the 3 patients treated with the Q1W regimen included infectious pleural effusion and 2 cases of general physical health deterioration, none of which was related to treatment. The Grade 5 SAEs in patients treated with the Q3W regimen included a fatal case of hypersensitivity considered related to study treatment, and a case of disease progression not related to treatment. The patient that died due to a related IRR of Grade 5 hypersensitivity received premedication including steroids and as remedial therapy during the event. Per the Investigator, the allergic reaction was the driver of the causality of the death, however, the patient's comorbidities, notably severe aortic stenosis, likely played a major contributing role to the outcome.

Among the non-NRG1+ cancer patients in EAP (8 non-NRG1+ Her3-mutant cancer) receiving zenocutuzumab 750 mg Q2W, two patients had SAEs, 1 of which was fatal. Reported events

were Grade 2 hyperbilirubinemia with concomitant Grade 2 elevated liver enzymes in 1 patient, and Grade 5 peritonitis in 1 patient. None of the SAEs was considered treatment-related.

In the MCLA-128-CL02 zenocutuzumab-based combination study, two patients died on study or within 30 days after the last study treatment. One patient (cohort 1 triplet) due to sepsis related to vinorelbine (with concomitant Grade 4 treatment-related neutrophil count decreased), and 1 patient (cohort 2) due to the disease indication.

The Applicant's Position:

AEs resulting in death were rare, not treatment-related, and were almost exclusively associated with the underlying disease. There were no zenocutuzumab-related deaths in the primary safety population of the eNRGy study, the NRG1+ EAP and the non-NRG1+ EAP (all at the RP2D regimen). The only treatment-related death was in the non-NRG1+ MCLA-128-CL01 dose expansion cohort, where there was one fatal case of hypersensitivity. The investigator also reported that the allergic reaction was the primary cause of death; however, the patient's comorbidities, notably severe aortic stenosis, likely played a major contributing role to the outcome.

The FDA's Assessment:

In the eNRGy study, on-treatment deaths occurred in twelve (7%) patients in the overall safety population, including six patients with NRG1+ NSCLC and three patients with NRG1+ PDAC. Based on FDA's assessment, seven of the 12 patients died due to disease progression during the on-treatment period. Five (2.9%) patients died due to TEAEs in the overall safety population (See Table 30 for details). Three (3%) patients with NSCLC died due to TEAEs: two patients died due to respiratory failure and one patient died due to cardiac failure. Two (5%) patients with PDAC died due to TEAEs: one patient died due to respiratory failure and one patient died due to COVID-19. A relationship to zenocutuzumab could not be definitively ruled out for these five deaths; however, in each case other contributing factors were present.

One additional death due to TEAE was reported with the 90-day safety update. This was a patient with NRG1+ NSCLC who died due to septic shock (see Table 30 for narrative).

One fatal case of hypersensitivity occurred in study MCLA-128-CL01 (Patient ID: (b) (6)). The patient was a 71 year old White woman with non-NRG1+, stage IV gastric adenocarcinoma with metastases to the liver and lymph nodes. Other pertinent medical history included severe aortic and mitral valve stenosis with no clinical manifestations. The patient's baseline LVEF was 56%. The patient was assigned to Part 2, Group D with zenocutuzumab 750 mg Q3W on a 3-week cycle. Prior to the first dose of zenocutuzumab, the patient received premedication with dexamethasone, dexchlorpheniramine maleate, and paracetamol. After administration of 60 mg out of the planned 750 mg of zenocutuzumab, the patient presented with Grade 4 hypersensitivity including dyspnea and desaturation and was transferred to the ICU. Treatment for the hypersensitivity reaction included epinephrine, fentanyl, midazolam, dexchlorpheniramine maleate, methylprednisolone, and oxygen. The patient experienced

cardiorespiratory arrest and died nine hours after treatment initiation. The investigator assessed the event as definitely related to the study drug. The FDA agrees with the investigator's assessment that this event of Grade 5 hypersensitivity was related to zenocutuzumab. While this death did not occur in the target population of NRG1+ NSCLC or PDAC, it is not expected that rates of hypersensitivity would differ between patients with NRG1+ NSCLC or PDAC and patient with other malignancies. The severity of this event and clear temporal relationship to the zenocutuzumab infusion indicate that hypersensitivity/IRR is an important risk of treatment with zenocutuzumab.

Table 41: Summary of Applicant Narratives for Patients in eNRGy Who Died ≤30 Days of Treatment due to Cause Other than Disease Progression (FDA Review)

Patient ID	Narrative	FDA's Assessment of Causality
(b) (6)	Patient was a 62 year old Caucasian male with NRG1+ NSCLC which progressed after initial treatment with cisplatin and vinorelbine and second-line treatment with nivolumab. At study entry, patient had Stage IV disease with metastases to the adrenals, bone, lung, lymph nodes and muscles. Other pertinent medical history at study entry included cough, dyspnea, pulmonary thrombosis, pulmonary effusion, and COPD. Fifteen days after starting the study drug and one day after the last study drug administration, the patient presented with sudden onset of dyspnea on exertion. Associated AEs were Grade 2 hypoxia and Grade 1 increased body temperature, with the same day of onset. Physician exam was notable for bilateral crackles, greater on the right side and decreased breath sounds at the left lung base. CT angiogram obtained the day of admission showed no evidence of PE and stable appearance of hilo mediastinal, lower cervical and bilateral supraclavicular lymphadenopathy, as well as stability of multiple pulmonary nodules. The imaging report described reduction in prior right pleural effusion and an increase in the left pleural effusion with greater parenchyma collapse. The patient underwent palliative sedation and died 15 days later. **The investigator attributed the cause of death to acute respiratory failure in the setting of disease progression, unrelated to zenocutuzumab.**	FDA agrees that this patient's death was likely unrelated to zenocutuzumab and most likely related to the patient's underlying NSCLC, with COPD as a possible contributing factor; however, the etiology of the findings on the imaging reports provided by the Applicant are unclear (i.e.. pneumonia vs disease progression). FDA cannot definitively conclude based on the information provided that the event was due to disease progression.
(b) (6)	Patient was a 68 year old Caucasian female with NRG1+ NSCLC which had progressed on initial systemic therapy with carboplatin, pembrolizumab and pemetrexed and second-line	Although it was not possible to obtain imaging to confirm

	therapy with docetaxel. At study entry, patient had Stage IV disease with metastases to the lungs, lymph nodes and peritoneum. Seven days after starting treatment with the study drug, the patient presented with respiratory failure thought to be secondary to pulmonary aspiration in the setting of a Grade 3 intestinal obstruction. Physical exam was consistent with intestinal obstruction. No imaging was obtained to confirm disease progression due to the patient's unstable clinical status. **The patient died the same day. The investigator attributed the cause of death to respiratory failure and disease progression.**	disease progression or pneumonia, respiratory failure secondary to pulmonary aspiration is plausible given the patient's baseline peritoneal metastases, which are described in the patient's baseline imaging report. However, the contribution of zenocutuzumab to the fatal event cannot be definitively excluded.
(b) (6)	Patient was a 55 year old White woman with NRG1+ PDAC who had received four prior lines of systemic therapy. At study entry, the patient had metastatic disease in the liver. Other pertinent medical history at study entry included increased AST and hepatomegaly. The patient experienced diarrhea up to Grade 3 in severity while on treatment with zenocutuzumab. The patient presented to the emergency room with COVID-19 and severe diarrhea 311 days after starting the study drug and 12 days after the most recent study drug administration. The patient subsequently developed hepatic failure including Grade 4 cytolysis, icteric cholestasis and Grade 2 increased bilirubin, as well as rapid clinical deterioration. A CT was obtained which showed stable disease. The patient later developed hepatic encephalopathy and died in the setting of ongoing COVID-19 infection. **The investigator attributed the cause of death to COVID-19 which was unrelated to zenocutuzumab.**	The history and hospitalization are consistent with Grade 5 infection. Given that imaging showed stable disease at the time of death, this death cannot be attributed to disease progression and the contribution of zenocutuzumab to the fatal event cannot be definitively excluded.
(b) (6)	Patient was an 85 year old Caucasian male with newly diagnosed, metastatic NRG1+ NSCLC. Other pertinent medical history included arteriopathy of the lower limbs, dyspnea, elevated NT-proBNP, hypertension and ischemic heart disease. Patient had a baseline LVEF of 60% at screening with a normal ECG. Fifteen days after starting the study drug, the patient had an SAE of cardiac failure (Grade 3) requiring hospitalization. ECHO obtained the day of hospitalization revealed R heart decompensation. A pleural drain was placed. CT angiography of the chest was performed	The history and hospitalization are consistent with cardiac failure. The patient's underlying ischemic heart disease and disease progression in the lung leading to right heart decompensation were likely contributing

	which showed stable disease with an anterior lingual mass, with lymphangitis and left pleural carcinomatosis, as well as a left lung base consolidation. Grade 2 pneumonia was reported and the study drug was interrupted. The patient was started on ramipril prior to discharge. Patient resumed study treatment 12 days later and a normal ECG was documented. Seven days after re-starting study treatment and 36 days after starting the study drug, the patient again developed cardiac failure requiring hospitalization. At this time, a CT was performed showing disease progression with "lymphangitis-like infiltration of the lung". The study treatment was discontinued. Six days later, the patient was hospitalized with cardiac failure and malnutrition (Grade 4) and discharged the same day. Three days later, the patient presented with respiratory deterioration and hypercapnia, and died one day later. **The investigator attributed the cause of death to cardiac failure, unrelated to zenocutuzumab.**	factors. However, given the known in-class safety risk of cardiotoxicity, treatment with zenocutuzumab may have also contributed to the fatal event.
(b) (6)	Patient was a 31 year old White man with NRG1+ PDAC who received three prior lines of systemic therapy, radiation, and surgery. At study entry, the patient had Stage IV disease with metastases to the liver, lung, and lymph nodes. Other relevant medical history included liver abscess and pulmonary embolism. Forty-four days after initiating treatment with the study drug and 16 days after the last study drug administration, the patient presented with lightheadedness and hypotension. The patient was found to have a new pulmonary abscess and complicated pleural effusion post R chest tube requiring hepatic drain replacement with interventional radiology. The patient received treatment with enoxaparin, metronidazole, and vancomycin. The patient was intubated and started on pressors for IR embolization of T7-T11 intercostal arterial trunk. A R surgical chest tube was placed, and the patient was extubated the next day. The patient was initially placed on 3L nasal cannula after extubation; however oxygen saturation dropped to 80% and the patient was placed on non-rebreather mask with minimal improvement. A lung ultrasound was performed which showed a new L pleural effusion. The following day, the patient was re-admitted to the ICU for nasal intermittent positive pressure ventilation (NIPPV) and diuretics and was subsequently intubated and started on pressors and inhaled epoprostenol. A tracheotomy tube was placed 7 days after admission to the ICU. The patient underwent left thoracentesis	The history and hospitalization are consistent with respiratory failure. While there is no imaging report to confirm disease progression, patient's respiratory failure was likely secondary to known pulmonary metastases and pulmonary abscess. However, the contribution of zenocutuzumab to the fatal event cannot be definitively excluded

	and 1.8 L of pleural fluid was removed. The patient died 52 days after the onset of the event. **The investigator attributed the cause of death to respiratory failure in the setting of clinical progression, not related to zenocutuzumab.**	
(b) (6) **(Submitted with 90-day SUR)**	Patient was a 74 year old Asian male with NRG1+ NSCLC metastatic to adrenal gland, bone, lung and lymph nodes. The patient had received prior systemic and radiation therapy for NSCLC. Other past medical history included atrial fibrillation with rapid ventricular response, bone pain, DVT, hypothyroidism, pulmonary embolism and left-sided pleural effusion. Eighteen days after starting study treatment and 4 days after the last study drug administration, the patient presented to the ER due to dyspnea and reported oxygen saturation of 75-80% at home. A chest X-ray and ECHO were performed which both showed a left pleural effusion. The patient had pCO2 of 60.6 mmHg and 50.4 mmHg (reference range: 38-54 mmHg). The patient developed a fever and was started on Tazocin for suspected sepsis. The patient was admitted to the hospital for further care. Oxygen saturation improved to >95% with 3L nasal cannula. The following morning, the patient developed altered mental status and hypotension. Vital signs were notable for a heart rate of 110 bpm, respiratory rate of 26 breaths per minute, blood pressure 70/53 mmHg and oxygen saturation 75-88%. The patient was started on levofloxacin. The patient had a DNR order in place, therefore no vasopressors were given and no additional examinations were performed. The patient died 2 days after presentation and 6 days after the last infusion of zenocutuzumab. Peripheral blood cultures showed no growth after 5 days. **The investigator attributed the patient's death to septic shock, not/unlikely related to zenocutuzumab.**	The history and hospitalization are consistent with sepsis. While a source of infection was not documented, the patient's clinical presentation is consistent with septic shock. However, the contribution of zenocutuzumab to the fatal event cannot be definitively excluded

Source: eNRGy CSR, 90-day SUR, and Applicant response to information requests

Serious Adverse Events

Data:

Serious AEs irrespective of causality occurring in ≥2 patients (1.1%) in the all NRG1+ tumor types population are presented in Table 30. Among the 42 patients (24.0%) with ≥1 SAE, the most common SOCs (≥5.0% per SOC) were infections and infestations (13 patients [7.4%]),

respiratory, thoracic, and mediastinal disorders (11 patients [6.3%]), and gastrointestinal disorders (9 patients [5.1%]).

Twenty-five NRG1+ NSCLC patients (25.3%) experienced at least 1 SAE, and 15 patients (15.2%) had Grade 3-4 SAEs. SAEs reported in more than 1 patient were dyspnea (4 patients [4.0%]) and pneumonia (2 patients [2.0%]). Three NRG1+ NSCLC patients (3.0%) had treatment-related SAEs, including 1 patient with Grade 2 fatigue and Grade 2 vomiting, 1 patient with Grade 3 nausea, and 1 patient with Grade 2 pneumonitis.

Nine NRG1+ PDAC patients (23.1%) experienced at least 1 SAE, and 7 patients (17.9%) had Grade 3-4 SAEs. All SAEs were reported in 1 patient each. None of the SAEs in NRG1+ PDAC patients were treatment-related.

Table 42. Applicant – Serious adverse events irrespective of causality in ≥2 patients in the all NRG1+ tumor types population in the eNRGy study (Safety Analysis Set)

	NRG1+ NSCLC (N=99)		NRG1+ PDAC (N=39)		All NRG1+ Tumor Types (N=175)	
Preferred Term	**All grades n (%)**	**Grade 3-4 n (%)**	**All grades n (%)**	**Grade 3-4 n (%)**	**All grades n (%)**	**Grade 3-4 n (%)**
Number of patients with ≥1 SAE	**25 (25.3)**	**15 (15.2)**	**9 (23.1)**	**7 (17.9)**	**42 (24.0)**	**28 (16.0)**
Dyspnea	4 (4.0)	3 (3.0)	0	0	4 (2.3)	3 (1.7)
Pneumonia	2 (2.0)	1 (1.0)	0	0	4 (2.3)	2 (1.1)
Abdominal pain	1 (1.0)	1 (1.0)	1 (2.6)	1 (2.6)	2 (1.1)	2 (1.1)
COVID-19[1]	1 (1.0)	0	1 (2.6)	0	2 (1.1)	0
Jaundice cholestatic	0	0	1 (2.6)	1 (2.6)	2 (1.1)	2 (1.1)
Nausea	1 (1.0)	1 (1.0)	1 (2.6)	0	2 (1.1)	1 (0.6)
Pulmonary embolism	0	0	0	0	2 (1.1)	2 (1.1)
Respiratory failure[2]	1 (1.0)	0	0	0	2 (1.1)	0
Sepsis	1 (1.0)	1 (1.0)	0	0	2 (1.1)	2 (1.1)

[1] *Acute respiratory failure was reported in 1 additional patient.*
[2] *COVID-19 pneumonia was reported in 1 additional patient.*
Source: Table 14.3.1.7

Serious adverse events irrespective of causality for the 15 NRG1+ cancer patients treated in the EAP are presented in Table 31. Five patients (33.3%) experienced at least 1 SAE, including 4 patients (26.7%) with Grade ≥3 SAEs. None of the SAEs were reported in more than 1 patient or considered related to study treatment. Four of the 5 patients had more than 1 SAE, including 1 patient with 8 SAEs and another patient with 6 SAEs.

Table 43. Applicant – Serious adverse events irrespective of causality in the all NRG1+ tumor types population in the EAP (Safety Analysis Set)

	NRG1+ NSCLC N=7		NRG1+ PDAC N=5		All NRG1+ tumor types N=15	
Primary system organ class Preferred term	**All grades n (%)**	**Grade 3-4 n (%)**	**All grades n (%)**	**Grade 3-4 n (%)**	**All grades n (%)**	**Grade 3-4 n (%)**
Number of patients with at least 1 AE	2 (28.6)	2 (28.6)	2 (40.0)	2 (40.0)	5 (33.3)	4 (26.7)
Cardiac disorders	1 (14.3)	1 (14.3)	0	0	1 (6.7)	1 (6.7)
Myocardial infarction	1 (14.3)	1 (14.3)	0	0	1 (6.7)	1 (6.7)
Gastrointestinal disorders	0	0	1 (20.0)	1 (20.0)	1 (6.7)	1 (6.7)
Abdominal pain	0	0	1 (20.0)	0	1 (6.7)	0
Enterocolitis	0	0	1 (20.0)	0	1 (6.7)	0
Gastric ulcer	0	0	1 (20.0)	1 (20.0)	1 (6.7)	1 (6.7)
Hematemesis	0	0	1 (20.0)	1 (20.0)	1 (6.7)	1 (6.7)
Nausea	0	0	1 (20.0)	0	1 (6.7)	0
Upper gastrointestinal hemorrhage	0	0	1 (20.0)	1 (20.0)	1 (6.7)	1 (6.7)
General disorders and administration site conditions	1 (14.3)	0	1 (20.0)	1 (20.0)	2 (13.3)	1 (6.7)
Fatigue	0	0	1 (20.0)	1 (20.0)	1 (6.7)	1 (6.7)
Pyrexia	1 (14.3)	0	0	0	1 (6.7)	0
Hepatobiliary disorders	1 (14.3)	1 (14.3)	0	0	1 (6.7)	1 (6.7)
Biliary dilatation	1 (14.3)	1 (14.3)	0	0	1 (6.7)	1 (6.7)
Jaundice	1 (14.3)	1 (14.3)	0	0	1 (6.7)	1 (6.7)
Injury, poisoning and procedural complications	1 (14.3)	1 (14.3)	0	0	1 (6.7)	1 (6.7)
Thoracic vertebral fracture	1 (14.3)	1 (14.3)	0	0	1 (6.7)	1 (6.7)
Investigations	2 (28.6)	1 (14.3)	0	0	2 (13.3)	1 (6.7)
Blast cells present	1 (14.3)	0	0	0	1 (6.7)	0
Blood bilirubin increased	1 (14.3)	1 (14.3)	0	0	1 (6.7)	1 (6.7)
Liver function test increased	1 (14.3)	1 (14.3)	0	0	1 (6.7)	1 (6.7)
Musculoskeletal and connective tissue disorders	1 (14.3)	1 (14.3)	1 (20.0)	1 (20.0)	2 (13.3)	2 (13.3)
Back pain	0	0	1 (20.0)	1 (20.0)	1 (6.7)	1 (6.7)
Muscular weakness	1 (14.3)	1 (14.3)	0	0	1 (6.7)	1 (6.7)
Nervous system disorders	1 (14.3)	1 (14.3)	0	0	1 (6.7)	1 (6.7)
Cerebrovascular accident	1 (14.3)	0	0	0	1 (6.7)	0
Hemorrhage intracranial	1 (14.3)	1 (14.3)	0	0	1 (6.7)	1 (6.7)
Psychiatric disorders	0	0	1 (20.0)	1 (20.0)	1 (6.7)	1 (6.7)
Confusional state	0	0	1 (20.0)	1 (20.0)	1 (6.7)	1 (6.7)

	NRG1+ NSCLC N=7		NRG1+ PDAC N=5		All NRG1+ tumor types N=15	
Reproductive system and breast disorders	0	0	1 (20.0)	1 (20.0)	1 (6.7)	1 (6.7)
Vaginal hemorrhage	0	0	1 (20.0)	1 (20.0)	1 (6.7)	1 (6.7)
Surgical and medical procedures	0	0	0	0	1 (6.7)	0
Cardiac operation	0	0	0	0	1 (6.7)	0

Note: A patient with multiple severity grades for an AE is only counted under the maximum grade.
Source: Table 14.3.1.6

A summary of SAEs by PT for all grades is presented in Table 32 for the MCLA-128-CL01 dose escalation. All individual SAEs occurred in a single patient (5 patients in total). Grade 3 SAEs were reported in 3 patients (10.7%) and included IRR, pleural effusion, and pneumonia aspiration.

Table 44. Applicant – MCLA-128-CL01 Dose escalation – SAEs by PT – all grades (Safety Set)

PT	Cohort 1 (40mg) (N=1) n	Cohort 2 (80mg) (N=2) n	Cohort 3 (160mg) (N=1) n	Cohort 4 (240mg) (N=3) n	Cohort 5 (360mg) (N=3) n	Cohort 6 (480mg) (N=3) n	Cohort 7 (600mg) (N=6) n	Cohort 8 (750mg) (N=6) n	Cohort 9 (900mg) (N=3) n	Total (N=28) n (%)
Patients with at least one SAE	0	0	1	0	0	0	1	2	1	5 (17.9)
Ileus	0	0	0	0	0	0	0	1	0	1 (3.6)
Dyspnea	0	0	1	0	0	0	0	0	0	1 (3.6)
Infusion-related reaction	0	0	0	0	0	0	0	1	0	1 (3.6)
Pleural effusion	0	0	0	0	0	0	1	0	0	1 (3.6)
Pneumonia aspiration	0	0	0	0	0	0	0	0	1	1 (3.6)
Tumor associated fever	0	0	1	0	0	0	0	0	0	1 (3.6)

Source: Table 14.3.1.17

Serious adverse events by PT for the MCLA-128-CL01 dose expansion are presented in Table 33. Among the 40 patients (31.5%) with SAEs, the most common events (≥5% per SOC) were gastrointestinal disorders (9 patients [7.1%], 7 treated with the Q3W regimen [6.9%] and 2 treated with the Q1W regimen [7.7%]), respiratory, thoracic, and mediastinal disorders (8 patients in total [6.3%] all treated with the Q3W regimen [7.9% of patients in this regimen]), and infections and

infestations (6 patients [4.7%], 5 treated with the Q3W regimen [5.0%] and 1 treated with the Q1W regimen [3.8%]).

Table 45. Applicant – MCLA-128-CL01 Dose Expansion: SAEs by PT in ≥1.5% patients by dose regimen (Safety Set)

PT	750 mg Q3W (N=101)		Q1W (N=26)		Total (N=127)	
	All Grades n (%)	Grade 3-4 n (%)	All Grades n (%)	Grade 3-4 n (%)	All Grades n (%)	Grade 3-4 n (%)
Patients with at least one SAE	34 (33.7)	25 (24.8)	6 (23.1)	1 (3.8)[1]	40 (31.5)	26 (20.5)
Dyspnea	4 (4.0)	3 (3.0)	0 (0.0)	0 (0.0)	4 (3.1)	3 (2.4)
Infusion-related reaction	3 (3.0)	2 (2.0)	0 (0.0)	0 (0.0)	3 (2.4)	2 (1.6)
Intestinal obstruction	3 (3.0)	2 (2.0)	0 (0.0)	0 (0.0)	3 (2.4)	2 (1.6)
Pulmonary embolism	3 (3.0)	3 (3.0)	0 (0.0)	0 (0.0)	3 (2.4)	3 (2.4)
General physical health deterioration	0 (0.0)	0 (0.0)	2 (7.7)	0 (0.0)	2 (1.6)	0 (0.0)
Tumor pain	2 (2.0)	2 (2.0)	0 (0.0)	0 (0.0)	2 (1.6)	2 (1.6)

Source: Table 14.3.1.21

Among the non-NRG1+ cancer patients in EAP (8 non-NRG1+ Her3-mutant cancer) receiving zenocutuzumab 750 mg Q2W, two patients had SAEs, 1 of which was fatal. Reported events were Grade 2 hyperbilirubinemia with concomitant Grade 2 elevated liver enzymes in 1 patient, and Grade 5 peritonitis in 1 patient. None of the SAEs was considered treatment-related.

In the MCLA-128-CL02 zenocutuzumab-based combination study, SAEs were reported in 2 patients (13.3%) in Cohort 1 doublet, and 8 patients (20.5%) in Cohort 1 triplet, including 4 patients (10.3%) who had ≥1 treatment-related SAE. One patient (2.6%) in Cohort 1 triplet had a fatal SAE, which was treatment-related. SAEs were reported in 9 patients (18.0%) in Cohort 2, 3 of whom (6.0%) had ≥1 treatment-related SAE. No fatal SAEs were reported in Cohort 2.

The Applicant's Position:

Based on the safety results, zenocutuzumab 750 mg IV Q2W was well tolerated in patients with NRG1+ cancer. There was a notably low rate of Grade 3-4 AEs, with no individual Grade 3-4 events observed at a frequency >5.1%. Among the 42 patients (24.0%) from the eNRGy study with ≥1 SAE, the most common SOCs (≥5.0% per SOC) were infections and infestations (13 patients [7.4%]), respiratory, thoracic, and mediastinal disorders (11 patients [6.3%]), and gastrointestinal disorders (9 patients [5.1%]). The safety profile of the zenocutuzumab 750 mg Q2W regimen was similar to those of the 750 mg Q3W and Q1W regimens administered to non-NRG1+ cancer patients.

The FDA's Assessment:

FDA generally agrees with the Applicant's position. Discrepancies in numbers of patients with specific serious adverse events (SAEs) were due to Office of Oncologic Disorders (OOD) standard grouping of preferred terms, which differed from groupings performed by the Applicant. In the eNRGy study, SAEs occurred in 42 (24%) patients in the primary safety population. The most frequent (occurring in ≥2% of patients) were pneumonia (n=6) and dyspnea (n=4).

SAEs occurred in 25 (25%) patients with NRG1+ NSCLC. Overall rates of SAEs were similar in patients with NSCLC, PDAC and other solid tumors, although the rate of respiratory SAEs was numerically higher in NSCLC patients as would be expected in this disease setting. The most frequent (occurring in ≥2% of patients) were pneumonia (n=4), dyspnea and fatigue (n=2 each). All other SAEs occurred in 1 patient each (See Table 44)

SAEs occurred in 9 (23%) patients with NRG1+ PDAC. All SAEs occurred in 1 patient each (See Table 44).

At the 90-day safety update, 4 additional patients with NSCLC had experienced an SAE, including Grade 2 tumor hemorrhage (n=1), septic shock (n=1, see death narratives), and Grade 3 pneumonia (n=2). There were no additional patients with NRG1+ PDAC who experienced SAEs. Additional SAEs reported in patients with other solid tumors included Grade 3 esophageal varices hemorrhage in 1 patient with NRG1+ cholangiocarcinoma, Grade 3 pleural effusion in 1 patient with NRG1+ breast cancer, and Grade 3 upper gastrointestinal hemorrhage in 1 patient with NRG1+ esophageal cancer.

FDA review of SAEs occurring in patients with non-NRG1+ cancers treated with zenocutuzumab 750 mg Q3W and zenocutuzumab Q1W did not reveal additional safety signals.

Table 46: Serious Adverse Events Occurring in the eNRGy Study (FDA Analysis)

	NSCLC N = 99 N (%)	PDAC N = 39 N (%)	OTHER N = 37 N (%)	All solid tumors N = 175 N (%)
Patients with serious AEs	**25 (25)**	**9 (23)**	**8 (22)**	**42 (24)**
Infections And Infestations				
Pneumonia (GT)[a]	4 (4.0)	0 (0.0)	2 (5)	6 (3.4)
Cellulitis	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.6)

	NSCLC N = 99 N (%)	PDAC N = 39 N (%)	OTHER N = 37 N (%)	All solid tumors N = 175 N (%)
Covid-19	1 (1.0)	1 (2.6)	0 (0.0)	2 (1.1)
Sepsis	1 (1.0)	0 (0.0)	1 (2.7)	2 (1.1)
Staphylococcal Infection	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.6)
Urinary Tract Infection	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.6)
Viral Infection	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.6)
Liver Abscess	0 (0.0)	1 (2.6)	0 (0.0)	1 (0.6)
Respiratory, Thoracic And Mediastinal Disorders				
Dyspnea	4 (4.0)	0 (0.0)	0 (0.0)	4 (2.3)
Acute Respiratory Failure	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.6)
Pneumonitis	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.6)
Pulmonary Hypertension	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.6)
Respiratory Failure	1 (1.0)	0 (0.0)	1 (2.7)	2 (1.1)
Pulmonary Embolism	0 (0.0)	0 (0.0)	2 (5)	2 (1.1)
Respiratory Disorder	0 (0.0)	1 (2.6)	0 (0.0)	1 (0.6)
Gastrointestinal Disorders				
Abdominal Pain	1 (1.0)	1 (2.6)	0 (0.0)	2 (1.1)
Ascites	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.6)

	NSCLC N = 99 N (%)	PDAC N = 39 N (%)	OTHER N = 37 N (%)	All solid tumors N = 175 N (%)
Dysphagia	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.6)
Ileus	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.6)
Nausea	1 (1.0)	1 (2.6)	0 (0.0)	2 (1.1)
Obstruction Gastric	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.6)
Vomiting	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.6)
Ileal Perforation	0 (0.0)	0 (0.0)	1 (2.7)	1 (0.6)
Cardiac Disorders				
Bradycardia	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.6)
Cardiac Failure	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.6)
Pericardial Effusion	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.6)
Tachycardia	0 (0.0)	1 (2.6)	0 (0.0)	1 (0.6)
General Disorders And Administration Site Conditions				
Fatigue (GT)[b]	2 (2.0)	0 (0.0)	0 (0.0)	2 (1.1)
Neoplasms Benign, Malignant And Unspecified (incl Cysts And Polyps)				
Non-small Cell Lung Cancer	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.6)
Tumor Pain	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.6)
Myelodysplastic Syndrome	0 (0.0)	1 (2.6)	0 (0.0)	1 (0.6)
Nervous System Disorders				

	NSCLC N = 99 N (%)	PDAC N = 39 N (%)	OTHER N = 37 N (%)	All solid tumors N = 175 N (%)
Carotid Artery Stenosis	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.6)
Dizziness	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.6)
Blood And Lymphatic System Disorders				
Lymphadenitis	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.6)
Anemia	0 (0.0)	1 (2.6)	0 (0.0)	1 (0.6)
Thrombocytopenia	0 (0.0)	1 (2.6)	0 (0.0)	1 (0.6)
Hepatobiliary Disorders				
Cholecystitis Acute	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.6)
Hyperbilirubinemia	0 (0.0)	0 (0.0)	1 (2.7)	1 (0.6)
Jaundice Cholestatic	0 (0.0)	1 (2.6)	1 (2.7)	2 (1.1)
Metabolism And Nutrition Disorders				
Decreased Appetite	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.6)
Dehydration	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.6)
Hyponatremia	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.6)
Renal And Urinary Disorders				
Acute Kidney Injury	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.6)
Injury, Poisoning And Procedural Complications				
Fall	0 (0.0)	0 (0.0)	1 (2.7)	1 (0.6)

	NSCLC N = 99 N (%)	PDAC N = 39 N (%)	OTHER N = 37 N (%)	All solid tumors N = 175 N (%)
Femoral Neck Fracture	0 (0.0)	0 (0.0)	1 (2.7)	1 (0.6)
Hip Fracture	0 (0.0)	0 (0.0)	1 (2.7)	1 (0.6)
Traumatic Fracture	0 (0.0)	1 (2.6)	0 (0.0)	1 (0.6)
Investigations				
Blood Creatinine Increased	0 (0.0)	1 (2.6)	0 (0.0)	1 (0.6)
Hepatic Enzyme Increased	0 (0.0)	0 (0.0)	1 (2.7)	1 (0.6)
Musculoskeletal And Connective Tissue Disorders				
Musculoskeletal Pain (GT)[c]	0 (0.0)	1 (2.6)	0 (0.0)	1 (0.6)
Vascular Disorders				
Hemorrhage (GT)[d]	0 (0.0)	1 (2.6)	0 (0.0)	1 (0.6)

a) Includes PT terms pneumonia, COVID-19 pneumonia, respiratory tract infection.
b) Includes PT terms fatigue, asthenia.
c) Includes PT term back pain.
d) Includes PT term hemorrhoidal hemorrhage.

Source: ADSL (Subject-Level Analysis Dataset) - 2024-03-04, ADAE (Adverse Event Analysis Dataset) - 2024-03-04. Variables used: USUBJID, TUMTYP, SAFFL, TRT01A, TRTEMFL, AEDECOD, AETOXGRN, AEACN, AEACNMED, AEACNOTH, AEACNPRO, AEACNTHE, AEACNTRA, AEBODSYS, AESER

Dropouts and/or Discontinuations Due to Adverse Effects

Data:

Table 47. Applicant - Adverse events leading to permanent treatment discontinuation in patients treated with zenocutuzumab 750 mg Q2W in the eNRGy study (Safety Analysis Set)

Preferred Term	NRG1+ NSCLC (N=99)		NRG1+ PDAC (N=39)		All NRG1+ Tumor Types (N=175)	
	All Grades n (%)	Grade 3-4 n (%)	All Grades n (%)	Grade 3-4 n (%)	All Grades n (%)	Grade 3-4 n (%)
Patients with ≥1 AE	10 (10.1)	5 (5.1)	2 (5.1)	1 (2.6)	14 (8.0)	6 (3.4)
Dyspnea	2 (2.0)	2 (2.0)	0	0	2 (1.1)	2 (1.1)
Respiratory failure	1 (1.0)	0	0	0	2 (1.1)	0
Acute respiratory failure	1 (1.0)	0	0	0	1 (0.6)	0
AST increased	1 (1.0)	1 (1.0)	0	0	2 (1.1)	1 (0.6)
ALT increased	1 (1.0)	1 (1.0)	0	0	1 (0.6)	1 (0.6)
Asthenia	1 (1.0)	1 (1.0)	0	0	1 (0.6)	1 (0.6)
Back pain	0	0	1 (2.6)	1 (2.6)	1 (0.6)	1 (0.6)
Decreased appetite	1 (1.0)	1 (1.0)	0	0	1 (0.6)	1 (0.6)
Dehydration	1 (1.0)	1 (1.0)	0	0	1 (0.6)	1 (0.6)
GGT increased	1 (1.0)	1 (1.0)	0	0	1 (0.6)	1 (0.6)
Hyponatremia	1 (1.0)	1 (1.0)	0	0	1 (0.6)	1 (0.6)
Sepsis	1 (1.0)	1 (1.0)	0	0	1 (0.6)	1 (0.6)
Blood ALP increased	1 (1.0)	0	0	0	1 (0.6)	0
Cardiac failure	1 (1.0)	0	0	0	1 (0.6)	0
Dysphagia	1 (1.0)	0	0	0	1 (0.6)	0
General physical health deterioration	0	0	1 (2.6)	0	1 (0.6)	0
Pneumonitis	1 (1.0)	0	0	0	1 (0.6)	0

Source: eNRGy CSR Table 14.3.1.9

As of the data cutoff date (31 Jul 2023), no patients in the NRG1+ EAP experienced an AE leading to treatment discontinuation.

In the MCLA-128-CL01 study, there were no AEs leading to treatment discontinuation in the dose escalation. During the dose expansion, 6 patients (4.7%) had AEs leading to treatment discontinuation, 2 with blood bilirubin increased (both treated with the Q1W regimen), 1 of whom also experienced Grade 2 vomiting; in addition 1 patient each had Grade 2 abdominal pain (patient treated with the Q1W regimen), Grade 5 hypersensitivity (patient treated with the Q3W regimen), Grade 2 spontaneous miscarriage (patient treated with the Q1W regimen), and Grade 3 dyspnea (patient treated with the Q3W regimen).

Except for the case of Grade 5 hypersensitivity, all other AEs that led to treatment discontinuation were considered not related to study treatment.

The Applicant's Position:

Overall, 14 patients with all NRG1+ tumor types (8.0%) experienced an AE leading to permanent treatment discontinuation, of which 6 patients (3.4%) had Grade 3-4 events (Table 34). For 3 of these 14 patients, the reported AE (Grade 3 dyspnea, Grade 3 sepsis, and Grade 2 pneumonitis) was recorded as the primary reason for treatment discontinuation by the investigator at the end of study.

The only AEs leading to treatment discontinuation reported in more than 1 patient were respiratory failure (3 patients [1.7%], including 1 acute case), dyspnea and AST increased (2 patients [1.1%] each). Five patients (2.9%) had AEs leading to treatment withdrawal with a fatal outcome (respiratory failure [3 patients; including 1 acute case], cardiac failure [1 patient], and dysphagia [1 patient]), all of which were in the context of disease progression. Grade 2 pneumonitis was the only event considered treatment-related by the investigator.

In the non-NRG1+ MCLA-128-CL01 study, the only AEs leading to treatment discontinuation that were ≥Grade 3, were Grade 3 dyspnea, and Grade 5 hypersensitivity.

The FDA's Assessment:

AEs leading to treatment discontinuation occurred in 3 (1.7%) patients in the primary safety population; all were NSCLC patients. AEs leading to treatment discontinuation included Grade 3 sepsis (n=1), Grade 2 pneumonitis (n=1) and Grade 3 dyspnea (n=1). FDA's assessment after review of narratives was that progressive disease was the primary reason for discontinuation in all other treatment discontinuations. Review of the 90-day safety update did not reveal a significant change in the rate of treatment discontinuation due to AEs. Two additional patients experienced AEs leading to discontinuation, including urinary tract infection in 1 patient with NRG+ NSCLC and fracture in 1 patient with NRG1+ gastric cancer.

Dose Interruption/Reduction Due to Adverse Effects

Data:

Table 48. Applicant – Adverse events leading to dosing interruptions in ≥2 patients in the all NRG1+ tumor types population (Safety Analysis Set)

	NRG1+ NSCLC (N=99)		NRG1+ PDAC (N=39)		All NRG1+ Tumor Types (N=175)	
Preferred Term	**All grades n (%)**	**Grade 3-4 n (%)**	**All grades n (%)**	**Grade 3-4 n (%)**	**All grades n (%)**	**Grade 3-4 n (%)**
Number of patients with ≥1 AE[1]	**29 (29.3)**	**15 (15.2)**	**13 (33.3)**	**10 (25.6)**	**53 (30.3)**	**29 (16.6)**
AST increased	2 (2.0)	2 (2.0)	1 (2.6)	1 (2.6)	5 (2.9)	4 (2.3)
COVID-19	4 (4.0)	0	1 (2.6)	0	5 (2.9)	0
Dyspnea[2]	4 (4.0)	0	0	0	4 (2.3)	0
ALT increased	2 (2.0)	2 (2.0)	0	0	3 (1.7)	3 (1.7)
Pneumonia	2 (2.0)	1 (1.0)	1 (2.6)	1 (2.6)	3 (1.7)	2 (1.1)
Blood bilirubin increased	0	0	1 (2.6)	0	2 (1.1)	1 (0.6)
Hyperbilirubinemia	0	0	1 (2.6)	1 (2.6)	2 (1.1)	2 (1.1)
Jaundice cholestatic	0	0	1 (2.6)	1 (2.6)	2 (1.1)	2 (1.1)

[1] *An AE leading to dosing interruption had action taken with study drug of 'Dose Interrupted', 'Dose Delayed' or 'Other Action Taken' which was not marked by the investigator as an IRR.*
[2] *Dyspnea exertional was reported in 1 additional patient.*
Source: Table 14.3.1.10

In the NRG1+ EAP, 6 patients with all NRG1+ tumor types (40.0%) in the EAP experienced at least 1 AE leading to dose interruption, delay, or modification, including 3 patients (20.0%) with Grade 3-4 events. The only AE reported in more than 1 patient was IRR (2 patients [13.3%]). The only treatment-related events were AEs of IRR reported in 2 patients (1 NRG1+ NSCLC and 1 NRG1+ PDAC).

During the dose escalation of the non-NRG1+ MCLA-128-CL01 study, 11 patients (39.3%) had AEs that resulted in a dose interruption, including 2 patients (7.1%) with Grade 3 events, whereas in the dose expansion 24 patients (18.9%) (20 patients [19.8%] treated with the Q3W regimen and 4 patients [15.4%] treated with the Q1W regimen) had AEs that resulted in a dose interruption.

The Applicant's Position:

In the eNRGy study, adverse events leading to a dosing interruption were defined as AEs that had action taken with study drug of 'Dose Interrupted', 'Dose Delayed' or 'Other Action Taken' and which were not marked by the investigator as an IRR. In total, 53 patients (30.3%) had ≥1 AE

leading to a dosing interruption; AEs in ≥2 patients in the all NRG1+ tumor types population are presented in Table 37. The most common AEs were under the SOCs of investigations (15 patients [8.6%]), infections and infestations (14 patients [8.0%]), and respiratory, thoracic, and mediastinal disorders (7 patients [4.0%]). The most common AEs were AST increased (5 patients [2.9%]), COVID-19 (5 patients [2.9%]), dyspnea (5 patients [2.9%], including 1 patient with exertional dyspnea), ALT increased (3 patients [1.7%]), and pneumonia (3 patients [1.7%]). In addition, blood bilirubin increased and/or hyperbilirubinemia and/or jaundice cholestatic led to dosing interruption in 4 patients [2.3%]). All other AEs were reported in 1 patient each. Nine patients (5.1%) had AEs leading to dosing interruptions that were treatment-related.

Incidences of AEs leading to a dose or infusion interruption in patients with NRG1+ NSCLC and NRG1+ PDAC were comparable to those in patients with all NRG1+ tumor types.

During the non-NRG1+ MCLA-128-CL01 dose expansion, AEs (regardless of causality) led to dose interruptions in less than 20% of the patients.

Note that zenocutuzumab dose reductions were not permitted.

The FDA's Assessment:

FDA assessed dosing interruptions separately from infusion interruptions due to IRRs. Excluding infusion interruptions due to IRRs, 53 (30%) patients in the eNRGy safety set had at least one AE leading to a dosage interruption. FDA generally agrees with the Applicant's position regarding frequencies of AEs; differences in percentages are due to use of OOD preferred grouped terms. The most common AEs leading to dosage interruptions in the primary safety population were AST increased, COVID-19 and dyspnea in five (2.9%) patients each; ALT increased and pneumonia in three (1.7%) patients each; and arrhythmia, acute kidney injury, blood bilirubin increased, cholestatic jaundice, hyperbilirubinemia, and neutropenia in two (1.1%) patients each. All other AEs leading to dosing interruptions occurred in one patient each.

In the NSCLC group, 29% of patients had at least one AE leading to a dosage interruption. Adverse reactions leading to dosage interruptions in ≥2% of patients included dyspnea, COVID-19, arrhythmia, increased ALT, increased AST, and pneumonia.

In the PDAC group, 33% of patients had at least one AE leading to a dosage interruption. Adverse reactions leading to dosage interruptions in ≥2% of patients included COVID-19, pneumonia, increased AST, neutropenia, abdominal pain, agitation, increased blood alkaline phosphatase, increased blood bilirubin, constipation, increased creatinine, hemorrhage, hyperbilirubinemia, cholestatic jaundice, tachycardia, traumatic fracture, and upper respiratory infection.

FDA notes that on review of the 90-day safety update, there was one additional NSCLC patient who experienced Grade 1 pneumonitis leading to treatment interruption.

Significant Adverse Events

Data:

Significant adverse events leading to treatment discontinuation or dose interruptions are presented in the sections above and Table 36 and Table 37.

Three AESIs were evaluated in the eNRGy study: IRRs, diarrhea, and decreased cardiac ejection fraction. AESIs observed in the eNRGy study are summarized by type of event and indication in this section.

Infusion-Related Reactions

Table 49. Applicant – Summary of infusion-related reactions (composite term) in the eNRGy study (Safety Analysis Set)

	NRG1+ NSCLC (N=99) n (%)	NRG1+ PDAC (N=39) n (%)	All NRG1+ Tumor Types (N=175) n (%)
Patients with ≥1 IRR[1]	12 (12.1)	6 (15.4)	23 (13.1)
Patients with:			
1 IRR	11 (11.1)	6 (15.4)	22 (12.6)
2 IRRs	1 (1.0)	0	1 (0.6)
Patients with a serious IRR	0	0	0
Patients with IRR by worst outcome			
Not recovered/not resolved/ongoing	3 (3.0)	1 (2.6)	4 (2.3)
Recovered/resolved	9 (9.1)	5 (12.8)	19 (10.9)
Patients with IRR by most severe action taken for study drug			
Drug withdrawn	0	0	0
Infusion interrupted	7 (7.1)	3 (7.7)	15 (8.6)
Not applicable	5 (5.1)	2 (5.1)	7 (4.0)
Other[2]	0	1 (2.6)	1 (0.6)
Patients with IRR by action taken (other treatment or action)			
Medication	5 (5.1)	4 (10.3)	11 (6.3)
Infusion number at first IRR			
1	12 (12.1)	6 (15.4)	23 (13.1)
Patients with completed infusion after first IRR	12 (12.1)	6 (15.4)	23 (13.1)

[1] *IRR was defined as a composite term for AEs that developed within 24 hours of study drug administration and reported as a sign or symptom of an IRR, as judged by the investigator.*
[2] *Other: infusion interrupted and duration prolonged when restarted.*
Source: eNRGy CSR Table 14.3.1.17, Listing 16.2.5.1, Listing 16.2.7.4

Table 50. Applicant – Infusion-related reactions (composite term) in patients treated with zenocutuzumab 750 mg Q2W in the NRG1+ EAP (Safety Analysis Set)

System organ class Preferred term	NRG1+ NSCLC N=7		NRG1+ PDAC N=5		All NRG1+ Tumor Types N=15	
	All Grades n (%)	Grade 3-4 n (%)	All Grades n (%)	Grade 3-4 n (%)	All Grades n (%)	Grade 3-4 n (%)
Patients with ≥1 IRR	2 (28.6)	0	2 (40.0)	0	4 (26.7)	0
Infusion-related reaction	1 (14.3)	0	2 (40.0)	0	3 (20.0)	0
Pruritus	1 (14.3)	0	0	0	1 (6.7)	0
Hot flush	1 (14.3)	0	0	0	1 (6.7)	0

Source: EAP Table 14.3.1.12

Table 51. Applicant – MCLA-128-CL01 Dose escalation: IRRs (composite term) by PT – all grades (Safety Set)

PT	Cohort 1 (40mg) (N=1) n	Cohort 2 (80mg) (N=2) n	Cohort 3 (160mg) (N=1) n	Cohort 4 (240mg) (N=3) n	Cohort 5 (360mg) (N=3) n	Cohort 6 (480mg) (N=3) n	Cohort 7 (600mg) (N=6) n	Cohort 8 (750mg) (N=6) n	Cohort 9 (900mg) (N=3) n	Total (N=28) n (%)
Patients with at least one IRR (composite term)[1]	0	1	1	1	2	1	4	2	1	13 (46.4)
Infusion-related reaction	0	1	1	0	1	1	4	2	0	10 (35.7)
Nausea	0	0	1	1	1	1	1	0	0	5 (17.9)
Vomiting	0	0	1	1	1	0	1	0	1	5 (17.9)
Abdominal pain	0	0	0	0	1	0	0	0	0	1 (3.6)
Chills	0	0	0	0	0	0	0	1	0	1 (3.6)
Headache	0	0	0	0	0	0	1	0	0	1 (3.6)
Non cardiac chest pain	0	0	0	0	0	0	0	1	0	1 (3.6)
Pyrexia	0	0	0	1	0	0	0	0	0	1 (3.6)
Tremor	0	0	0	1	0	0	0	0	0	1 (3.6)

Source: Table 14.3.1.36
[1] Composite term defined as any AE that developed within 24 h of study drug administration reported as a sign or symptom of an IRR, as judged by the Investigators.

Table 52. Applicant – MCLA-128-CL01 Dose Expansion: IRRs (composite term) by PT by dose regimen (Safety Set)

PT	750 mg Q3W (N=101)		Q1W (N=26)		Total (N=127)	
	All Grades n (%)	Grade 3-4 n (%)	All Grades n (%)	Grade 3-4 n (%)	All Grades n (%)	Grade 3-4 n (%)
Patients with at least one IRR (composite term)[1]	19 (18.8)	3 (3.0)	2 (7.7)	0 (0.0)	21 (16.5)	3 (2.4)
Infusion-related reaction	9 (8.9)	2 (2.0)	0 (0.0)	0 (0.0)	9 (7.1)	2 (1.6)
Chills	4 (4.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (3.1)	0 (0.0)
Hypersensitivity	3 (3.0)	0 (0.0)	1 (3.8)	0 (0.0)	4 (3.1)	0 (0.0)
Vomiting	3 (3.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.4)	0 (0.0)
Bronchospasm	0 (0.0)	0 (0.0)	1 (3.8)	0 (0.0)	1 (0.8)	0 (0.0)
Cough	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.8)	1 (0.8)
Drug hypersensitivity	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
Dyspnea	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.8)	1 (0.8)
Hyperhidrosis	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
Hypertension	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.8)	1 (0.8)
Hypoxia	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.8)	1 (0.8)
Myalgia	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.8)	1 (0.8)
Nausea	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
Pyrexia	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)

Source: Table 14.3.1.38
[1] Composite term defined as any AE that developed within 24 h of study drug administration reported as a sign or symptom of an IRR, as judged by the Investigators.

An AE of IRR was reported in 1 patient out of the 8 patients in the non-NRG1+ *HER3*-mutant cancer patients from the non-NRG1+ EAP.

In the MCLA-128-CL02 zenocutuzumab-based combination study, 20 out of 104 patients (1 patient in cohort 1 doublet, 7 patients in cohort 1 triplet, and 12 patients in cohort 2) experienced an IRR (composite term).

Diarrhea

In the eNRGy study, based on an analysis of AEs according to the list of MedDRA PTs, the AESI of diarrhea was reported in 49 patients with all NRG1+ tumor types (28.0%), including Grade 3 events in 4 patients (2.3%), 1 of whom had 2 Grade 3 events. Two patients (1.1%) had diarrhea reported as an IRR. Thirty-one patients (17.7%) had treatment-related diarrhea, including 3 patients (1.7%) with Grade 3 events. No patients had diarrhea leading to treatment withdrawal or a dose or infusion interruption, and none of the cases were reported as SAEs.

The frequency of diarrhea was higher in NRG1+ PDAC patients (15 patients [38.5%]) compared to NRG1+ NSCLC patients (26 patients [26.3%]), which was expected given the nature of the underlying disease.

In the NRG1+ EAP, diarrhea was reported in 4 patients (26.7%); all events were nonserious and Grade 1-2 in severity. Two patients had events of diarrhea considered treatment-related by the investigator. None of the cases were reported as IRRs and none resulted in a change in study treatment.

In the non-NRG1+ MCLA-128-CL01 study, during the dose escalation 6 patients (21.4%) experienced diarrhea as a related AE. During the dose expansion, the overall frequency of diarrhea was 32.3% (29.7% in patients treated with the Q3W regimen and 42.3% in patients treated with the Q1W regimen), with a low rate (1.6%) of Grade 3-4 events (2.0% in patients treated with the Q3W regimen and none in patients treated with the Q1W regimen) and no events requiring treatment discontinuation, other than the fatal hypersensitivity.

In the MCLA-128-CL02 zenocutuzumab-based combination study, the most frequent AE irrespective of causality (≥20% of patients) was diarrhea in all cohorts: 46.7% in the Cohort 1 patients who received doublet therapy, 71.8% in the Cohort 1 triplet, and 34.0% in Cohort 2.

Decreased Cardiac Ejection Fraction

No patients had investigator-reported AEs of cardiac ejection fraction decreased in the eNRGy study. The AESI of decreased cardiac ejection fraction was observed in 3 patients (1.7%), all of whom experienced events of cardiac failure; none of these 3 patients had associated on-treatment LVEF decreases by MUGA/ECHO.

One NRG1+ NSCLC patient had 2 events of cardiac failure, the first of which was a Grade 3 SAE that led to a dose interruption and the second was a fatal event. Neither AE was considered treatment-related. The patient had a baseline LVEF value (ECHO) of 60% and no on-treatment measurements.

The 2 remaining patients had non-serious AEs of Grade 1 (not treatment-related) and Grade 2 (treatment-related) cardiac failure; neither event led to a dose interruption. Both patients had LVEF measurements within normal limits at baseline. The patient with Grade 2 treatment-related cardiac failure had on-treatment measurements that were also within normal limits (68.2% at Cycle 5 Day 1 and 70.4% at the final study visit). No on-treatment cardiac scans were recorded for the patient with Grade 1 cardiac failure.

Analysis of LVEF shifts from baseline to worst on-treatment assessment was performed in 95 of the 175 patients (54.3%) in the Safety Analysis Set who had a baseline assessment and ≥1 post-baseline assessment. No Grade 3 or 4 LVEF decreases were reported during the study.

No AEs of cardiac failure or decreased cardiac ejection fraction were reported in the EAP. The only event reported in the cardiac disorders system organ class was a Grade 3 SAE of myocardial infarction that was not treatment-related. Study treatment was delayed due to this event.

Note that outcomes of ECHO analyses were not requested to be collected in the EAP database, therefore, there are no calculated measures of LVEF values from ECHO analyses.

In the non-NRG1+ MCLA-128-CL01 study, during the dose escalation and expansion part, no patients were identified as having an emergent Grade 3 or Grade 4 LVEF decrease on study.

During the dose escalation, of the 22 patients evaluable for decreased LVEF on study, 3 patients (13.6%) were identified as having an emergent Grade 2 LVEF decrease on study. During the dose expansion, Of the 69 patients evaluable for decreased LVEF on study, 5 patients (7.2%) had an emergent Grade 2 LVEF decrease on study, 3 patients who received the Q3W regimen and 2 who received Q1W.

The Applicant's Position:

Based on the primary safety data in the eNRGy study, the analyses of the 3 prespecified AESIs showed no safety risks of concern.

- IRRs were observed in 13.1% of patients. There were no Grade 3-4 events or treatment discontinuations due to IRRs.
- Diarrhea was observed in 28.0% of patients, and only 2.3% of patients had Grade 3-4 events. No events of diarrhea led to treatment discontinuation.
- No patients had investigator-reported AEs of cardiac ejection fraction decreased.

Based on data review, the applicant included premedication and management of IRRs in the proposed prescribing information.

General adherence to standard practice and published guidelines for managing diarrhea associated with zenocutuzumab treatment was recommended in clinical studies. Specific management of diarrhea in patients receiving zenocutuzumab is not warranted.

No specific cardiac evaluations or monitoring are required for patients receiving zenocutuzumab 750 mg Q2W. For patients with reduced LVEF and/or cardiac disease, manage according to routine clinical practice.

The FDA's Assessment:

FDA does not agree with the Applicant's position that analyses of the 3 prespecified AESIs showed no safety risks of concern, specifically regarding the risk of serious and life-threatening infusion-related reactions/hypersensitivity and left ventricular dysfunction in patients receiving zenocutuzumab. FDA's analysis of each AESI is presented below:

Infusion-Related Reactions

In the primary safety population, IRRs occurred in 13% of patients. Incidence of IRR was similar in NSCLC (12%) and PDAC (15%) patients. The majority (91%) of IRRs occurred during the first infusion, and all IRRs were Grade 1-2. The median time to onset was 63 minutes (range: 13 minutes to 240 minutes) from the start of infusion. The rate of IRR reported in the primary safety population with the 90-day safety update was similar at 14% (n=28). All additional IRRs reported were Grade 1-2. Of the 28 patients with at least one IRR reported, 26 had a single IRR. The majority (96%) of these IRRs occurred during the first infusion, however there was one patient with a first IRR occurring during the 9th infusion of zenocutuzumab. Of the 2 patients

with more than one IRR, one patient had IRRs during the first and second infusions, and one patient had IRRs during the first and 16th infusions.

In the supportive safety population, there was one patient with a Grade 5 hypersensitivity reaction (see Deaths) and 2 patients with Grade 3 IRRs. Of the 2 patients with Grade 3 IRRs, one patient experienced an IRR with the Cycle 2, Day 1 infusion, and the other patient experienced two Grade 3 IRRs, one with the Cycle 1, Day 1 infusion and one with the Cycle 2, Day 1 infusion. All three patients were assigned to zenocutuzumab 750 mg every 3 weeks. While these events did not occur in the primary safety population, incidence of IRR/hypersensitivity would not be expected to differ based on tumor type or dosage. Therefore, FDA considers serious and life-threatening IRR/hypersensitivity to be a significant risk of treatment with zenocutuzumab and will include a Warning for "IRR/Hypersensitivity/Anaphylactic Reactions" in the USPI.

Decreased cardiac ejection fraction

In the primary safety population, AEs with the PT cardiac failure were reported in three (1.7%) patients, two with NRG1+ NSCLC and one with NRG1+ breast cancer; none of these patients had documented decreases in LVEF by ECHO or MUGA. No additional AESIs of decreased cardiac ejection fraction were reported with the 90-day safety update. Clinical information on each patient is summarized below:

- One patient with NSCLC had two AEs of cardiac failure, one Grade 3 event and one Grade 5 event. This patient experienced right heart decompensation in the setting of progressive disease in the lung (see Table 39 for narrative).
- Grade 2 cardiac failure was reported in an 84 year old female with NRG1+ NSCLC and a prior medical history of hypertension (treated with amlodipine and valsartan), cerebral infarction, hyperlipidemia and internal carotid artery stenosis. This patient had an LVEF of 68% recorded on screening ECHO and on ECHO performed per protocol on C5D1. Fifteen days after the C5D1 ECHO was performed, the patient developed grade 1 lower extremity edema. Approximately 4 months later, the patient was diagnosed with worsening internal carotid artery stenosis and underwent left carotid artery stent placement. This event was considered unrelated to study treatment by the investigator. The patient's ECHO on C10D15 showed an LVEF of 67%, and the patient was again reported to have Grade 1 edema. The patient was reported to have Grade 2 cardiac failure 546 days after starting the study drug. The diagnosis of cardiac failure was based on a cardiologist's assessment of LV diastolic dysfunction from a subsequent ECHO (LVEF 66%). The patient was started on furosemide 10 mg PO daily. No action was taken with zenocutuzumab. The patient had grade 1 edema which did not resolve with initiation of furosemide. The patient later discontinued treatment due to progressive disease. At the final study visit, the patient's ECHO demonstrated an LVEF of 70%.
- Grade 1 cardiac failure was reported in a 59 year old female with NRG1+ breast cancer. The patient's baseline MUGA scan demonstrated an LVEF of 70%. The report of cardiac failure was based on an asymptomatic elevation of NT-ProBNP identified on labs obtained as per safety monitoring outlined in the protocol. The patient's baseline NT-

ProBNP was 16 pmol/l (High: >18 pmol/l), and 50 pmol/l 32 days after starting study treatment. There was no additional cardiac imaging performed and no cardiologist was consulted. The patient did not receive any medical treatment for the AE of cardiac failure and no action was taken with zenocutuzumab. The patient died due to progressive disease 56 days after beginning study treatment and 24 days after the onset of Grade 1 cardiac failure.

In the primary safety population, 2 of 95 (2%) evaluable patients had asymptomatic decreases in LVEF (Grade 2) on ECHO. On review of the 90-day safety update, an asymptomatic decrease in LVEF (Grade 2) was reported in 1 additional patient. None of these events were reported as AEs by the investigator.

One SAE of Grade 3 cardiac failure was reported in the supportive safety population:

- This event was reported in a 73-year-old female with stage IV non-NRG1+ endometrial cancer with metastases to liver, lung and lymph nodes, and with a pertinent medical history of liver cirrhosis, COPD, and alcohol and tobacco abuse. The patient's screening MUGA scan demonstrated an LVEF of 78%. Sixty-seven days after beginning study treatment, the patient experienced an AE of Grade 2 dyspnea. A MUGA scan was performed 13 days later, which demonstrated an LVEF of 79%. An EKG was performed 4 days after the MUGA scan which was notable for sinus tachycardia (106 bpm), normal conduction times, Q wave in inferior lead and a negative T-wave in aVL. A proBNP obtained the same day was 86 pg/mL (normal: <125) and a CK-MB 10.2. Cardiology was consulted and an ECHO was performed. The ECHO demonstrated a preserved LVEF with significant left ventricular hypertrophy and disturbed relaxation with increased filling pressures. The patient was reported to have Grade 3 cardiac failure. The patient was treated with metoprolol for tachycardia, and no other medical interventions were provided. Study treatment was discontinued 135 days after treatment initiation for progressive disease.

FDA considers left ventricular dysfunction to be a potential significant risk of treatment with zenocutuzumab and will include a Warning in the USPI.

Diarrhea

Diarrhea was the most commonly reported AE in the primary safety population, occurring in 26% of NSCLC patients and 38% of PDAC patients. Grade 3-4 diarrhea was reported in 2% of NSCLC patients and 5% of PDAC patients. No SAE of diarrhea occurred in the primary safety population, and there were no drug interruptions or discontinuations due to diarrhea. FDA review of the 90-day safety update did not alter the original assessment of the risk of diarrhea with zenocutuzumab.

Although interstitial lung disease (ILD)/pneumonitis was not a pre-specified AESI in the eNRGy study, it is a significant risk with other HER2-directed therapies. In the primary safety population, ILD/pneumonitis occurred in 2 (1.1%) patients; both of these patients were NSCLC patients. The incidence of ILD/pneumonitis was 2% in the NSCLC group. One patient had an event of Grade 2 ILD/pneumonitis leading to treatment discontinuation; this patient had not received any prior systemic or radiation therapy for NSCLC. A second NSCLC patient had an event of Grade 1 pneumonitis leading to treatment interruption. On review of the 90-day safety update, there was one additional patient with an event of Grade 1 pneumonitis leading to treatment interruption.

FDA considers interstitial lung disease/pneumonitis to be a potential significant risk of treatment with zenocutuzumab and will include a Warning in the USPI.

Treatment Emergent Adverse Events and Adverse Reactions

Data:

Table 53. Applicant - Overall summary of treatment-emergent adverse events in NRG1+ cancer patients treated with zenocutuzumab 750 mg Q2W in the eNRGy study (Safety Analysis Set)

Patients with:	NRG1+ NSCLC (N=99) n (%)	NRG1+ PDAC (N=39) n (%)	All NRG1+ Tumor Types (N=175) n (%)
At least 1 AE	89 (89.9)	38 (97.4)	159 (90.9)
At least 1 SAE	25 (25.3)	9 (23.1)	42 (24.0)
AE leading to withdrawal from study drug	10 (10.1)	2 (5.1)	14 (8.0)
AE leading to death	5 (5.1)	2 (5.1)	8 (4.6)
AE by worst CTCAE grade:			
Grade 1	23 (23.2)	6 (15.4)	34 (19.4)
Grade 2	35 (35.4)	12 (30.8)	61 (34.9)
Grade 3	22 (22.2)	17 (43.6)	48 (27.4)
Grade 4	4 (4.0)	1 (2.6)	8 (4.6)
Grade 5	5 (5.1)	2 (5.1)	8 (4.6)
At least 1 treatment-related AE	65 (65.7)	28 (71.8)	110 (62.9)
AE by worst relationship:			
Definitely related	21 (21.2)	9 (23.1)	37 (21.1)
Probably related	16 (16.2)	8 (20.5)	28 (16.0)
Possibly related	28 (28.3)	11 (28.2)	45 (25.7)
Not / Unlikely related	24 (24.2)	10 (25.6)	49 (28.0)

Patients with:	NRG1+ NSCLC (N=99) n (%)	NRG1+ PDAC (N=39) n (%)	All NRG1+ Tumor Types (N=175) n (%)
AE by action taken with study drug:			
Infusion interrupted[1]	7 (7.1)	4 (10.3)	16 (9.1)
Dose interrupted[2]	29 (29.3)	13 (33.3)	53 (30.3)
Drug withdrawn	10 (10.1)	2 (5.1)	14 (8.0)
Unknown	2 (2.0)	0	2 (1.1)
Not applicable	87 (87.9)	38 (97.4)	156 (89.1)
AE requiring additional treatment:	73 (73.7)	33 (84.6)	133 (76.0)
Medication	72 (72.7)	32 (82.1)	128 (73.1)
Transfusion	3 (3.0)	3 (7.7)	10 (5.7)
Other	16 (16.2)	9 (23.1)	33 (18.9)
At least 1 AE of special interest[3]	35 (35.4)	19 (48.7)	68 (38.9)
At least 1 IRR[4]	12 (12.1)	6 (15.4)	23 (13.1)

CTCAE=Common Terminology Criteria for Adverse Events

1 *AEs leading to an infusion interruption had action taken with study drug of 'Dose Interrupted' or 'Other Action Taken' and were marked as an IRR by the investigator.*

2 *AEs leading to a dose interruption had action taken with study drug of 'Dose Interrupted', 'Dose Delayed' or 'Other Action Taken' and were not marked as an IRR by the investigator.*

3 *AESIs in this study included IRR, diarrhea, and decreased cardiac ejection fraction.*

4 *IRR was defined as a composite term for AEs that developed within 24 hours of study drug administration and reported as a sign or symptom of an IRR, as judged by the investigator.*

Source: eNRGy CSR Table 14.3.1.1, Table 14.3.1.13

Table 54. Applicant - Overall summary of adverse events in NRG1+ cancer patients treated with zenocutuzumab 750 mg Q2W in the NRG1+ EAP (Safety Analysis Set)

Patients with:	NRG1+ NSCLC (N=7) n (%)	NRG1+ PDAC (N=5) n (%)	All NRG1+ Tumor Types (N=15) n (%)
At least 1 AE	6 (85.7)	3 (60.0)	12 (80.0)
At least 1 SAE	2 (28.6)	2 (40.0)	5 (33.3)
AE leading to withdrawal of study drug	0	0	0
AE leading to death	0	1 (20.0)	1 (6.7)
At least 1 treatment-related AE	5 (71.4)	2 (40.0)	8 (53.3)
AE leading to dose adjustment/delay/interruption	3 (42.9)	2 (40.0)	6 (40.0)
At least 1 IRR[1]	2 (28.6)	2 (40.0)	4 (26.7)

1 *Composite term defined as an AE that developed within 24 hours of study drug administration reported as a sign or symptom of an IRR, as judged by the investigator.*

Source: EAP CSR Table 14.3.1.1

Table 55. Applicant – MCLA-128-CL01 Dose Escalation: overview of AEs in patients treated with zenocutuzumab Q3W regimen – all grades (Safety Set)

	Cohort 1 (40mg) (N=1) n	Cohort 2 (80mg) (N=2) n	Cohort 3 (160mg) (N=1) n	Cohort 4 (240mg) (N=3) n	Cohort 5 (360mg) (N=3) n	Cohort 6 (480mg) (N=3) n	Cohort 7 (600mg) (N=6) n	Cohort 8 (750mg) (N=6) n	Cohort 9 (900mg) (N=3) n	Total (N=28) n (%)
Patients with at least one AE	1	2	1	3	3	3	6	6	3	28 (100.0)
Patients with at least one SAE	0	0	1	0	0	0	1	2	1	5 (17.9)
Patients with AE leading to withdrawal from study drug	0	0	0	0	0	0	0	0	0	0 (0.0)
Patients with AE leading to death	0	0	0	0	0	0	0	0	0	0 (0.0)
Patients with AE by worst CTCAE grade										
Grade 1	1	0	0	2	0	0	1	0	1	5 (17.9)
Grade 2	0	0	1	0	1	2	3	2	1	10 (35.7)
Grade 3	0	2	0	1	2	1	2	4	1	13 (46.4)
Patients with at least one treatment-related AE	0	2	1	2	3	2	6	6	3	25 (89.3)
Patients with AE by worst relationship										
Definitely related	0	1	1	1	2	1	5	2	0	13 (46.4)
Probably related	0	1	0	0	1	1	0	2	0	5 (17.9)
Possibly related	0	0	0	1	0	0	1	2	3	7 (25.0)
Not / Unlikely related	1	0	0	1	0	1	0	0	0	3 (10.7)
Patients with an AE by action taken with study drug										
Dose interrupted	0	1	1	0	1	0	3	3	2	11 (39.3)
Patients with additional treatments provided for any AE										
None	1	2	1	3	3	3	5	6	3	27 (96.4)

	Cohort 1 (40mg) (N=1) n	Cohort 2 (80mg) (N=2) n	Cohort 3 (160mg) (N=1) n	Cohort 4 (240mg) (N=3) n	Cohort 5 (360mg) (N=3) n	Cohort 6 (480mg) (N=3) n	Cohort 7 (600mg) (N=6) n	Cohort 8 (750mg) (N=6) n	Cohort 9 (900mg) (N=3) n	Total (N=28) n (%)
Medication (remedial due to AE)	0	2	1	2	3	3	6	5	1	23 (82.1)
Transfusion	0	0	0	1	0	0	2	3	1	7 (25.0)
Other	0	2	1	0	1	1	2	3	2	12 (42.9)
Patients with at least one IRR[1]	0	1	1	1	2	1	4	2	1	13 (46.4)
Patients with at least one DLT	0	0	0	0	0	0	0	0	0	0 (0.0)

Source: Table 14.3.1.1
[1] Composite term of any AE that developed within 24 h of study drug administration reported as a sign or symptom of an IRR, as judged by the Investigators.
CTCAE = Common terminology criteria for adverse events; DLT = dose limiting toxicity; IRR = infusion-related reaction

Table 56. Applicant – MCLA-128-CL01 Dose Expansion: overview of AEs (Safety Set) by dose regimen

	750 mg Q3W (N=101)		Q1W (N=26)		Total (N=127)	
	All Grades n (%)	Grade 3-4 n (%)	All Grades n (%)	Grade 3-4 n (%)	All Grades n (%)	Grade 3-4 n (%)
Patients with at least one AE	96 (95.0)	45 (44.6)	25 (96.2)	3 (11.5)	121 (95.3)	48 (37.8)
Patients with at least one SAE	34 (33.7)	25 (24.8)	6 (23.1)	1 (3.8)	40 (31.5)	26 (20.5)
Patients with AE leading to withdrawal from study drug	2 (2.0)	1 (1.0)	4 (15.4)	0 (0.0)	6 (4.7)	1 (0.8)
Patients with AE leading to death	2 (2.0)	0 (0.0)	3 (11.5)	0 (0.0)	5 (3.9)	0 (0.0)
Patients with AE by worst CTCAE grade						
Grade 1	14 (13.9)	NA	3 (11.5)	NA	17 (13.4)	NA
Grade 2	36 (35.6)	NA	16 (61.5)	NA	52 (40.9)	NA
Grade 3	41 (40.6)	NA	3 (11.5)	NA	44 (34.6)	NA
Grade 4	3 (3.0)	NA	0 (0.0)	NA	3 (2.4)	NA
Grade 5	2 (2.0)	NA	3 (11.5)	NA	5 (3.9)	NA
Patients with at least one treatment-related AE	57 (56.4)	5 (5.0)	17 (65.4)	0 (0.0)	74 (58.3)	5 (3.9)
Patients with AE by worst relationship						
Definitely Related	31 (30.7)	3 (3.0)	8 (30.8)	0 (0.0)	39 (30.7)	3 (2.4)

	750 mg Q3W (N=101)		Q1W (N=26)		Total (N=127)	
	All Grades n (%)	Grade 3-4 n (%)	All Grades n (%)	Grade 3-4 n (%)	All Grades n (%)	Grade 3-4 n (%)
Probably Related	20 (19.8)	2 (2.0)	4 (15.4)	0 (0.0)	24 (18.9)	2 (1.6)
Possibly Related	6 (5.9)	0 (0.0)	5 (19.2)	0 (0.0)	11 (8.7)	0 (0.0)
Not/Unlikely Related	39 (38.6)	40 (39.6)	8 (30.8)	3 (11.5)	47 (37.0)	43 (33.9)
Patients with an AE by action taken with study drug						
Dose interrupted	20 (19.8)	6 (5.9)	4 (15.4)	0 (0.0)	24 (18.9)	6 (4.7)
Patients with additional treatments provided for any AE						
None	88 (87.1)	17 (16.8)	23 (88.5)	2 (7.7)	111 (87.4)	19 (15.0)
Medication	76 (75.2)	30 (29.7)	20 (76.9)	2 (7.7)	96 (75.6)	32 (25.2)
Transfusion	12 (11.9)	4 (4.0)	3 (11.5)	2 (7.7)	15 (11.8)	6 (4.7)
Other	35 (34.7)	16 (15.8)	5 (19.2)	1 (3.8)	40 (31.5)	17 (13.4)
Patients with at least one IRR[1]	19 (18.8)	3 (3.0)	2 (7.7)	0 (0.0)	21 (16.5)	3 (2.4)

Source: Table 14.3.1.3
[1] Composite term defined as any AE that developed within 24 h of study drug administration reported as a sign or symptom of an IRR, as judged by the Investigators.

Table 57. Applicant – MCLA-128-CL02: Overall summary of adverse events in metastatic breast cancer patients treated with zenocutuzumab 750 mg Q3W in combination with trastuzumab ± vinorelbine (Cohort 1) or endocrine therapy (Cohort 2) in MCLA-128-CL02 (Safety Set)

Number of patients with ≥1:	Cohort 1 Doublet (N=15) n (%)	Cohort 1 Triplet (N=39) n (%)	Cohort 2 (N=50) n (%)
AE	15 (100.0)	39 (100.0)	48 (96.0)
Treatment-related AE	13 (86.7)	37 (94.9)	40 (80.0)
SAE	2 (13.3)	8 (20.5)	9 (18.0)
Treatment-related SAEs	0	4 (10.3)	3 (6.0)
Fatal SAEs	0	1 (2.6)	0
Treatment-related fatal SAEs	0	1 (2.6)	0
AE leading to discontinuation	0	1 (2.6)	3 (6.0)
Treatment-related AEs leading to discontinuation	0	1 (2.6)	2 (4.0)
AE leading to zenocutuzumab dose modification	0	0	2 (4.0)
Treatment-related AEs leading to zenocutuzumab dose modification	0	0	0
AE leading to dose interruption of zenocutuzumab	0	5 (12.8)	8 (16.0)
Treatment-related AEs leading to dose interruption of zenocutuzumab	0	5 (12.8)	8 (16.0)
AE requiring concomitant or additional treatment	12 (80.0)	37 (94.9)	38 (76.0)
Infusion-related reaction[1]	1 (6.7)	7 (17.9)	12 (24.0)

[1] Composite term including all AEs that developed within 24 h of study drug administration reported as a sign or symptom of an IRR, as judged by the investigator.
Source: MCLA-128-CL02 Table 14.3.1.1a, Table 14.3.1.1b, Table 14.3.1.14a, Table 14.3.1.14b

Based on FDA guidance 2006 on the adverse drug reactions section of labeling, the applicant provides the assessment below limited to those events for which there is some basis to believe there is a causal relationship between occurrence of an adverse event and the use of a drug.

Table 58. Applicant – Adverse drug reactions in NRG1+ cancer patients treated with zenocutuzumab 750 mg Q2W in the eNRGy study (Safety Analysis Set)

System Organ Class Adverse Reaction	All NRG1+ Tumor Types (N=175)	
	All Grades n (%)	Grade 3-4 n (%)
Gastrointestinal disorders		
Diarrhea[1]	47 (26.9)	4 (2.3)
Nausea	26 (14.9)	3 (1.7)
Constipation	22 (12.6)	0
Vomiting	21 (12.0)	1 (0.6)
Abdominal pain[2]	19 (10.9)	4 (2.3)
Stomatitis[3]	11 (6.3)	0
General disorders and administration site conditions		
Fatigue[4]	34 (19.4)	4 (2.3)
Injury, poisoning and procedural complications		
IRR[5]	22 (12.6)	0
Respiratory, thoracic and mediastinal disorders		
Dyspnea	23 (13.1)	5 (2.9)
Pneumonitis	2 (1.1)	0
Skin and subcutaneous tissue disorders		
Rash[6]	22 (12.6)	0
Metabolism and nutrition disorders		
Decreased appetite	15 (8.6)	2 (1.1)

1 *Includes diarrhea and post-procedural diarrhea.*
2 *Includes abdominal pain and abdominal pain upper.*
3 *Includes stomatitis and mucosal inflammation.*
4 *Includes fatigue and asthenia.*
5 *Includes chills, IRR, nausea, cough, diarrhea, back pain, body temperature increased, dyspnea, face edema, fatigue, non-cardiac chest pain, oropharyngeal discomfort, paresthesia, pyrexia, and vomiting. AEs that were considered IRRs were counted under the composite term 'IRR', irrespective of the reported PT.*
6 *Includes rash, dermatitis acneiform, erythema, dermatitis, dermatitis contact, rash maculopapular, rash erythematous.*

Note: anemia is not included in this table because decreased hemoglobin is already included in the table of lab abnormalities (Table 21) that have worsened ≥ 20%
Source: eNRGy CSR Table 14.3.1.3.6, Ad Hoc Listing 16.2.7.5 Module 5.3.5.3

The Applicant's Position:

Please note that assessment of treatment-emergent adverse events from the single arm eNRGy study was presented regardless of investigator or applicant's assessment relatedness to study drug. The majority of AEs and investigator-assessed related AEs in the eNRGy study were mild to moderate in severity, across regimens and tumor types. AEs resulting in death were rare, not

treatment-related, and were almost exclusively associated with the underlying disease. The safety profile of zenocutuzumab in NRG1+ cancer patients (all tumor types) who received 750 mg Q2W in the eNRGy study was generally consistent with the 750 mg Q3W regimen in non-NRG1+ cancer patients.

ADRs attributed to zenocutuzumab were identified through an evaluation of TEAEs in patients with all NRG1+ tumor types in the eNRGy study. The following rules were used in this assessment:

- TEAEs reported in ≥10% of patients with all NRG1+ tumor types were considered to have met the ADR threshold.
- TEAEs reported in >1% of patients with all NRG1+ tumor types were evaluated in the context of a potential plausible biological or pharmacological association with zenocutuzumab.
- Medically significant events with a high probability of association with zenocutuzumab were evaluated (regardless of frequency).
- All serious TEAEs, including all fatal events, and events leading to drug withdrawal were reviewed.
- All laboratory parameters were reviewed. Note: No Grade 3 or 4 laboratory abnormalities were observed at a frequency ≥15% of patients with all NRG1+ tumor types in the eNRGy study.
- Similar medical concepts were grouped by MedDRA PT.

Based on medical assessment, the most frequently reported ADRs (≥10%) were diarrhea, fatigue, nausea, dyspnea, IRR, rash, constipation, vomiting, and abdominal pain, with few Grade 3-4 events.

The FDA's Assessment:

FDA generally agrees with the Applicant's position; however FDA does not incorporate attribution to treatment into the safety review.

FDA generally agrees with the data presented in Applicant's Table 42; however, following FDA's review of the death narratives provided by the Applicant, FDA determined that the Applicant's Table includes 3 patients who died due to disease progression rather than AEs (see Section 8.2.2 Deaths).

FDA generally agrees with rates of TEAEs by preferred term presented by the Applicant; however, differences in rates reflect the use of OOD preferred grouping, which differed from groupings performed by the Applicant. The most common (≥10%) TEAEs in the primary safety population were diarrhea (28%), musculoskeletal pain (23%), fatigue (20%), nausea (17%),

infusion-related reactions (13%), dyspnea (14%), constipation (13%), vomiting (12%), rash, abdominal pain (11% each), and edema (10%).

Incidence of all-grade TEAEs were similar among tumor types, however; incidence of Grade 3-4 AEs was higher in patients with PDAC (46%) than NSCLC patients (26%). Rates of certain TEAEs also differed between patients with NSCLC and PDAC. Respiratory AEs were more common in NSCLC patients and gastrointestinal AEs were more common in patients with PDAC, consistent with the disease effect in these populations. The TEAEs which occurred more frequently (difference ≥10%) in NSCLC patients than in patients with PDAC were dyspnea (18% in NSCLC and 5% in PDAC) and cough (14% in NSCLC and 0% in PDAC). TEAEs which occurred more frequently (difference ≥10%) in patients with PDAC included diarrhea (38% in PDAC and 26% in NSCLC), nausea (26% in PDAC and 11% in NSCLC), vomiting (23% in PDAC and 8% in NSCLC), abdominal pain (18% in PDAC and 8% in NSCLC), and COVID-19 (18% in PDAC and 8% in NSCLC).

In the NSCLC group, clinically relevant adverse reactions occurring in less than 10% of patients were stomatitis (7%), vomiting (8%), cardiac failure and pneumonitis (2% each). Refer to Significant Adverse Events above for FDA's analysis of cardiac failure and pneumonitis.

In the PDAC group, clinically relevant adverse reactions in less than 10% of patients were decreased appetite (5%), and rash (8%), including the preferred terms dermatitis acneiform, erythema, dermatitis, dermatitis contact, rash maculopapular and rash erythematous.

Table 59: Adverse Reactions Occurring in ≥10% of Patients (FDA Review)

	NSCLC N = 99		**PDAC N = 39**		**All solid tumors N = 175**	
	All grades n (%)	**Grade 3-4 n (%)**	**All grades n (%)**	**Grade 3-4 n (%)**	**All grades n (%)**	**Grade 3-4 n (%)**
Patients with TEAEs	89 (90)	26 (26)	38 (97)	18 (46)	159 (91)	56 (32)
Gastrointestinal Disorders						
Diarrhea[a]	25 (25)	2 (2.0)	14 (36)	2 (5)	47 (27)	4 (2.3)
Nausea	10 (11)	1 (1.0)	9 (23)	2 (5)	28 (16)	3 (1.7)
Constipation	9 (9)	0 (0.0)	6 (15)	0 (0.0)	22 (13)	0 (0.0)
Abdominal Pain[b]	8 (8)	1 (1.0)	7 (18)	2 (5)	20 (11)	4 (2.3)
Vomiting	8 (8)	0 (0.0)	9 (23)	1 (2.6)	21 (12)	1 (0.6)

	NSCLC N = 99		PDAC N = 39		All solid tumors N = 175	
	All grades n (%)	Grade 3-4 n (%)	All grades n (%)	Grade 3-4 n (%)	All grades n (%)	Grade 3-4 n (%)
Stomatitis[c]	7 (7)	0 (0.0)	4 (10)	0 (0.0)	11 (6)	0 (0.0)
Abdominal Distension	1 (1.0)	1 (1.0)	5 (13)	0 (0.0)	6 (3.4)	1 (0.6)
Musculoskeletal and Connective Tissue Disorders						
Musculoskeletal pain[d]	23 (23)	1 (1.0)	11 (28)	1 (2.6)	41 (23)	2 (1.1)
General Disorders and Administration Site Conditions						
Fatigue[e]	17 (17)	2 (2.0)	8 (21)	2 (5)	35 (20)	4 (2.3)
Edema[f]	11 (11)	0 (0.0)	5 (13)	0 (0.0)	17 (10)	0 (0.0)
Pyrexia[g]	7 (7)	0 (0.0)	4 (10)	0 (0.0)	14 (8)	0 (0.0)
Respiratory, Thoracic and Mediastinal Disorders						
Dyspnea[h]	18 (18)	5 (5)	2 (5)	0 (0.0)	25 (14)	5 (2.9)
Cough[i]	15 (15)	1 (1.0)	0 (0.0)	0 (0.0)	15 (9)	1 (0.6)
Injury, Poisoning, and Procedural Complications						
Infusion-related reactions[j]	12 (12)	0 (0.0)	6 (15)	0 (0.0)	23 (13)	0 (0.0)
Skin and Subcutaneous Tissue Disorders						
Rash[k]	14 (14)	0 (0.0)	2 (5)	0 (0.0)	20 (11)	0 (0.0)
Dry Skin	2 (2.0)	0 (0.0)	4 (10)	0 (0.0)	8 (4.6)	0 (0.0)
Infections and Infestations						
Covid-19	8 (8)	0 (0.0)	7 (18)	0 (0.0)	16 (9)	0 (0.0)
Metabolism and Nutrition Disorders						

	NSCLC N = 99		PDAC N = 39		All solid tumors N = 175	
	All grades n (%)	Grade 3-4 n (%)	All grades n (%)	Grade 3-4 n (%)	All grades n (%)	Grade 3-4 n (%)
Decreased Appetite	11 (11)	1 (1.0)	2 (5)	1 (2.6)	15 (9)	2 (1.1)
Nervous System Disorders						
Headache	5 (5)	0 (0.0)	1 (2.6)	0 (0.0)	10 (6)	0 (0.0)
Vascular Disorders						
Hemorrhage[l]	4 (4.0)	0 (0.0)	5 (13)	2 (5)	9 (5)	2 (1.1)
Psychiatric Disorders						
Anxiety	1 (1.0)	0 (0.0)	4 (10)	0 (0.0)	8 (4.6)	0 (0.0)

a. Includes diarrhea, post-procedural diarrhea
b. Includes abdominal pain, abdominal pain upper, gastrointestinal pain
c. Includes stomatitis, mucosal inflammation
d. Includes back pain, pain in extremity, musculoskeletal chest pain, myalgia, arthralgia, musculoskeletal pain, non-cardiac chest pain, bone pain, musculoskeletal stiffness, neck pain, spinal pain
e. Includes fatigue, asthenia
f. Includes edema, edema peripheral, face edema, localized edema, peripheral swelling
g. Includes pyrexia, body temperature increased
h. Includes dyspnea, dyspnea exertional
i. Includes cough, productive cough
j. Includes chills, IRR, nausea, cough, diarrhea, back pain, body temperature increased, dyspnea, face edema, fatigue, non-cardiac chest pain, oropharyngeal discomfort, paresthesia, pyrexia, and vomiting. AEs that were considered IRRs were counted under the composite term 'IRR', irrespective of the reported PT
k. Includes rash, erythema, dermatitis acneiform, dermatitis contact, dermatitis, eczema, rash erythematous, rash maculo-papular
l. Includes hematuria, hemorrhoidal hemorrhage, epistaxis, hemoptysis, hematochezia

Source: ADSL (Subject-Level Analysis Dataset) - 2024-03-04, ADAE (Adverse Event Analysis Dataset) - 2024-03-04. Variables used: USUBJID, TUMTYP, SAFFL, TRT01A, TRTEMFL, AEDECOD, AETOXGRN, AEACN, AEACNMED, AEACNOTH, AEACNPRO, AEACNTHE, AEACNTRA, AEBODSYS, AESER

FDA review of the 90-day safety update did not identify any new or worsening safety signals.

Laboratory Findings

Data:

Data of laboratory abnormalities are presented for the eNRGy study.

Table 60. Applicant - Laboratory abnormalities (≥20%) that worsened from baseline in NRG1+ cancer patients treated with zenocutuzumab 750 mg Q2W (Safety Analysis Set)

Laboratory Abnormality	All NRG1+ Tumor Types (N=175)	
	All Grades n (%)	Grade 3-4 n (%)
Chemistry		
Increased ALT (IU/L)	58 (33.1)	7 (4.0)
Increased ALP (IU/L)	52 (29.7)	6 (3.4)
Decreased magnesium (mmol/L)	47 (26.9)	6 (3.4)
Increased GGT (IU/L)	45 (25.7)	19 (10.9)
Increased AST (IU/L)	44 (25.1)	8 (4.6)
Decreased phosphate (mmol/L)	42 (24.0)	5 (2.9)
Decreased potassium (mmol/L)	40 (22.9)	3 (1.7)
Decreased sodium (mmol/L)	37 (21.1)	10 (5.7)
Hematology		
Decreased hemoglobin (g/L)	54 (30.9)	10 (5.7)

Source: eNRGy CSR Table 14.3.2.9

The Applicant's Position:

All laboratory parameters were reviewed. No Grade 3 or 4 laboratory abnormalities were observed at a frequency ≥15% of patients with all NRG1+ tumor types in the eNRGy study. The most common Grade 3-4 laboratory abnormalities (≥2%) were increased GGT, decreased hemoglobin, decreased sodium, increased AST, increased ALT, increased ALP, decreased magnesium, and decreased phosphate.

The FDA's Assessment:

FDA's analysis of selected laboratory abnormalities that worsened from baseline are summarized in Table 59. FDA generally agrees with the Applicant's assessment. Increases in ALT and bilirubin were more common in PDAC patients than NSCLC patients. Overall, the abnormalities observed in PDAC patients are consistent with the expected abnormalities in patients with advanced disease.

Table 61. FDA's Analysis of Laboratory Abnormalities by Preferred Term (Safety Population)

	NSCLC N = 99	PDAC N = 39	All solid tumors N = 175

	All Grades n/N evaluable (%)	Grades 3-4 n/N evaluable (%)	All Grades n/N evaluable (%)	Grades 3-4 n/N evaluable (%)	All Grades n/N evaluable (%)	Grades 3-4 n/N evaluable (%)
Hemoglobin decreased	33/95 (35)	4/95 (4.2)	9/39 (23)	4/39 (10)	56/170 (33)	10/170 (6)
ALT increased	29/96 (30)	3/96 (3.1)	20/39 (51)	2/39 (5)	58/171 (34)	7/171 (4.1)
ALP increased	26/96 (27)	0/96 (0.0)	11/39 (28)	3/39 (8)	53/171 (31)	6/171 (3.5)
Magnesium decreased	26/93 (28)	4/93 (4.3)	9/38 (24)	1/38 (2.6)	48/166 (29)	6/166 (3.6)
Phosphate decreased	24/92 (26)	1/92 (1.1)	11/35 (31)	1/35 (2.9)	43/162 (27)	5/162 (3.1)
GGT increased	22/95 (23)	5/95 (5)	9/39 (23)	6/39 (15)	46/170 (27)	19/170 (11)
AST increased	21/96 (22)	3/96 (3.1)	12/39 (31)	2/39 (5)	44/171 (26)	8/171 (4.7)
Potassium decreased	20/96 (21)	2/96 (2.1)	10/39 (26)	1/39 (2.6)	40/171 (23)	3/171 (1.8)
Albumin decreased	18/96 (19)	1/96 (1.0)	10/39 (26)	0/39 (0.0)	37/171 (22)	1/171 (0.6)
Sodium decreased	18/96 (19)	5/96 (5)	11/39 (28)	4/39 (10)	37/171 (22)	10/171 (6)
Platelets decreased	12/95 (13)	4/95 (4.2)	10/39 (26)	4/39 (10)	29/170 (17)	8/170 (4.7)
APTT increased	11/78 (14)	1/78 (1.3)	7/32 (22)	2/32 (6)	24/139 (17)	4/139 (2.9)
Leukocytes decreased	10/95 (11)	0/95 (0.0)	8/39 (21)	1/39 (2.6)	24/169 (14)	1/169 (0.6)
Bilirubin increased	7/96 (7)	0/96 (0.0)	12/39 (31)	2/39 (5)	27/171 (16)	5/171 (2.9)

Vital Signs

Data:

In the eNRGy trial, changes in systolic or diastolic blood pressure following initiation of zenocutuzumab were infrequent, occurring in approximately 2-11% of patients with all NRG1+ tumor types. Increased pulse rate (≥100 bpm and increase >25% from baseline) was reported in

46 patients with all NRG1+ tumor types (26.3%), including 27.3% of NRG1+ NSCLC and 30.8% of NRG1+ PDAC patients.

In the MCLA-128-CL01 dose escalation, vital sign abnormalities reported at least once during treatment in more than 10% of the patients included pulse rate ≥100 bpm with increase ≥25% from baseline (9 patents [32.1%]), systolic blood pressure (SBP) ≥160 mmHg with increase ≥20 mmHg from baseline (4 patients [14.3%]) and SBP ≤90 mmHg with decrease ≥20 mmHg from baseline (3 patients [10.7%]).

In the MCLA-128-CL01 dose expansion, the only vital sign abnormality on-treatment reported in ≥10% of patients was pulse rate increase 100 bpm with an increase ≥25% from baseline (26 patients [20.5%]).

Data from assessments of vital signs and other examinations related to safety were not systematically captured in the EAP.

The Applicant's Position:

Analysis of the vital signs' parameters did not suggest any safety concerns with dosing of zenocutuzumab.

The FDA's Assessment:

FDA agrees with the Applicant's position. The median heart rate in the eNRGy study was 78 beats per minute (range 43-145). The median temperature was 36.6 degrees Celsius (range 35-38.1). The median respiratory rate was 18 breaths per minute (range 8-40). The median systolic blood pressure was 120 mmHg (range 71-200). The median diastolic blood pressure was 73 mmHg (range 22-118).

Electrocardiograms (ECGs)

Data:

Clinically notable treatment-emergent increases in ECG corrected QT intervals compared to baseline, or prolongations during treatment and up to 30 days after the last study drug infusion, are reported in Table 51.

In patients with all NRG1+ tumor types, on-treatment corrected QT interval by Fridericia (QTcF) values >480 ms and ≤500 ms were reported in 6 patients (3.4%) and QTcF values >500 ms were reported in 2 patients (1.1%; 552 ms, 545 ms) during the eNRGy study. Twelve patients with all NRG1+ tumor types (6.9%) had an on-treatment increase in QTcF >60 ms at any point in the study; all cases were isolated. Six patients (3.4%) had both a concomitant QTcF value >480 ms and an increase of >60 ms.

Patients with any clinically significant change in ECG parameters during the eNRGy study (N=6) are described in detail in the eNRGy CSR.

Table 62. Applicant – Treatment-emergent electrocardiogram abnormalities in NRG1+ cancer patients treated with zenocutuzumab 750 mg Q2W in the eNRGy study (Safety Analysis Set)

Number of patients with:	NRG1+ NSCLC (N=99) n (%)	NRG1+ PDAC (N=39) n (%)	All NRG1+ Tumor Types (N=175) n (%)
QT			
New value >450 and ≤480 ms	6 (6.1)	2 (5.1)	13 (7.4)
New value >480 and ≤500 ms	1 (1.0)	0	1 (0.6)
New value >500 ms	3 (3.0)	1 (2.6)	4 (2.3)
Increase from baseline of >30 ms to ≤60 ms	26 (26.3)	9 (23.1)	44 (25.1)
Increase from baseline of >60 ms	11 (11.1)	10 (25.6)	25 (14.3)
QTcF			
New value >450 and ≤480 ms	14 (14.1)	6 (15.4)	26 (14.9)
New value >480 and ≤500 ms	4 (4.0)	1 (2.6)	6 (3.4)
New value >500 ms	1 (1.0)	1 (2.6)	2 (1.1)
Increase from baseline of >30 ms to ≤60 ms	19 (19.2)	11 (28.2)	37 (21.1)
Increase from baseline of >60 ms	7 (7.1)	4 (10.3)	12 (6.9)
QTcB			
New value >450 and ≤480 ms	31 (31.3)	12 (30.8)	56 (32.0)
New value >480 and ≤500 ms	12 (12.1)	3 (7.7)	17 (9.7)
New value >500 ms	6 (6.1)	2 (5.1)	9 (5.1)
Increase from baseline of >30 ms to ≤60 ms	29 (29.3)	14 (35.9)	54 (30.9)
Increase from baseline of >60 ms	8 (8.1)	4 (10.3)	13 (7.4)
QRS			
Increase from baseline of >25% and >120 ms	0	0	0

ms=millisecond; QRS=Q-, R-, S-wave; QTcF=corrected QT interval by Fridericia; QTcB=corrected QT interval by Bazett (as calculated from QT and RR).
Note: patients are counted once per QT parameter with their worst value and worst change, respectively.
Source: eNRGy CSR Table 14.3.4.1

The Applicant's Position:

Analysis of the ECG parameters did not suggest any cardiac safety concerns with the dosing of zenocutuzumab.

The FDA's Assessment:
Refer to section 6 (Clinical Pharmacology) for FDA's analysis of ECG data.

QT

Data:

Please see the above subsection on Electrocardiograms (ECG).

The Applicant's Position:

According to ICH E14 Q&A large targeted proteins and monoclonal antibodies have a low likelihood of direct ion channel interactions and a thorough QT/QTc study is not necessary, unless the potential for proarrhythmic risk is suggested by mechanistic considerations or data from clinical or nonclinical studies.

As there are no mechanistic considerations that zenocutuzumab would bind to the human ether-a-go-go related gene (hERG; encoding the pore-forming subunit of the rapid component of the delayed rectifier K(+) channel, Kv11.1 expressed amongst others in the heart) or cause cardiotoxicity, no dedicated TQT study in patients was performed for zenocutuzumab. The Applicant had implemented routine ECG assessments in the eNRGy with zenocutuzumab.

The FDA's Assessment:

FDA agrees with the Applicant's assessment. No dedicated thorough QT study was performed given zenocutuzumab is a bispecific antibody.

Immunogenicity

Data:

A review of data regarding immunogenicity is presented and summarized in section 6.3.1.

The Applicant's Position:

There is a low risk of immunogenicity for zenocutuzumab with no known impact on PK, efficacy, or safety.

The FDA's Assessment:
Refer to section 6 (Clinical Pharmacology) for FDA's analysis of immunogenicity data.

8.2.3 Analysis of Submission-Specific Safety Issues

The Applicant's Position:

No specific safety issues other than the AESI data presented under section 8.2.3 Significant Adverse Events.

The FDA's Assessment:

FDA agrees with the Applicant's position. Refer to FDA review under section 8.2.3 for discussion of AESIs.

8.2.4 Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Data:

Not applicable.

The Applicant's Position:

Not applicable.

The FDA's Assessment:

FDA agrees with the Applicant's position.

8.2.5 Safety Analyses by Demographic Subgroups

Data:

Intrinsic Factors

Exposure to study treatment and analyses of AEs, AEs related to study drug, and SAEs were performed for the following intrinsic subgroups for NRG1+ NSCLC, NRG1+ PDAC, and for patients with all NRG1+ tumor types:

- Age: <65 years-old, ≥65 years-old
- Sex: male, female
- Race: White, Asian, Other

Table 63. Applicant – Overall adverse event summary in NRG1+ cancer patients treated with zenocutuzumab 750 mg Q2W in the eNRGy study by age (Safety Analysis Set)

Patients with:	NRG1+ NSCLC (N=99)		NRG1+ PDAC (N=39)		All NRG1+ Tumor Types (N=175)	
	<65 yrs (N=46) n (%)	≥65 yrs (N=53) n (%)	<65 yrs (N=30) n (%)	≥65 yrs (N=9) n (%)	<65 yrs (N=100) n (%)	≥65 yrs (N=75) n (%)
At least 1 AE	43 (93.5)	46 (86.8)	30 (100)	8 (88.9)	95 (95.0)	64 (85.3)
Any Grade 3-4 AE	14 (30.4)	15 (28.3)	13 (43.3)	7 (77.8)	37 (37.0)	25 (33.3)
At least 1 SAE	10 (21.7)	15 (28.3)	8 (26.7)	1 (11.1)	21 (21.0)	21 (28.0)
At least 1 treatment-related AE	32 (69.6)	33 (62.3)	22 (73.3)	6 (66.7)	67 (67.0)	43 (57.3)
At least 1 AE leading to withdrawal of study treatment	4 (8.7)	6 (11.3)	2 (6.7)	0	7 (7.0)	7 (9.3)
At least 1 AE leading to dose interruption	12 (26.1)	17 (32.1)	12 (40.0)	1 (11.1)	31 (31.0)	22 (29.3)

Source: eNRGy CSR Table 14.3.1.2.2, Table 14.3.1.4.2, Table 14.3.1.6.2, Table 14.3.1.9.2, Table 14.3.1.10.2

Table 64. Applicant – Overall adverse event summary in all NRG1+ cancer patients treated with zenocutuzumab 750 mg Q2W in the eNRGy study by sex (Safety Analysis Set)

Patients with:	NRG1+ NSCLC (N=99)		NRG1+ PDAC (N=39)		All NRG1+ Tumor Types (N=175)	
	Male (N=38) n (%)	Female (N=61) n (%)	Male (N=20) n (%)	Female (N=19) n (%)	Male (N=71) n (%)	Female (N=104) n (%)
At least 1 AE	32 (84.2)	57 (93.4)	20 (100)	18 (94.7)	64 (90.1)	95 (91.3)
Any Grade 3-4 AE	7 (18.4)	22 (36.1)	10 (50.0)	10 (52.6)	23 (32.4)	39 (37.5)
At least 1 SAE	5 (13.2)	20 (32.8)	5 (25.0)	4 (21.1)	14 (19.7)	28 (26.9)
At least 1 treatment-related AE	26 (68.4)	39 (63.9)	15 (75.0)	13 (68.4)	45 (63.4)	65 (62.5)
At least 1 AE leading to withdrawal of study treatment	3 (7.9)	7 (11.5)	1 (5.0)	1 (5.3)	5 (7.0)	9 (8.7)
At least 1 AE leading to dose interruption	8 (21.1)	21 (34.4)	7 (35.0)	6 (31.6)	21 (29.6)	32 (30.8)

Source: eNRGy CSR Table 14.3.1.2.1, Table 14.3.1.4.1, Table 14.3.1.6.1, Table 14.3.1.9.1, Table 14.3.1.10.1

Table 65. Applicant – Overall adverse event summary in all NRG1+ cancer patients treated with zenocutuzumab 750 mg Q2W in the eNRGy study by race (Safety Analysis Set)

Patients with:	All NRG1+ Tumor Types (N=175)		
	White (N=94) n (%)	Asian (N=63) n (%)	Other[1] (N=9) n (%)
At least 1 AE	91 (96.8)	51 (81.0)	8 (88.9)
Any Grade 3-4 AE	40 (42.6)	14 (22.2)	3 (33.3)
At least 1 SAE	28 (29.8)	12 (19.0)	0
At least 1 treatment-related AE	63 (67.0)	36 (57.1)	4 (44.4)
At least 1 AE leading to withdrawal of study treatment	10 (10.6)	2 (3.2)	0
At least 1 AE leading to dose interruption	33 (35.1)	14 (22.2)	2 (22.2)

[1] *Other includes race of 'Black or African American' (n=4) and 'Other' (n=5) as recorded in demography.*
Source: eNRGy CSR Table 14.3.1.2.3, Table 14.3.1.4.3, Table 14.3.1.6.3, Table 14.3.1.9.3, Table 14.3.1.10.3

Table 66. Applicant – MCLA-128-CL01 Dose Escalation: patient demographics

	Cohort 1 (40 mg) (N=1) n	Cohort 2 (80 mg) (N=2) n	Cohort 3 (160 mg) (N=1) n	Cohort 4 (240 mg) (N=3) n	Cohort 5 (360 mg) (N=3) n	Cohort 6 (480 mg) (N=3) n	Cohort 7 (600 mg) (N=6) n	Cohort 8 (750 mg) (N=6) n	Cohort 9 (900 mg) (N=3) n	Total (N=28) n (%)
Age (years)										
Mean (SDev)	54.0	68.5 (0.7)	25.0	58.7 (22.4)	67.0 (16.5)	61.0 (12.2)	64.3 (6.0)	59.2 (11.1)	44.0 (12.5)	58.9 (14.1)
Median	54.0	68.5	25.0	54.0	76.0	55.0	64.0	60.5	48.0	59.5
Min; Max	54; 54	68; 69	25; 25	39; 83	48; 77	53; 75	57; 74	39; 71	30; 54	25; 83
Age group (years)										
<65	1	0	1	2	1	2	3	4	3	17 (60.7)
≥65	0	2	0	1	2	1	3	2	0	11 (39.3)
Sex										
Male	0	1	1	3	2	1	3	4	2	17 (60.7)
Female	1	1	0	0	1	2	3	2	1	11 (39.3)

	Cohort 1 (40 mg) (N=1) n	Cohort 2 (80 mg) (N=2) n	Cohort 3 (160 mg) (N=1) n	Cohort 4 (240 mg) (N=3) n	Cohort 5 (360 mg) (N=3) n	Cohort 6 (480 mg) (N=3) n	Cohort 7 (600 mg) (N=6) n	Cohort 8 (750 mg) (N=6) n	Cohort 9 (900 mg) (N=3) n	Total (N=28) n (%)
Race										
White	1	2	1	3	3	3	6	6	3	28 (100.0)
ECOG PS										
0	1	1	1	1	0	2	2	2	2	12 (42.9)
1	0	1	0	2	3	1	4	4	1	16 (57.1)

Source: Table 14.1.3.1

Table 67. Applicant – MCLA-128-CL01 Dose Expansion: patient demographics

	Group A BC (N=14)	Group B CRC (N=1)	Group C OC (N=37)	Group D GC or GEC (N=40)	Group E EC (N=21)	Group F non-NRG1+ NSCLC (N=11)	Total (N=124)
Age (years)							
Mean (SDev)	54.4 (10.8)	57.0	55.1 (11.7)	59.2 (13.0)	67.2 (5.9)	60.5 (11.1)	58.9 (11.8)
Median	52.5	57.0	56.0	60.0	68.0	59.0	59.0
Min; Max	38; 70	57; 57	31; 81	30; 81	53; 77	43; 85	30; 85
Age group (years), n (%)							
<65	10 (71.4)	1 (100.0)	28 (75.7)	24 (60.0)	5 (23.8)	7 (63.6)	75 (60.5)
≥65	4 (28.6)	0 (0.0)	9 (24.3)	16 (40.0)	16 (76.2)	4 (36.4)	49 (39.5)
Sex, n (%)							
Male	0 (0.0)	1 (100.0)	0 (0.0)	35 (87.5)	0 (0.0)	7 (63.6)	43 (34.7)
Female	14 (100.0)	0 (0.0)	37 (100.0)	5 (12.5)	21 (100)	4 (36.4)	81 (65.3)
Race							
White	14. (100.0)	1 (100)	34 (91.9)	39 (97.5)	18 (85.7)	9 (81.8)	115 (92.7)
Asian	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.8)	2 (18.2)	3 (2.4)
Black or African American	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.5)	0 (0.0)	0 (0.0)	1 (0.8)

	Group A BC (N=14)	Group B CRC (N=1)	Group C OC (N=37)	Group D GC or GEC (N=40)	Group E EC (N=21)	Group F non-NRG1+ NSCLC (N=11)	Total (N=124)
Hispanic or Latino	0 (0.0)	0 (0.0)	2 (5.4)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.6)
Not reported	0 (0.0)	0 (0.0)	1 (2.7)	0 (0.0)	2 (9.5)	0 (0.0)	3 (2.4)
ECOG PS, n (%)							
0	3 (21.4)	1 (100.0)	17 (45.9)	16 (40.0)	8 (38.1)	2 (18.2)	47 (37.9)
1	11 (78.6)	0 (0.0)	20 (54.1)	24 (60.0)	13 (61.9)	9 (81.8)	77 (62.1)

Source: Table 14.1.3.

Extrinsic Factors

Exposure to study treatment and analyses of AEs, AEs related to study drug, and SAEs were performed for the following extrinsic subgroup for NRG1+ NSCLC, NRG1+ PDAC and for patients with all NRG1+ tumor types:

- Geographic Region (North America, Europe, Asia)

Table 68. Applicant – Overall adverse event summary in NRG1+ cancer patients treated with zenocutuzumab 750 mg Q2W in the eNRGy study by geographic region (Safety Analysis Set)

Patients with:	All NRG1+ Tumor Types (N=175)		
	North America (N=69) n (%)	Europe (N=51) n (%)	Asia (N=55) n (%)
At least 1 AE	65 (94.2)	50 (98.0)	44 (80.0)
Any Grade 3-4 AE	29 (42.0)	24 (47.1)	9 (16.4)
At least 1 SAE	16 (23.2)	16 (31.4)	10 (18.2)
At least 1 treatment-related AE	49 (71.0)	31 (60.8)	30 (54.5)
At least 1 AE leading to withdrawal of study treatment	6 (8.7)	7 (13.7)	1 (1.8)
At least 1 AE leading to dose interruption	22 (31.9)	20 (39.2)	11 (20.0)

Source: eNRGy CSR Table 14.3.1.2.4, Table 14.3.1.4.4, Table 14.3.1.6.4, Table 14.3.1.9.4, Table 14.3.1.10.4

The Applicant's Position:

The subgroup analysis of safety with zenocutuzumab 750 mg Q2W was performed using data from the eNRGy study only.

The subgroup analysis of safety with zenocutuzumab 750 mg Q2W was not performed for the EAP due to the small number of patients enrolled.

Overall, the safety profile of zenocutuzumab 750 mg Q2W in older patients (≥65 years) was consistent with that in younger patients (<65 years). In the all NRG1+ tumor types population, the proportions of patients with any Grade 3-4 AE, any AE leading to study treatment withdrawal, and any AE leading to dose interruption were similar between subgroups.

The safety profile of zenocutuzumab in NRG1+ NSCLC and NRG1+ PDAC patients <65 years and ≥65 years was consistent with the all NRG1+ tumor types patient population. Of note, a numerical difference was observed in the proportion of NRG1+ PDAC patients ≥65-years-old who experienced Grade 3-4 AEs (77.8%) compared with patients ≥65 years in the all NRG1+ tumor types population (33.3%); although the number of patients included in the NRG1+ PDAC subgroup was small (n=9) (Table 48).

In the all NRG1+ tumor types population, the frequency of AEs in men and women who received zenocutuzumab 750 mg Q2W were generally similar, with the exception of numerical difference observed in SAEs; 26.9% of women experienced an SAE compared with 19.7% of men (Table 49). The safety profiles of zenocutuzumab in men and women in the NRG1+ NSCLC and NRG1+ PDAC indications were consistent with the all NRG1+ tumor types patient population. Of note, a higher proportion (>10% difference) of women with NRG1+ NSCLC had any Grade 3-4 AE (36.1%), any SAE (32.8%), or any AE leading to dose interruption (34.4%) compared with men (18.4%, 13.2%, and 21.1%, respectively). In addition, the frequency of anemia (19.7% vs 7.9%) and dyspnea (23.0% vs 7.9%) were numerically higher in females with NRG1+ NSCLC than males with NRG1+ NSCLC.

The distribution of AEs by race did not reveal notable race-related differences in the safety profile of zenocutuzumab 750 mg Q2W in patients with all NRG1+ tumor types. The overall frequency of some AEs (e.g., treatment related AEs, SAEs, etc.) were higher in White patients compared to Asian patients. The safety profiles in NRG1+ NSCLC and NRG1+ PDAC patients were consistent with the all NRG1+ tumor types population.

The distribution of AEs by geographic region did not reveal notable differences in the safety profile of zenocutuzumab 750 mg Q2W across geographic subgroups in patients with all NRG1+ tumor types. The overall frequency of some AEs (e.g., treatment related AEs, SAEs, etc.) were higher in patients treated in North America or Europe than in Asia. In NRG1+ NSCLC and NRG1+ PDAC patients, the distribution of AEs by geographic region was consistent with the all NRG1+ cancer population (all tumor types). No notable differences in the safety profile of zenocutuzumab 750 mg Q2W were observed across regional subgroups.

The FDA's Assessment:

Safety Analysis by Age Group

FDA generally agrees with the Applicant's position. Numbers of patients with study treatment discontinued due to AEs differs from the Applicant based on the FDA review of patient narratives. As shown in Table 67, the incidence of TEAEs, SAEs, deaths and AEs leading to treatment discontinuation were similar in patients <65 years and ≥65 years.

In the primary safety population, AEs reported with higher frequency (difference of ≥10%) in patients <65 years than in patients ≥65 years were diarrhea and musculoskeletal pain. No AEs were reported with lower frequency (difference of ≥10%) in patients <65 years than in patients ≥65 years (see Table 59).

Table 69: Summary of AEs by Age <65 and Age ≥65 (FDA Review)

	Age >=65 N = 75 N (%)	**Age <65 N = 100 N (%)**
All-Grade TEAEs	64 (85)	95 (95)
Grade 3-4 TEAEs	22 (29)	34 (34)
Grade 3	20 (27)	28 (28)
Grade 4	2 (2.7)	6 (6)
Grade 5 (Deaths due to TEAEs)	2 (2.7)	3 (3.0)
Serious TEAEs (SAEs)	21 (28)	21 (21)
Study treatment discontinued due to AEs	2 (2.7)	1 (1.0)

Source: ADSL (Subject-Level Analysis Dataset) - 2024-03-04, ADAE (Adverse Event Analysis Dataset) - 2024-03-04. Variables used: USUBJID, TRT01A, SAFFL, TRTEMFL, AETOXGRN, AESER

Table 70: AEs ≥10% Occurring in Patients <65 and ≥65 (FDA Review)

	Age >=65 N = 75		Age <65 N = 100	
	All grades n (%)	Grade 3 n (%) Grade 4 n (%)	All grades n (%)	Grade 3 n (%) Grade 4 n (%)
Patients with TEAEs	64 (85)	20 (27)	95 (95)	34 (34)
Gastrointestinal Disorders				
Diarrhea[a]	16 (21)	0 (0.0)	33 (33)	4 (4.0)
Nausea	12 (16)	2 (2.7)	18 (18)	1 (1.0)
Vomiting	10 (13)	1 (1.3)	11 (11)	0 (0.0)
Constipation	9 (12)	0 (0.0)	13 (13)	0 (0.0)
Abdominal Pain[b]	5 (7)	0 (0.0)	15 (15)	4 (4.0)
General Disorders And Administration Site Conditions				
Fatigue[c]	13 (17)	2 (2.7)	22 (22)	2 (2.0)
Edema[d]	10 (13)	0 (0.0)	9 (9)	0 (0.0)
Musculoskeletal And Connective Tissue Disorders				
Musculoskeletal Pain[e]	12 (16)	0 (0.0)	29 (29)	2 (2.0)
Infusion-related reactions[f]	10 (13)	0 (0.0)	13 (13)	0 (0.0)
Metabolism And Nutrition Disorders				

	Age >=65 N = 75		Age <65 N = 100	
	All grades n (%)	Grade 3 n (%) Grade 4 n (%)	All grades n (%)	Grade 3 n (%) Grade 4 n (%)
Decreased Appetite	9 (12)	2 (2.7)	6 (6)	0 (0.0)
Infections And Infestations				
Covid-19	3 (4.0)	0 (0.0)	13 (13)	0 (0.0)
Respiratory, Thoracic And Mediastinal Disorders				
Dyspnea[g]	12 (16)	3 (4.0)	13 (13)	2 (2.0)
Cough[h]	8 (11)	1 (1.3)	7 (7)	0 (0.0)
Skin And Subcutaneous Tissue Disorders				
Rash[i]	11 (15)	0 (0.0)	12 (12)	0 (0.0)

a. Includes diarrhea, post-procedural diarrhea
b. Includes abdominal pain, gastrointestinal pain, abdominal pain upper
c. Includes fatigue, asthenia
d. Includes edema, edema peripheral, face edema, localized edema, peripheral swelling
e. Includes back pain, pain in extremity, musculoskeletal chest pain, myalgia, arthralgia, non-cardiac chest pain, musculoskeletal stiffness, neck pain, spinal pain, musculoskeletal pain, bone pain
f. Includes chills, IRR, nausea, cough, diarrhea, back pain, body temperature increased, dyspnea, face edema, fatigue, non-cardiac chest pain, oropharyngeal discomfort, paresthesia, pyrexia, and vomiting. AEs that were considered IRRs were counted under the composite term 'IRR', irrespective of the reported PT
g. Includes dyspnea, dyspnea exertional
h. Includes cough, productive cough
i. Includes rash, erythema, dermatitis acneiform, dermatitis contact, eczema, rash erythematous, dermatitis, rash maculo-papular

Source: ADSL (Subject-Level Analysis Dataset) - 2024-03-04, ADAE (Adverse Event Analysis Dataset) - 2024-03-04. Variables used: USUBJID, TRT01A, SAFFL, TRTEMFL, AEDECOD, AETOXGRN, AEBODSYS, AESER

Safety Analysis by Sex

FDA generally agrees with the Applicant's position. Numbers of patients who discontinued study treatment due to AEs differs from the Applicant based on FDA's review of patient narratives. As shown in Table 69, rates of all-grade AEs, grade 3-4 AEs, SAEs, deaths and discontinuations were similar between male and female patients. Rates of specific PTs were also generally similar between male and female patients (see table below). The only PT that was reported more frequently (≥10% difference) in female than in male patients was constipation.

Table 71: Summary of AEs by Sex (FDA Review)

	Male N = 71 N (%)	**Female N = 104 N (%)**
All-Grade TEAEs	64 (90)	95 (91)
Grade 3-4 TEAEs	23 (32)	39 (38)
Grade 3	18 (25)	30 (29)
Grade 4	3 (4.2)	6 (6)
Grade 5 (Deaths due to TEAEs)	3 (4.2)	2 (1.9)
Serious TEAEs (SAEs)	14 (20)	28 (27)
Study treatment discontinued due to AEs	1 (1.4)	2 (1.9)

Source: ADSL (Subject-Level Analysis Dataset) - 2024-03-04, ADAE (Adverse Event Analysis Dataset) - 2024-03-04. Variables used: USUBJID, TRT01A, SAFFL, TRTEMFL, AETOXGRN, AESER

Table 72: AEs ≥10% Occurring in Male and Female Patients

	Male N = 71		**Female N = 104**	
	All grades n (%)	**Grade 3-4 n (%)**	**All grades n (%)**	**Grade 3-4 n (%)**
Patients with TEAEs	64 (90)	23 (32)	95 (91)	39 (38)
Gastrointestinal Disorders				

	Male N = 71		Female N = 104	
	All grades n (%)	**Grade 3-4 n (%)**	**All grades n (%)**	**Grade 3-4 n (%)**
Diarrhea[a]	23 (32)	2 (2.8)	26 (25)	2 (1.9)
Nausea	14 (20)	1 (1.4)	16 (15)	2 (1.9)
Abdominal Pain[b]	7 (10)	2 (2.8)	13 (13)	2 (1.9)
Vomiting	6 (8)	1 (1.4)	15 (14)	0 (0.0)
Constipation	4 (6)	0 (0.0)	18 (17)	0 (0.0)
General Disorders and Administration Site Conditions				
Fatigue[c]	14 (20)	1 (1.4)	21 (20)	3 (2.9)
Edema[d]	5 (7)	0 (0.0)	14 (13)	0 (0.0)
Pyrexia[e]	3 (4.2)	0 (0.0)	11 (11)	0 (0.0)
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal Pain[f]	14 (20)	0 (0.0)	27 (26)	2 (1.9)
Injury, Poisoning and Procedural Complications				
Infusion related reaction[g]	11 (15)	0 (0.0)	12 (12)	0 (0.0)
Metabolism and Nutrition Disorders				
Decreased Appetite	8 (11)	1 (1.4)	7 (7)	1 (1.0)
Skin and Subcutaneous Tissue Disorders				
Rash[h]	8 (11)	0 (0.0)	15 (14)	0 (0.0)
Respiratory, Thoracic and Mediastinal Disorders				

	Male N = 71		Female N = 104	
	All grades n (%)	Grade 3-4 n (%)	All grades n (%)	Grade 3-4 n (%)
Dyspnea[i]	7 (10)	0 (0.0)	18 (17)	5 (4.8)
Cough[j]	4 (6)	0 (0.0)	11 (11)	1 (1.0)

a. Includes diarrhea, post-procedural diarrhea
b. Includes abdominal pain, gastrointestinal pain, abdominal pain upper
c. Includes fatigue, asthenia
d. Includes edema, edema peripheral, localized edema, face edema, peripheral swelling
e. Includes pyrexia, body temperature increased
f. Includes back pain, pain in extremity, musculoskeletal chest pain, myalgia, arthralgia, musculoskeletal pain, non-cardiac chest pain, bone pain, musculoskeletal stiffness, neck pain, spinal pain
g. Includes chills, IRR, nausea, cough, diarrhea, back pain, body temperature increased, dyspnea, face edema, fatigue, non-cardiac chest pain, oropharyngeal discomfort, paresthesia, pyrexia, and vomiting. AEs that were considered IRRs were counted under the composite term 'IRR', irrespective of the reported PT
h. Includes rash, dermatitis, dermatitis acneiform, dermatitis contact, eczema, erythema, rash erythematous, rash maculo-papular
i. Includes dyspnea, dyspnea exertional
j. Includes cough, productive cough

Source: ADSL (Subject-Level Analysis Dataset) - 2024-03-04, ADAE (Adverse Event Analysis Dataset) - 2024-03-04. Variables used: USUBJID, TRT01A, SAFFL, TRTEMFL, AEDECOD, AETOXGRN, AEBODSYS, AESER

Safety Analysis by Race

FDA generally agrees with the Applicant's position, however; as the majority of patients enrolled on the eNRGy trial were White or Asian, definitive conclusions regarding the safety profile of zenocutuzumab in patients of races that were underrepresented in this study cannot be made. Rates of Grade 3 AEs and SAEs were higher (difference ≥10%) in White patients than in Asian patients (Table 62). The most commonly reported AEs by PT were generally similar between White and Asian patients. AEs that differed by ≥10% included musculoskeletal pain, which occurred in 34% and 8% of White and Asian patients, respectively; diarrhea, which occurred in 33% and 21% of White and Asian patients, respectively; fatigue, which occurred in 24% and 6% of White and Asian patients, respectively; and rash, which occurred in 18% and 8% of White and Asian patients, respectively (Table 63). Out of the 63 patients with a reported race of Asian in the primary safety population, 55 (87%) were treated at sites in Asia. Differences in rates of AEs between Asian and White patients may be due to differences in reporting at Asian sites rather than biological differences. See FDA's analysis of safety by region below.

Table 73: Summary of AEs by Race (FDA Review)

	Black or African American N = 4 N (%)	**Asian N = 63 N (%)**	**White N = 94 N (%)**	**Other/Not Reported N = 14 N (%)**
All-Grade TEAEs	4 (100)	51 (81)	91 (97)	13 (93)
Grade 3-4 TEAEs	1 (25)	14 (22)	34 (36)	7 (50)
Grade 3	1 (25)	11 (17)	30 (32)	6 (43)
Grade 4	0 (0.0)	3 (4.8)	4 (4.3)	1 (7)
Grade 5 (Deaths due to TEAEs)	0 (0.0)	0 (0.0)	5 (5)	0 (0.0)
Serious TEAEs (SAEs)	0 (0.0)	12 (19)	28 (30)	2 (14)
Study treatment discontinued due to AEs	0 (0.0)	1 (1.6)	2 (2.1)	0 (0.0)

Source: ADSL (Subject-Level Analysis Dataset) - 2024-03-04, ADAE (Adverse Event Analysis Dataset) - 2024-03-04. Variables used: USUBJID, TRT01A, SAFFL, TRTEMFL, AETOXGRN, AESER

Table 74: AEs Occurring in ≥10% by Race (FDA Review)

	BLACK OR AFRICAN AMERICAN N = 4		ASIAN N = 63		WHITE N = 94		OTHER/NOT REPORTED N = 14	
	All grades n (%)	Grades 3-4 n (%)	All grades n (%)	Grades 3-4 n (%)	All grades n (%)	Grades 3-4 n (%)	All grades n (%)	Grades 3-4 n (%)
Patients with TEAEs	4 (100)	1 (25)	51 (81)	14 (22)	91 (97)	34 (36)	13 (93)	7 (50)
General Disorders and Administration Site Conditions								
Fatigue[a]	1 (25)	1 (25)	4 (6)	0 (0.0)	23 (24)	3 (3.2)	7 (50)	0 (0.0)
Edema[b]	0 (0.0)	0 (0.0)	6 (10)	0 (0.0)	12 (13)	0 (0.0)	1 (7)	0 (0.0)
Pyrexia[c]	0 (0.0)	0 (0.0)	4 (6)	0 (0.0)	10 (11)	0 (0.0)	0 (0.0)	0 (0.0)
Endocrine Disorders								
Hyperthyroidism	1 (25)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Renal and Urinary Disorders								
Proteinuria	1 (25)	0 (0.0)	1 (1.6)	0 (0.0)	1 (1.1)	0 (0.0)	1 (7)	0 (0.0)
Gastrointestinal Disorders								
Diarrhea[d]	0 (0.0)	0 (0.0)	13 (21)	1 (1.6)	31 (33)	3 (3.2)	5 (36)	0 (0.0)
Nausea	0 (0.0)	0 (0.0)	8 (13)	1 (1.6)	20 (21)	2 (2.1)	2 (14)	0 (0.0)
Vomiting	0 (0.0)	0 (0.0)	7 (11)	1 (1.6)	12 (13)	0 (0.0)	2 (14)	0 (0.0)

	BLACK OR AFRICAN AMERICAN N = 4		ASIAN N = 63		WHITE N = 94		OTHER/NOT REPORTED N = 14	
	All grades n (%)	Grades 3-4 n (%)	All grades n (%)	Grades 3-4 n (%)	All grades n (%)	Grades 3-4 n (%)	All grades n (%)	Grades 3-4 n (%)
Constipation	0 (0.0)	0 (0.0)	5 (8)	0 (0.0)	15 (16)	0 (0.0)	2 (14)	0 (0.0)
Abdominal Pain[e]	0 (0.0)	0 (0.0)	3 (4.8)	1 (1.6)	13 (14)	3 (3.2)	4 (29)	0 (0.0)
Hemorrhoids	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.1)	0 (0.0)	2 (14)	0 (0.0)
Infections and Infestations								
Covid-19	0 (0.0)	0 (0.0)	6 (10)	0 (0.0)	9 (10)	0 (0.0)	1 (7)	0 (0.0)
Urinary Tract Infection[f]	0 (0.0)	0 (0.0)	4 (6)	0 (0.0)	4 (4.3)	0 (0.0)	2 (14)	0 (0.0)
Paronychia	0 (0.0)	0 (0.0)	3 (4.8)	0 (0.0)	3 (3.2)	0 (0.0)	2 (14)	0 (0.0)
Pneumonia[g]	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)	6 (6)	2 (2.1)	2 (14)	1 (7)
Respiratory and Mediastinal Disorders								
Dyspnea[h]	0 (0.0)	0 (0.0)	7 (11)	2 (3.2)	15 (16)	2 (2.1)	3 (21)	1 (7)
Cough[i]	0 (0.0)	0 (0.0)	4 (6)	0 (0.0)	9 (10)	1 (1.1)	2 (14)	0 (0.0)
Metabolism and Nutrition Disorders								
Decreased Appetite	0 (0.0)	0 (0.0)	6 (10)	1 (1.6)	7 (7)	1 (1.1)	2 (14)	0 (0.0)
Skin and Subcutaneous Tissue Disorders								

	BLACK OR AFRICAN AMERICAN N = 4		ASIAN N = 63		WHITE N = 94		OTHER/NOT REPORTED N = 14	
	All grades n (%)	Grades 3-4 n (%)	All grades n (%)	Grades 3-4 n (%)	All grades n (%)	Grades 3-4 n (%)	All grades n (%)	Grades 3-4 n (%)
Rash[j]	0 (0.0)	0 (0.0)	5 (8)	0 (0.0)	17 (18)	0 (0.0)	0 (0.0)	0 (0.0)
Musculoskeletal and Connective Tissue Disorders								
Musculoskeletal Pain[k]	0 (0.0)	0 (0.0)	5 (8)	1 (1.6)	32 (34)	1 (1.1)	4 (29)	0 (0.0)
Nervous System Disorders								
Neuropathy Peripheral[l]	0 (0.0)	0 (0.0)	2 (3.2)	0 (0.0)	7 (7)	0 (0.0)	2 (14)	0 (0.0)
Psychiatric Disorders								
Depression	0 (0.0)	0 (0.0)	2 (3.2)	0 (0.0)	4 (4.3)	0 (0.0)	2 (14)	0 (0.0)
Hepatobiliary Disorders								
Hepatic Cytolysis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (14)	1 (7)
Injury, Poisoning, and Procedural Complications								
Infusion related reaction[m]	2 (50)	0 (0.0)	5 (8)	0 (0.0)	14 (15)	0 (0.0)	2(14)	0 (0.0)

a. Includes fatigue, asthenia.
b. Includes edema, edema peripheral, localized edema, face edema, peripheral swelling.
c. Includes pyrexia, body temperature increased.
d. Includes diarrhea, post-procedural diarrhea.
e. Includes abdominal pain, gastrointestinal pain, abdominal pain upper.
f. Includes urinary tract infection, cystitis.
g. Includes pneumonia, lower respiratory tract infection.
h. Includes dyspnea, dyspnea exertional.

i. Includes cough, productive cough.
j. Includes rash, dermatitis, dermatitis acneiform, eczema, erythema, rash erythematous, rash maculo-papular.
k. Includes musculoskeletal pain, back pain, myalgia, musculoskeletal chest pain, pain in extremity, neck pain, arthralgia, non-cardiac chest pain, musculoskeletal stiffness, spinal pain, musculoskeletal pain, bone pain.
l. Includes paraesthesia, neuropathy peripheral, hypoaesthesia, dysaesthesia, neuralgia, peripheral sensory neuropathy.
m. Includes chills, IRR, nausea, cough, diarrhea, back pain, body temperature increased, dyspnea, face edema, fatigue, non-cardiac chest pain, oropharyngeal discomfort, paresthesia, pyrexia, and vomiting. AEs that were considered IRRs were counted under the composite term 'IRR', irrespective of the reported PT.

Source: ADSL (Subject-Level Analysis Dataset) - 2024-03-04, ADAE (Adverse Event Analysis Dataset) - 2024-03-04. Variables used: USUBJID, TRT01A, SAFFL, TRTEMFL, AEDECOD, AETOXGRN, AEBODSYS, AESER

Safety Analysis by Region

FDA notes that rates of Grade 3-4 AEs and SAEs were higher in Europe and North America than in Asia, reflecting the differences observed in racial subgroups. Infusion-related reactions were more commonly reported in North America (25% of patients) than in Asia (3.6% of patients) or Europe (8% of patients). The lower incidence of AEs in Asia may be due to reporting differences by region. An information request was sent to the Applicant to provide any additional information or insight to help to elucidate the reason for the differences observed by race and region. The Applicant responded that differences in rates of gastrointestinal AEs (e.g. diarrhea, nausea) may be due to a lower proportion of patients with PDAC treated at Asian sites. The Applicant also suggested that geographic variation in reporting practices for AEs associated with disease progression (e.g., dyspnea in NSCLC patients) and patient-self-reporting of specific symptoms (e.g., fatigue) may have led to the observed differences in rates of AEs. The Applicant did not identify any single site in Asia with notably lower reporting of AEs relative to other Asian sites. PK parameters and duration of treatment exposure were higher in Asian than non-Asian patients, therefore the lower rate of AEs in patients of Asian race is unlikely to be due to lower drug exposure.

Table 75: Summary of AEs by Region (FDA Review)

	NORTH AMERICA N = 69 N (%)	**ASIA N = 55 N (%)**	**EUROPE N = 51 N (%)**
All-Grade TEAEs	65 (94)	44 (80)	50 (98)
Grade 3-4 TEAEs	27 (39)	9 (16)	20 (39)
Grade 3	22 (32)	8 (15)	18 (35)

	NORTH AMERICA N = 69 N (%)	ASIA N = 55 N (%)	EUROPE N = 51 N (%)
Grade 4	5 (7)	1 (1.8)	2 (3.9)
Grade 5 (Deaths due to TEAEs)	2 (2.9)	0 (0.0)	3 (6)
Serious TEAEs (SAEs)	16 (23)	10 (18)	16 (31)
Patients discontinued due to AE	1 (1.4)	1 (1.8)	1 (2.0)

Source: ADSL (Subject-Level Analysis Dataset) - 2024-03-04, ADAE (Adverse Event Analysis Dataset) - 2024-03-04. Variables used: USUBJID, TRT01A, SAFFL, TRTEMFL, AETOXGRN, AESER

Table 76: AEs in ≥10% by Region (FDA Review)

	NORTH AMERICA N = 69		ASIA N = 55		EUROPE N = 51	
	All grades n (%)	Grades 3-4 n (%)	All grades n (%)	Grades 3-4 n (%)	All grades n (%)	Grades 3-4 n (%)
Patients with TEAEs	65 (94)	27 (39)	44 (80)	9 (16)	50 (98)	20 (39)
Gastrointestinal Disorders						
Diarrhea[a]	19 (28)	1 (1.4)	11 (20)	1 (1.8)	19 (37)	2 (3.9)
Nausea	17 (25)	0 (0.0)	5 (9)	1 (1.8)	8 (16)	2 (3.9)
Abdominal Pain[b]	13 (19)	4 (6)	2 (3.6)	0 (0.0)	5 (10)	0 (0.0)
Vomiting	10 (14)	0 (0.0)	4 (7)	1 (1.8)	7 (14)	0 (0.0)
Constipation	9 (13)	0 (0.0)	3 (5)	0 (0.0)	10 (20)	0 (0.0)

	NORTH AMERICA N = 69		ASIA N = 55		EUROPE N = 51	
	All grades n (%)	**Grades 3-4 n (%)**	**All grades n (%)**	**Grades 3-4 n (%)**	**All grades n (%)**	**Grades 3-4 n (%)**
General Disorders and Administration Site Conditions						
Fatigue[c]	18 (26)	2 (2.9)	2 (3.6)	0 (0.0)	15 (29)	2 (3.9)
Chills	7 (10)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)
Edema[d]	8 (12)	0 (0.0)	5 (9)	0 (0.0)	6 (12)	0 (0.0)
Pyrexia[e]	7 (10)	0 (0.0)	3 (5)	0 (0.0)	4 (8)	0 (0.0)
Musculoskeletal and Connective Tissue Disorders						
Musculoskeletal Pain[f]	25 (36)	1 (1.4)	3 (5)	1 (1.8)	13 (25)	0 (0.0)
Metabolism and Nutrition Disorders						
Decreased Appetite	8 (12)	1 (1.4)	4 (7)	1 (1.8)	3 (6)	0 (0.0)
Infections and Infestations						
Covid-19	3 (4.3)	0 (0.0)	6 (11)	0 (0.0)	7 (14)	0 (0.0)
Respiratory, Thoracic and Mediastinal Disorders						
Dyspnea[g]	12 (17)	2 (2.9)	3 (5)	0 (0.0)	10 (20)	3 (6)
Cough[h]	4 (6)	0 (0.0)	3 (5)	0 (0.0)	8 (16)	1 (2.0)
Nervous System Disorders						
Neuropathy Peripheral[i]	7 (10)	0 (0.0)	1 (1.8)	0 (0.0)	3 (6)	0 (0.0)

	NORTH AMERICA N = 69		ASIA N = 55		EUROPE N = 51	
	All grades n (%)	Grades 3-4 n (%)	All grades n (%)	Grades 3-4 n (%)	All grades n (%)	Grades 3-4 n (%)
Psychiatric Disorders						
Anxiety	8 (12)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Skin and Subcutaneous Tissue Disorders						
Rash[j]	8 (12)	0 (0.0)	6 (11)	0 (0.0)	9 (18)	0 (0.0)
Injury, Poisoning, and Procedural Complications						
Infusion related reaction	17 (25)	0 (0.0)	2 (3.6)	0 (0.0)	4 (8)	0 (0.0)

a. Includes diarrhea, post-procedural diarrhea.
b. Includes abdominal pain, gastrointestinal pain, abdominal pain upper.
c. Includes fatigue, asthenia.
d. Includes edema, edema peripheral, face edema, localized edema, peripheral swelling.
e. Includes pyrexia, body temperature increased.
f. Includes pain in extremity, myalgia, back pain, neck pain, musculoskeletal chest pain, arthralgia, bone pain, musculoskeletal stiffness, spinal pain, musculoskeletal pain, non-cardiac chest pain.
g. Includes dyspnea, dyspnea exertional.
h. Includes cough, productive cough.
i. Includes neuropathy peripheral, peripheral sensory neuropathy, hypoaesthesia, paraesthesia, dysaesthesia, neuralgia.
j. Includes rash, dermatitis, dermatitis acneiform, eczema, erythema, rash erythematous, rash maculo-papular.
k. Includes chills, IRR, nausea, cough, diarrhea, back pain, body temperature increased, dyspnea, face edema, fatigue, non-cardiac chest pain, oropharyngeal discomfort, paresthesia, pyrexia, and vomiting. AEs that were considered IRRs were counted under the composite term 'IRR', irrespective of the reported PT.

Source: ADSL (Subject-Level Analysis Dataset) - 2024-03-04, ADAE (Adverse Event Analysis Dataset) - 2024-03-04. Variables used: USUBJID, TRT01A, SAFFL, TRTEMFL, AEDECOD, AETOXGRN, AEBODSYS, AESER

8.2.6 Specific Safety Studies/Clinical Trials

Data:
Not applicable.

The Applicant's Position:

Not applicable.

The FDA's Assessment:

FDA agrees with the Applicant's position.

8.2.7 Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant's Position:

Carcinogenicity studies have not been performed with zenocutuzumab as they are not considered appropriate for this class of biological product, in line with the ICH S6 (R1) and ICH S9 guidelines.

The FDA's Assessment:

FDA agrees that carcinogenicity studies are not warranted to support this BLA submission.

Human Reproduction and Pregnancy

The Applicant's Position:

The effect of zenocutuzumab on a pregnant woman is unknown. There is limited experience because the study protocol excluded pregnant females and also required contraception for male and female patients during treatment with zenocutuzumab and for 6 months after last dose of zenocutuzumab. Exposure to zenocutuzumab may cause fetal harm. Females should be advised of the potential risk to the fetus and to use effective contraception. To minimize exposure of a breastfed child to zenocutuzumab, patients will be advised to not breastfeed for 2 months following the final dose of zenocutuzumab based on 5 times the half-life (upper 90% interval of half-life was 11 days). [Module 2.7.4]

The FDA's Assessment:

FDA does not agree with the Applicant; see Section 5. Based on the mechanism of action of zenocutuzumab and embryo-fetal harm reported with HER-2 directed products, FDA recommends including a box warning for embryo-fetal toxicity and advising females of reproductive potential to use effective contraception during treatment with zenocutuzumab and for 2 months after the last dose.

Pediatrics and Assessment of Effects on Growth

The Applicant's Position:

The safety and effectiveness of zenocutuzumab has not been established in pediatric patients. An agreed iPSP was issued by the FDA for zenocutuzumab for "full drug and disease-specific waiver across all pediatric age groups".

The FDA's Assessment:
FDA agrees with the Applicant's position (See Section 10).

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Data and The Applicant's Position:

There were no reports of overdose, intentional or otherwise, by investigators in the MCLA-128-CL01/eNRGy study or the NRG1+ EAP, or any other study in which patients have been treated with zenocutuzumab. Zenocutuzumab is administered as an IV infusion by a healthcare professional in a controlled healthcare setting including drug accountability, which minimizes the chances of overdose and of absence of reporting of accidental overdose.

This product has no known pharmacologic characteristics that could render it as a potential drug for abuse or illegal use. During this development program, there has been no evidence of zenocutuzumab abuse or intentional misuse.

No relevant studies or information regarding the investigation of the dependence potential of zenocutuzumab have been reported.

The nonclinical and clinical data do not suggest a risk of physical dependence and subsequent withdrawal symptoms with abrupt cessation of zenocutuzumab. No withdrawal or rebound effects were reported in patients discontinuing the MCLA128CL01/eNRGy study or the EAP.

The FDA's Assessment:
The nonclinical studies were not designed to evaluate these endpoints, nor are these studies warranted. Otherwise, FDA agrees with the Applicant's position.

8.2.8 Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Applicant's Position:

Zenocutuzumab has not been approved and marketed in any region.

The FDA's Assessment:

FDA agrees with the Applicant's position.

Expectations on Safety in the Postmarket Setting

The Applicant's Position:

Safety in the postmarket setting is expected to be generally similar to that observed in the clinical studies reviewed in this application.

Based on experience with zenocutuzumab and the available literature, risk management measures for IRRs, decreased cardiac ejection fraction, and diarrhea were mandatory in all zenocutuzumab protocols. Review of safety data does not suggest specific monitoring or management is warranted, except for IRRs that may be related to treatment with zenocutuzumab. Patients should be observed closely for IRRs, and zenocutuzumab should be discontinued in patients with life-threatening IRRs. Zenocutuzumab should only be administered in a setting with emergency resuscitation equipment and staff who are trained to monitor for IRRs and to administer emergency medications. IRRs are included in the warnings and precautions of the USPI.

Nonclinical reproductive and juvenile toxicity studies have not been performed with zenocutuzumab. However, based on a review of approved products and published literature, the overall weight of evidence is that HER2 and/or HER3 inhibition can cause embryotoxicity. It can therefore not be excluded that zenocutuzumab may cause harm to the human fetus. This supports adding a warning in the label for the risk of embryo-fetal toxicity. In routine clinical practice, cancer patients will be thoroughly counselled against pregnancy by their HCPs before commencing zenocutuzumab. In addition, the proposed label will include recommendations for female and male contraception.

All safety concerns that have been identified are adequately represented in the safety database for zenocutuzumab. Additional ongoing safety data from the eNRGy study will be submitted with the 90-day Safety Update Report to further elucidate the safety profile of zenocutuzumab.

Routine pharmacovigilance will also be conducted to further characterize the safety profile of zenocutuzumab (i.e., adverse reaction reporting) and monitor for unexpected adverse events (i.e., signal detection). The review of the safety profile of zenocutuzumab will also be reflected in data and post-marketing reporting of adverse experience requirement per 21 CFR 600.80.

The FDA's Assessment:
FDA disagrees with the Applicant's position that review of the safety data suggests that no specific monitoring or management is warranted. In addition to IRR/hypersensitivity/anaphylaxis, FDA is including Warnings for ILD/pneumonitis and left ventricular dysfunction in the USPI. FDA is also issuing safety PMRs to further characterize the risk of IRR/hypersensitivity/anaphylaxis, ILD/pneumonitis, and left ventricular dysfunction in the postmarket setting (see Section 13, Postmarketing and Commitment, for additional details).

8.2.9 Integrated Assessment of Safety

The Applicant's Position:

As discussed and agreed with the FDA, an integrated analysis of safety is not applicable in this application. The primary safety data supporting the indication at the proposed dose is based on a single data source: eNRGy study.

The overall duration of exposure and safety profile of zenocutuzumab 750 mg IV Q2W in the 99 NRG1+ NSCLC and 39 NRG1+ PDAC patients were consistent with the 175 patients with all NRG1+ tumor types. The safety results in these patient populations were similar with regard to the reported type, frequency, and severity of event terms for AEs, SAEs, and AEs leading to dose/infusion interruption or treatment discontinuations. No tumor indication-specific safety signals were apparent across NRG1+ tumor types. The safety data for patients with all NRG1+ tumor types included in this application provide a comprehensive review of zenocutuzumab safety in this initial BLA.

Based on the safety results presented, zenocutuzumab 750 mg IV Q2W was well tolerated in patients with NRG1+ cancer. This conclusion is further supported by a low rate of treatment discontinuations (8.0%) and notably low Grade 3-4 AEs, with no individual Grade 3-4 events observed at a frequency >5.1%. The majority of AEs and investigator-assessed related AEs were mild to moderate in severity, across regimens and tumor types. AEs resulting in death were rare, not treatment-related, and were almost exclusively associated with the underlying disease. Based on medical assessment, the most frequently reported ADRs (≥10%) were diarrhea, fatigue, nausea, dyspnea, IRR, rash, constipation, vomiting, and abdominal pain, with few Grade 3-4 events.

Most frequently occurring AEs, including diarrhea, were well managed with routine clinical care and the safety guidance provided in the study protocol. Administration of premedications is recommended to manage events of IRR.

The safety profile of the zenocutuzumab 750 mg Q2W regimen was similar to those of the 750 mg Q3W and Q1W regimens administered to non-NRG1+ cancer patients.

In summary, the safety data presented are supportive of a positive risk/benefit profile for zenocutuzumab 750 mg IV Q2W administered to an NRG1+ cancer population with unmet medical need.

The FDA's Assessment:

Safety data from the eNRGy study and EAP were not pooled because methods for collecting and characterizing data were not similar enough between the studies to pool (e.g. different schedules for collection, different rules for reporting etc.)

The primary safety population for this BLA comprises 175 patients treated on the eNRGy study

at the recommended dosage, including 99 patients with NRG1+ NSCLC and 39 patients with NRG1+ PDAC. The most common adverse events (≥10%) were diarrhea (28%), musculoskeletal pain (23%), fatigue (20%), nausea (17%), infusion-related reactions (13%), dyspnea (14%), constipation (13%), vomiting (12%), rash, abdominal pain (11% each), and edema (10%). The most frequent Grade 3-4 adverse reactions (≥2%) were anemia, diarrhea, abdominal pain, dyspnea and fatigue. Serious adverse reactions occurred in in 42 (24%) patients in the primary safety population. The most frequent (≥2%) were pneumonia (n=6) and dyspnea (n=4). Fatal adverse reactions occurred in five (2.9%) patients in the primary safety population. Fatal adverse reactions in the NSCLC population included respiratory failure (n=2) and cardiac failure (n=1). Fatal adverse reactions in the PDAC population included respiratory failure (n=1) and COVID-19 (n=1).

Important safety signals identified included infusion related reactions/hypersensitivity, interstitial lung disease/pneumonitis and left ventricular dysfunction. These safety concerns will be addressed in the Warnings and Precautions section of the USPI, and through safety PMRs. The safety profile for zenocutuzumab is considered acceptable when assessed in the context of a life-threatening disease.

8.3. Statistical Issues

The FDA's Assessment:

The eNRGy study is 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. In this submission, the eNRGy study enrolled a total 129 patients from different tumor types, but the approval is limited to previously-treated NSCLC (N = 64) and PDAC patient population (N = 30). The efficacy evaluation is based on ORR as assessed by BICR per RECIST 1.1 criteria and DOR.

There were no major statistical issues in the review of this application. Since the approval of this application is based on a single arm trial, the consideration of statistical issues is only applicable to the design and conduct of the single arm trial. With a single-arm design, time to event endpoints, such as PFS and OS, are difficult to interpret due to the lack of comparator. Therefore, the PFS and OS results are considered descriptive only. In addition, the sample size for PDAC patient is small, and as a result, the number of PDAC responders is also small. The estimated median DOR based on the PDAC responders is not stable due to the small sample size, small number of responders and the shape of the observed survival function, and should be interpreted with caution. Additional sample size and additional follow-up for DOR is likely to better characterize the median DOR, especially for PDAC patients. These data will be requested as part of PMRs for both indications to verify and confirm the clinical benefit of zenocutuzumab.

8.4. Conclusions and Recommendations

The FDA's Assessment:

The eNRGy study is a multicenter, single-arm, open label trial of zenocutuzumab in patients with advanced unresectable or metastatic NSCLC (n=75), PDAC (n=30), or other solid tumors harboring an *NRG1* fusion following progression with prior systemic therapy or who have no satisfactory alternative treatment options. The primary endpoint of the study is overall response rate (ORR) per blinded independent central review (BICR) according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Duration of response (DOR) is a key secondary endpoint. The primary efficacy populations were comprised of 64 patients with previously treated NSCLC and 30 patients with previously treated PDAC.

The ORR as assessed by BICR in the primary efficacy NSCLC population (n=64) was 33% (95% CI: 22, 46) with a median DOR 7.4 months (95% CI: 4.0, 16.6) for the 21 responders; 43% of responders had a DOR ≥ 6 months. The ORR as assessed by BICR in the relapsed or refractory *NRG1*+ PDAC population was 40% (95% CI: 23, 59). The percentage of responders

with a DOR of ≥6 months was 67%, and the percentage of responders with a DOR of ≥12 months was 17%. These efficacy data represent a clinically meaningful treatment effect in patients with previously-treated NRG1+ NSCLC and PDAC and is considered substantial evidence of effectiveness for both settings.

The ORR in the treatment-naïve NSCLC population (n=11) was 36% (95% CI: 11, 70). Given the small sample size of this population, the point estimate and lower limit of the 95% confidence interval compared to current standard of care first-line therapies for metastatic NSCLC, and the inconsistent literature reports describing the magnitude of responses to standard chemo-immunotherapy in patients with NSCLC harboring an NRG1 fusion, these data are considered supportive of the primary efficacy population (b) (4)

The safety profile of zenocutuzumab is acceptable for the intended population when considered in the context of a life-threatening disease. Important toxicities of zenocutuzumab that were noted in this review include infusion related reactions, left ventricular dysfunction, and pneumonitis. These adverse events are addressed in the Warnings and Precautions in the product label. Instructions for monitoring and dose modifications are provided in the USPI.

Based on the evaluation of clinical data from the eNRGy study, the review team recommends accelerated approval for zenocutuzumab for the treatment of patients with advanced unresectable or metastatic NSCLC or PDAC harboring an *NRG1* fusion with disease progression on or after prior systemic therapy. To verify clinical benefit and the safety of zenocutuzumab, efficacy and safety data from additional patients in the ongoing eNRGy study will be submitted as part of post-marketing requirements (PMRs). Given the rarity of *NRG1* fusions and the high ORR observed in the eNRGy study relative to that of available second or later line therapies for NSCLC and PDAC, the conduct of a randomized trial in these populations is considered infeasible. In this context, the efficacy and safety findings support a favorable benefit:risk assessment for zenocutuzumab for the treatment of adult patients with NSCLC and PDAC harboring *NRG1* fusions with disease progression on or after prior systemic therapy.

X X

Primary Statistical Reviewer	Statistical Team Leader
Qingyu (Sophia) Chen	Xiaoxue Li

X	X
Primary Clinical Reviewer	Clinical Team Leader
Kristin Wessel and Shruti Gandhy	Amy Barone and Sandra Casak

9 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

FDA did not refer this application to an advisory committee or seek input from other external consultants because this application did not raise significant public health questions regarding the role of zenocutuzumab for the proposed indication.

10 Pediatrics

The Applicant's Position:

The safety and effectiveness of zenocutuzumab has not been established in pediatric patients. An agreed iPSP was issued by the FDA for zenocutuzumab for "full drug and disease-specific waiver across all pediatric age groups".

The FDA's Assessment:

FDA agrees with the Applicant's position.

The Applicant submitted a request for a full waiver of the pediatric requirements for the proposed indication based on the rarity of the condition in pediatric patients, making the necessary studies impossible or highly impracticable to conduct. The Oncology Subcommittee of Pediatric Review Committee (OCE PeRC) agreed with the Applicant's request for a full waiver and justification that the necessary studies would be impossible or highly impracticable to conduct due to the rarity of the condition in children.

11 Labeling Recommendations

Data:
N/A

The Applicant's Position:

This is an original application. Please see annotated label in Module 1.14.1.2 for proposed labeling.

The FDA's Assessment: The proposed labeling submitted by the Applicant required extensive revision by FDA.

The format, language, and content of the proposed labeling was evaluated and revised for consistency with 21 Code of Federal Regulations (CFR), labeling guidances and current labeling practices of the Office of Oncologic Diseases. The table below summarizes key changes.

Section	Applicant's Proposed Labeling	FDA's proposed labeling
Boxed Warning		FDA added a boxed warning for Embryo-Fetal Toxicity based on the HER2 mechanism of action that causes oligohydramnios in pregnancy.
1.1 and 1.2		The Applicant proposed that both indications include: (b) (4) FDA removed this text because (b) (4)
2.1		The Applicant proposed to state that (b) (4), FDA deleted this text because (b) (4) for BIZENGRI.
2.2		FDA added a new subsection, 2.2 Recommended Evaluation Before Initiating BIZENGRI, for safety.
2.3 and 2.4		FDA provided minor editorial revisions.
2.5 Dosage Modifications		FDA added text for clarity, and added rows to the table to provide dosage modification advice for interstitial lung disease and left ventricular dysfunction.
2.6 Preparation		FDA provided minor editorial revisions.
2.7 Administration		FDA removed (b) (4) because the Applicant did not provide supportive data.

5.1 Infusion-Related Reactions		FDA added "Hypersensitivity/Anaphylactic Reactions" based on the safety of the eNRGy study.
5.2 Interstitial Lung Disease		FDA added this new warning, based on the safety based on the safety of the eNRGy study including two cases of Grade 2 pneumonitis.
5.3 Left Ventricular Dysfunction		FDA added this new warning, based on the safety based on the safety of the eNRGy study, including one fatal case.
6.1 Clinical Trials Experience		FDA revised the text in Section 6 for consistency with oncology labeling.
8 Use in Specific Populations		FDA revised the text in Section 8.1 to include animal studies demonstrating embryo lethality and revised Section 8.2 to include lactation consideration advice. In section 8.3, FDA removed (b) (4) due to the lack of evidence supporting this advice.
8.5 Geriatric Use		FDA provided minor editorial revisions.
11 Description		FDA provided minor editorial revisions.
12.1 Mechanism of Action		FDA revised the text for clarity and brevity.
12.2 Pharmacodynamics		FDA removed extraneous text and retained statement for consistency with 21 CFR 201.57(c)(13)(i)(B) requirements.
12.3 Pharmacokinetics		FDA added the metabolism pathway and revised the text for clarity and brevity.
12.6 Immunogenicity		FDA revised the text for consistency with the recently published Guidance for Industry: Immunogenicity Information in Human Prescription Therapeutic Protein and Select Drug Product Labeling.
14 Clinical Studies 14.1		14.1 Advanced Unresectable or Metastatic NRG1 Fusion-Positive Non-Small Cell Lung Cancer FDA provided minor editorial revisions and added a new table *Efficacy Results by NRG1 Gene Fusion Partner in NRG1 Fusion* FDA removed (b) (4)
14.2		14.2 Advanced Unresectable or Metastatic NRG1 Fusion-Positive Pancreatic Adenocarcinoma, FDA provided minor editorial revisions and added a new table: *Efficacy Results by NRG1 Gene Fusion Partner in NRG1 Fusion*
16		FDA provided minor revision for clarity.
17		FDA added patient counseling advice for: Infusion-Related Reactions/Hypersensitivity/Anaphylaxis Interstitial Lung Disease (ILD)/Pneumonitis Left Ventricular Dysfunction Embryo-Fetal Toxicity

APPEARS THIS WAY ON ORIGINAL

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

12 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:

There were no significant safety concerns identified during the BLA review requiring risk management beyond labeling or warranting consideration for a Risk Evaluation and Mitigation Strategy (REMS). Zenocutuzumab will be prescribed by oncologists who are trained in monitoring, diagnosing, and managing serious toxicities caused by antineoplastic drugs and biologics including targeted therapies. Safety concerns are adequately addressed by information in the Warnings and Precautions and Dosage and Administration sections of product labeling.

13 Postmarketing Requirements and Commitment

The FDA's Assessment:

As the review team is recommending accelerated approval for zenocutuzumab pursuant to section 506(c) of the FDCA and 21 CFR 601.41, the Applicant will be required to continue the eNRGy study to verify and describe the clinical benefit of zenocutuzumab in patients with NRG1+ NSCLC and PDAC with disease progression on or after prior systemic therapy.

The review team recommends the following PMRs/PMCs:

PMR 1:

Complete a clinical trial intended to verify and describe the clinical benefit of zenocutuzumab 750 mg intravenously every two weeks in at least 100 evaluable adult patients with advanced unresectable or metastatic non-small cell lung cancer harboring a neuregulin 1 (*NRG1)* gene fusion with disease progression on or after prior systemic therapy . To characterize response rate and duration, patients will be followed for at least 12 months from the onset of response.

Trial Completion:	02/2026
Final Report Submission:	08/2026

PMR 2:

Complete a clinical trial intended to verify and describe the clinical benefit of zenocutuzumab 750 mg intravenously every two weeks in at least 50 evaluable adult patients with advanced unresectable or metastatic pancreatic adenocarcinoma harboring a neuregulin 1 (*NRG1)* gene fusion with disease progression on or after prior systemic therapy (or who are not eligible for standard of care therapy). To characterize response rate and duration, patients will be followed for at least 12 months from the onset of response.

Trial Completion:	02/2026
Final Report Submission:	08/2026

PMR 3:

Conduct a comprehensive integrated safety analyses in a sufficient number of adult patients from clinical trials to adequately characterize the known serious risks of infusion-related reactions/hypersensitivity/anaphylaxis, interstitial lung disease/pneumonitis, and left ventricular dysfunction following exposure to zenocutuzumab. The integrated safety analysis should include all adverse events, major safety events, dose-reductions, dose interruptions, and withdrawals,

when all patients have completed at least two years of treatment with zenocutuzumab or withdrew earlier.

Draft Protocol Submission (Analysis Plan):	01/2025
Final Protocol Submission (Analysis Plan):	05/2025
Study Completion:	12/2026
Final Submission:	06/2027

PMC 1:

Develop and validate a neutralizing antibody (NAb) assay and submit a full validation report of the developed NAb assay. The assay format should be adequately justified to be suitable for the detection of NAbs. This NAb assay will be used to test available confirmed anti-drug antibody positive samples from banked and ongoing clinical studies. Include the updated NAb results analyzed using the validated NAb assay to address the effects of neutralizing antibody on the pharmacokinetics, pharmacodynamics, safety, and effectiveness of zenocutuzumab.

Draft Protocol Submission (Analysis Plan):	01/2025
Final Protocol Submission (Analysis Plan):	05/2025
Study Completion:	06/2025
Final Report Submission:	08/2025

PMC 2:

Conduct an appropriate analytical and clinical validation study to establish and support the availability of an in vitro diagnostic device using clinical trial data that demonstrates the device is essential to the safe and effective use of zenocutuzumab for the treatment of adult patients with advanced unresectable or metastatic non-small cell lung cancer harboring a neuregulin 1 (*NRG1)* gene fusion with disease progression on or after prior systemic therapy.

Final Report Submission:	03/2028

PMC 3:

Conduct an appropriate analytical and clinical validation study to establish and support the availability of an in vitro diagnostic device using clinical trial data that demonstrates the device

is essential to the safe and effective use of zenocutuzumab for the treatment of adult patients with advanced unresectable or metastatic pancreatic adenocarcinoma harboring a neuregulin 1 (*NRG1)* gene fusion with disease progression on or after prior systemic therapy.

Final Report Submission: 03/2028

While the review team found that the majority of patients in the eNRGy study are White or Asian and that the racial demographics are not representative of the racial and ethnic diversity of the U.S. population, FDA will not require a PMC/PMR given that zenocutuzumab is intended for a rare, biomarker-selected population.

FDA PMC/PMR Checklist for Trial Diversity and U.S. Population Representativeness

The following were evaluated and considered as part of FDA's review:		Is a PMC/PMR needed?
x	The patients enrolled in the clinical trial are representative of the racial, ethnic, and age diversity of the U.S. population for the proposed indication.	__ Yes _x_ No
x□	Does the FDA review indicate uncertainties in the safety and/or efficacy findings by demographic factors (e.g. race, ethnicity, sex, age, etc.) to warrant further investigation as part of a PMR/PMC?	__ Yes _x No
□	Other considerations (e.g.: PK/PD), if applicable:	__ Yes _x No

14 Division Director (DHOT) (NME ONLY)

X

15 Division Director (OCP)

X

16 Division Director (OB)

X

17 Division Director (Clinical)

X

18 Office Director (or designated signatory authority)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X _____

19 Appendices

19.1. References

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19.2. Financial Disclosure

The Applicant's Position:

Covered Clinical Study (Name and/or Number):* eNRGy

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: eNRGy CSR: 98 MCLA-128-CL01 CSR: 16		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: N/A Significant payments of other sorts: N/A Proprietary interest in the product tested held by investigator: N/A Significant equity interest held by investigator in study: N/A Sponsor of covered study: N/A		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☒ Not applicable
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☒ Not applicable
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☒ Not applicable

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

The FDA's Assessment:

FDA agrees with the Applicant's position.

19.3. Nonclinical Pharmacology/Toxicology

Data:

Not applicable.

The Applicant's Position:

Not applicable.

The FDA's Assessment:

Not applicable.

19.4. OCP Appendices (Technical documents supporting OCP recommendations)

19.4.1. Population PK Analysis

19.4.1.1 Executive Summary

The FDA's Assessment:

The final model was a two compartmental model with combined linear and saturable clearance. The linear clearance was found to decrease with time, up to an estimated maximal drop of approximately 16%. The final model was determined to be reasonably well describe the observed PK profile of zenocutuzumab.

Among all tested covariates, baseline sum of lesions, baseline alanine aminotransferase, baseline total bilirubin, baseline creatinine clearance, number of previous lines of therapy and drug product batch were not found to be statistically significant. Central volume and linear clearance were found to increase with body surface area (BSA). The clearance decreased with age and baseline albumin levels, while this parameter increased with increasing baseline alkaline phosphatase (ALP) levels. The maximal saturable clearance increased with increasing baseline aspartate aminotransferase

(AST), which was approximately 20% lower for fully active Eastern Cooperative Oncology Group (ECOG) patients, and 35% higher for anti-drug antibody (ADA) positive patients. The linear clearance was also approximately 20% and 25% larger for males and non NRG1 patients.

In addition, the central volume was approximately 20% larger for males and non NRG1(neuregulin-1 gene) patients, and approximately 10% lower for Asian patients, respectively. However, none of these covariates were considered to be clinically meaningful to warrant dosing adjustment for application of zenocutuzumab.

19.4.1.2. PPK Assessment Summary

The Applicant's Position:

The PK of zenocutuzumab was described with a 2-compartment model with both linear and non-linear clearance. A time-dependent decrease in linear clearance was characterized. There were no clinically relevant differences in clearance (CL), volume of distribution, and other PK parameters of zenocutuzumab based on tumor type (NSCLC vs PDAC vs other tumor types). None of the included statistically significant covariate effects were considered strong enough to warrant *a priori* dosing adjustments.

General Information		
Objectives of PPK Analysis		• To develop an adequate structural PK model for zenocutuzumab. • To develop an adequate random effect structure to describe the inter individual variability (IIV) on the PK parameters. • To perform a formal covariate analysis to evaluate which parameter-covariate relationships explain part of the IIV. • To assess the covariate impact on exposure at steady state. • To derive exposure metrics based on the individual model parameters obtained from the final model.
Study Included		MCLA-128-CL01
Dose(s) Included		40 mg Q3W, 80 mg Q3W, 160 mg Q3W, 240 mg Q3W, 360 mg Q3W, 480 mg Q3W, 600 mg Q3W, 750 mg Q3W and 900 mg Q3W, 400 mg Q1W and 750 mg Q2W.
Population Included		Patients with solid tumours.
	General	

<table>
<tr><td>Population Characteristics (Table 54 and Table 55)</td><td></td><td>Age: median 60.0 (22.0 – 88.0) years.
Weight: 67.0 (38.4 – 126.0) kg.
Female: 180 (60%), Male: 128 (40%).
Asian: 64 (20%), Black or African American: 6 (2%), Caucasian: 230 (72%), Not Reported:12 (4%), Other: 6 (2%).
NRG1-fusion: 167 (53%), No NRG1-fusion: 148 (47%), missing NRG1-fusion status: 3 (1%).</td></tr>
<tr><td></td><td>Organ Impairment</td><td>ALB: median 39.0 (range 20.0-49.0) g/L
AST: 27.0 (11.0-206) IU/L
ALP: 108 (35.0-1062) IU/L
ALT: 19.0 (4.00-226) IU/L
BILI: 8.55 (2.22-30.8) µM
CREAT: 67.2 (31.8-153) µmol/L</td></tr>
<tr><td></td><td>Pediatrics (if any)</td><td>Not included.</td></tr>
<tr><td colspan="2">No. of Patients, PK Samples, and BLQ</td><td>In total 4916 PK samples from 323 patients were available. All pre-dose samples (n=369) were excluded, leaving 4547 observsations from 322 patients. 38 post-dose samples were BLQ and were excluded. 1 sample was excuded due to a suspected data error (double observation record) and for 567 samples the concentration was not available. In the final dataset 3941 PK samples from 318 patients were evaluated.
Table 7.1:3: Overview of number of observations and subjects ignored in the analysis
<table>
<tr><th>Step</th><th>description</th><th>Obs in</th><th>IDs in</th><th>Obs dropped</th><th>IDs dropped</th></tr>
<tr><td>0</td><td>Original dataset</td><td>4916</td><td>323</td><td>0</td><td>0</td></tr>
<tr><td>1</td><td>All pre-dose observation before start of first infusion)</td><td>4547</td><td>322</td><td>369</td><td>1</td></tr>
<tr><td>2</td><td>BLQ samples</td><td>4509</td><td>322</td><td>38</td><td>0</td></tr>
<tr><td>3</td><td>Suspected data error (double observation record)</td><td>4508</td><td>322</td><td>1</td><td>0</td></tr>
<tr><td>4</td><td>Ignored missing DV (MDV)</td><td>3941</td><td>318</td><td>567</td><td>4</td></tr>
<tr><td>5</td><td>Total</td><td>3941</td><td>318</td><td>975</td><td>5</td></tr>
</table>
Dropped records are listed sequentially. This means that for each step the number of dropped records opposed to the previous step is displayed. This does not take into account an overlap in dropped records</td></tr>
<tr><td>Sampling Schedule</td><td>Rich Sampling</td><td>Q3W: Cycle 1 Day 1 (C1D1) pre-dose, C1D1 end-of-infusion (EOI), 1,2,4,8 and 24h after C1D1 EOI, any time on day 3 or 4, 8 and 15 and on day 1 of cycle 2, 3 and 4 at pre-dose and EOI.
Q1W: C1D1 pre-dose, C1D1 EOI, 2,4, and 24 h after C1D1 EOI, C1D8 and C1D15 pre-dose and C1D22 pre-dose and EOI. In cycles 2 and 3 pre-dose and EOI on day 15. In cycle 4 pre-dose on day 1 and</td></tr>
</table>

		pre-dose and EOI on day 15. Every 2 cycles thereafter a pre-dose on day 15. Q2W: C1D1 pre-dose, C1D1 EOI, 2, 4, 24 h after C1D1 EOI, pre-dose and EOI on day 15. In cycles 2 and 3, a pre-dose an EOI on day 1, and a pre-dose on day 15. In cycle 4 and every two cycles thereafter, a pre-dose on day 1.
	In ITT Population	Schedule for Q2W mentiond under Rich Sampling above.
Covariates Evaluated	Static	Weight, body surface area (BSA), sex, age, race, baseline serum albumin, baseline alanine aminotransferase, baseline asparate aminotransferase, baseline alkaline phosphatase, baseline total bilirubin, baseline creatinine clearance, number of previous lines of therapy, ADA status, sum of lesions, drug roduct batch, NRG1 gene fusion and ECOG performance status.
	Time-varying	None.

Final Model	**Summary**	**Acceptability [FDA's comments]**
Software and Version	NONMEM (Version 7.5.1, Icon Development Solutions, Ellicott City, Maryland USA) with GFortran (version 9.4.0). PsN (version 5.3.0). R (Version 4.2.1, The R foundation for Statistical Computing). Rstudio (version 2022.07.1, RStudio Inc, Boston, USA).	Acceptable
Model Structure	A 2-compartment model structure with linear and non-linear clearance. The linear part of the clearance decreased in a time-dependent manner.	Acceptable
Model Parameter Estimates	Table 56	Acceptable
Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap)	All structural model parameters were estimated with a reasonable RSE, only for Km (28%), Imax (29%) and TW50 (49%) RSE was higher than 20%. The higher uncertainty for Km can be explained by the sparsity of low concentrations from low doses. The higher uncertainty of Imax and TW50 might only affect time to steady-state. Of the identified covariate relationships, the	Acceptable

	highest RSE was observed for the effect of age on clearance (49%) and Aspartate Aminotransferase at baseline on Vmax (42%). Shrinkage for clearance and cenral volume of distribution (V1) were 12 and 19%, respectively. Shrinkage for Vmax was 44%, which again can be explained by the sparsity of low concentrations.	
BLQ for Parameter Accuracy	BLQ observations (n=38) were excluded from the analysis so no further BLQ methods were implemented.	Acceptable
GOF, VPC	Figure 15 and Figure 16	Acceptable
Significant Covariates and Clinical Relevance	Figure 17 Baseline BSA, sex, NRG1-fusion and race were included as covariate for V1. Baseline BSA, sex, Alkaline phosphatase at baseline, albumin, NRG1-fusion status and age were included as covariates for clearance. Aspartate Aminotransferase at baseline, ADA ane ECOG were included as covariate for Vmax. Within the NRG1 subpopulation, the magnitude of covariate effects on exposures was generally modest. Most statistically significant covariates result in ≤20% change in exposure. Males had 23% lower exposures compares to feamles, and patients with below median BSA had 29% higher exposure compared to above median BSA. None of the covariate effects were considered strong enough to warrant *a priori* dosing adjustments.	Acceptable
Analysis Based on Simulation (optional)	Simulation up to 200 weeks to calculate accumulation rate at 750 mg Q2W showed median time to steady state of 8 weeks and median accumulation ratio of 1.6-fold.	Acceptable
Labeling Language	**Description**	**Acceptability** **[FDA's comments]**
12.3 PK	Steady state of zenocutuzumab-zbco concentrations are reached by a median	Acceptable.

	time of 8 weeks after repeated dosing with the 750 mg every 2 weeks regimen and the median accumulation ratio is 1.6-fold. Distribution The zenocutuzumab-zbco geometric mean for volume of distribution is 6.1 L (b) (4) Elimination (b) (4) Specific Populations (b) (4)	(b) (4) zenocutuzumab PK was studied and compared in limited number of cancer types. (b) (4)

Table 77. Applicant - Summary of Baseline Continuous Characteristics and Laboratory Values in the Dataset.

variable	N	Min	q5	q25	Median	q75	q95	Max	Mean	SD	geomean	geoSD
Weight at baseline (kg) (WT)	318	38.4	46.1	56.0	67.0	78.1	96.7	126	68.3	15.7	66.5	1.26
Body surface area at baseline (m^2) (BSA)	311	1.30	1.44	1.58	1.73	1.91	2.16	2.37	1.75	0.224	1.74	1.14
Age (years) (AGE)	318	22.0	32.0	52.0	60.0	69.0	78.0	88.0	59.2	13.5	57.4	1.30
Serum albumin at baseline (g/L) (ALB)	318	20.0	29.6	35.7	39.0	42.0	45.0	49.0	38.4	4.80	38.1	1.15
Aspartate Aminotransferase at baseline (IU/L) (AST)	318	11.0	14.0	19.0	27.0	38.0	94.0	206	36.0	29.6	29.4	1.79
Alkaline phosphatase at baseline (IU/L) (ALP)	317	35.0	58.6	78.0	108	164	431	1062	157	146	124	1.85
Alanine Aminotransferase (IU/L) (ALT)	318	4.00	8.00	13.0	19.0	31.0	56.7	226	25.7	22.1	20.5	1.89
Total bilirubin at baseline (µM) (BILI)	318	2.22	3.71	6.00	8.55	11.0	18.8	30.8	9.28	4.68	8.29	1.61
Creatinine clearance at baseline (µM) (CREAT)	318	31.8	41.9	55.8	67.2	79.6	115	153	70.2	21.7	67.2	1.34
Sum of lesions; as marker of tumour burden (SLES)	299	10.0	17.0	42.0	71.0	106	162	277	79.2	47.2	64.7	1.98

Source: Final Report Population PK Analysis, 13DEC2023, Table 7.1.5.

Table 78. Applicant - Frequencies of categorical covariates from all subjects used for PK analysis.

		N (%)
Variable	Value	Final PK dataset
Anti drug antibody status (ADA)	Missing covariate data	3 (1)
	Negative/not confirmed	271 (85)
	Positive/Confirmed	44 (14)
Drug product batch used (BATCH)	DP1	185 (58)
	DP2	83 (26)
	DP3	50 (16)
ECOG status at baseline (ECOG)	Able to carry out work of a light or sedentary nature	181 (57)
	Fully active	130 (41)
	Unable to carry out any work activities	7 (2)
NRG1 fusion (NRG1)	Missing covariate data	3 (1)
	No	148 (47)
	Yes	167 (53)
Number of previous lines of therapy [categorized 1] (NPTC1)	>3 prior therapies	104 (33)
	2-3 prior therapies	130 (41)
	No prior therapy	14 (4)
	One prior therapy	70 (22)
Race (RACE)	Asian	64 (20)
	Black or African American	6 (2)
	Caucasian	230 (72)
	Not reported	12 (4)
	Other	6 (2)
Sex (SEX)	Female	190 (60)
	Male	128 (40)

Source: Final Report Population PK Analysis, 13DEC2023, Table 7.1.6.

Table 79. Applicant - Parameter Estimates and SE from Final Population PK Model.

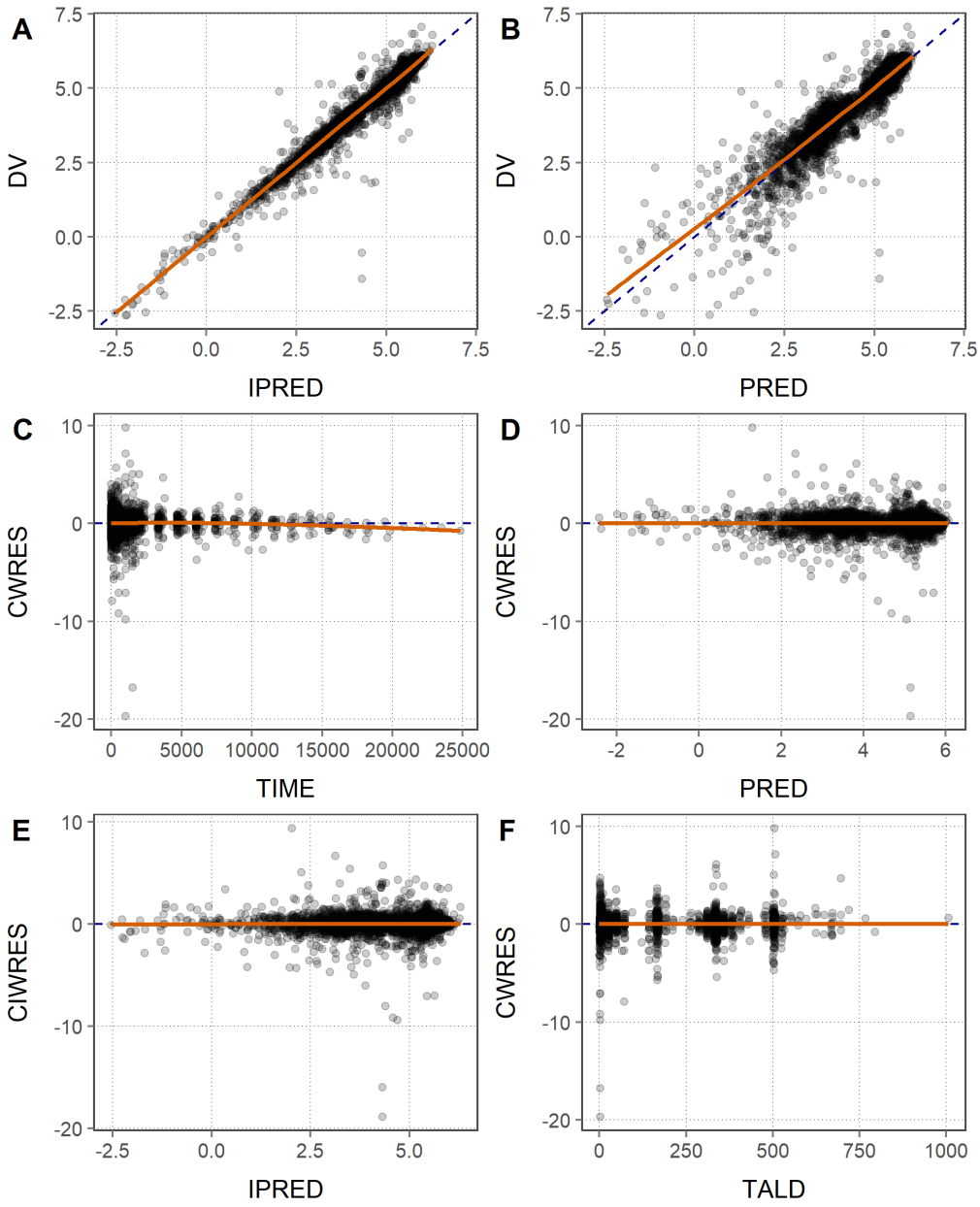
Parameter [unit]	Estimate	SE	95% CI[a]	RSE (%)[b]	CV (%)[c]	ρ[d]
Structural, Θ						
CL [L/h][e]	0.0204	0.00133	(0.0177, 0.0230)	6.5	-	-
V1 [L][f]	2.89	0.0670	(2.76, 3.02)	2.3	-	-
Vmax [mg/h][g]	0.336	0.0404	(0.256, 0.415)	12	-	-
Km [µg/mL]	0.614	0.169	(0.283, 0.945)	28	-	-
Q [L/h]	0.0288	0.00281	(0.0233, 0.0343)	9.8	-	-
V2 [L]	3.12	0.306	(2.52, 3.72)	9.8	-	-
Imax	0.164	0.0479	(0.0699, 0.258)	29	-	-
TW50 [week]	1.74	0.857	(0.0573, 3.42)	49	-	-
effect of BSA on V1	0.913	0.121	(0.676, 1.15)	13	-	-
effect of AGE on CL	−0.133	0.0648	(−0.260, −0.00563)	49	-	-
effect of ALB on CL	−0.617	0.127	(−0.865, −0.368)	21	-	-
effect of AST on Vmax	0.195	0.0811	(0.0357, 0.354)	42	-	-
effect of ALP on CL	0.103	0.0318	(0.0407, 0.165)	31	-	-
effect of BSA on CL	1.26	0.163	(0.941, 1.58)	13	-	-
effect of ADA on Vmax	1.36	0.128	(1.11, 1.61)	9.4	-	-
effect of ECOG 0 on Vmax	0.783	0.0517	(0.681, 0.884)	6.6	-	-
effect of non NRG1 on V1	1.17	0.0326	(1.10, 1.23)	2.8	-	-
effect of non NRG1 on CL	1.26	0.0482	(1.17, 1.36)	3.8	-	-
effect of Asian on V1	0.911	0.0263	(0.860, 0.963)	2.9	-	-
effect of Male on V1	1.20	0.0364	(1.13, 1.27)	3.0	-	-
effect of Male on CL	1.18	0.0476	(1.09, 1.28)	4.0	-	-
Inter-Individual Variability, Ω						
ω^2 CL	0.0703	0.00822	(0.0541, 0.0864)	12	27.0	-
ω_{xy} CL×V1	0.0271	0.00440	(0.0184, 0.0357)	16	-	+0.58
ω^2 V1	0.0310	0.00372	(0.0237, 0.0383)	12	17.8	-
ω^2 Vmax	0.0956	0.0195	(0.0575, 0.134)	20	31.7	-
Residual Error, Σ						
σ add. log PK	0.305	0.0364	(0.233, 0.376)	12	31.2	-

OFV = −4182.584
Condition number $\kappa = 204$

[a] Interval calculated as $\hat{\theta} \pm \Phi(1-\alpha/2) \cdot se(\hat{\theta})$; [b] RSE (%) calculated as $|100 \cdot se(\hat{\theta})/\hat{\theta}|$; [c] CV for random effects calculated as $100\sqrt{\exp(\text{variance}) - 1}$, with variance ω^2 or σ^2; [d] Correlation coefficient ρ calculated as $\omega_{xy}/\sqrt{\omega_x^2\omega_y^2}$
[e] Typical value for CL = $0.0204 \cdot (BSA/1.73)^{1.26} \cdot (AGE/60)^{-0.133} \cdot (ALB/39)^{-0.617} \cdot (ALP/108)^{0.103}$ (·1.18 if male) (·1.26 if non NRG1); [f] Typical value for V1 = $2.89 \cdot (BSA/1.73)^{0.913}$ (·1.20 if male) (·1.17 if non NRG1) (·0.911 if Asian);
[g] Typical value for Vmax = $0.336 \cdot (AST/27)^{0.195}$ (·1.36 if ADA) (·0.783 if ECOG 0);

Source: Final Report Population PK Analysis, 13DEC2023, Table 7.2:10.

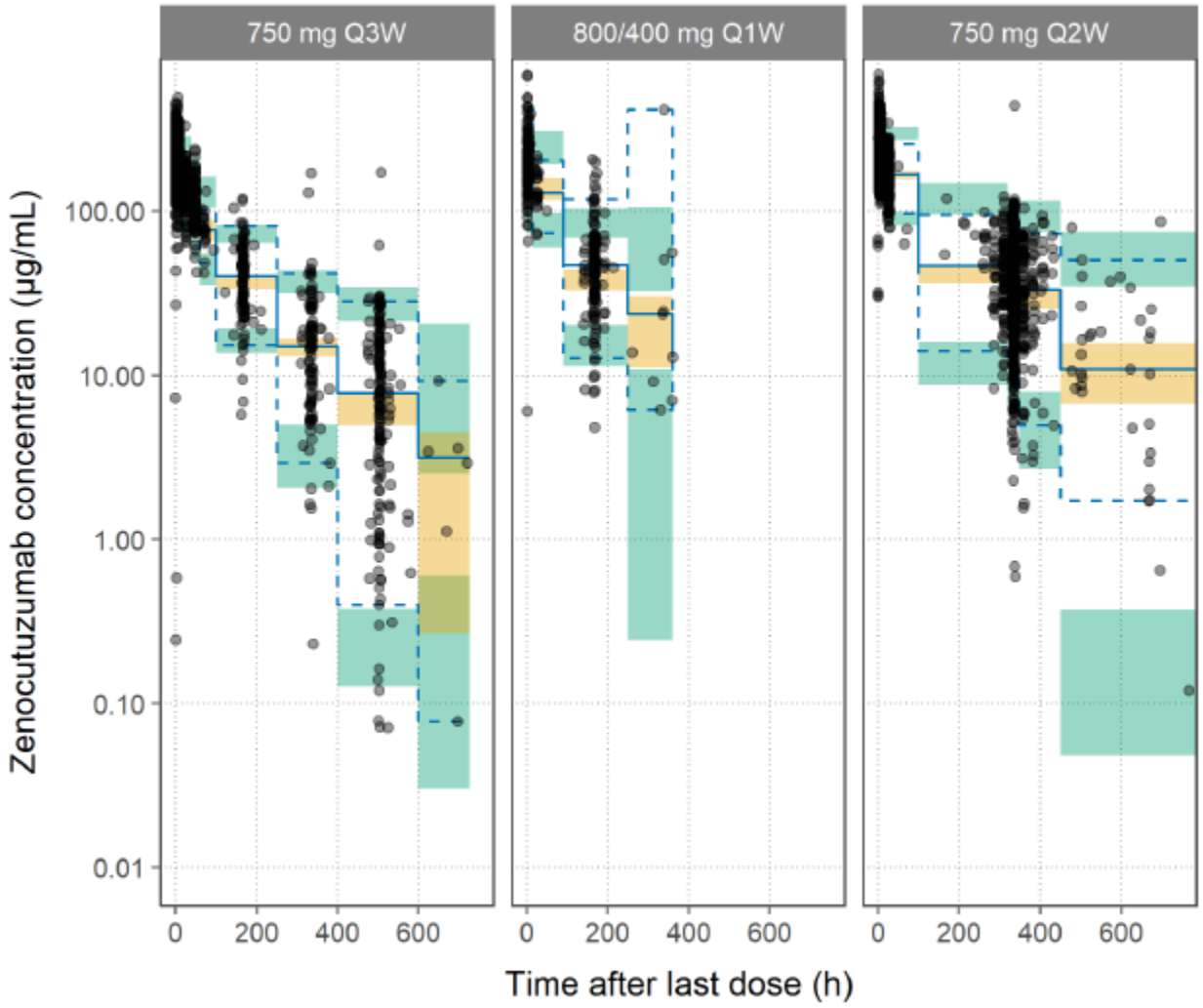
Figure 16. Applicant - Goodness-of-fit Plots for the Final Population PK Model (OBS-PRED/IPRED, CWRES-TIME/PRED).



Source: Final Report Population PK Analysis, 13DEC2023, Figure 7.2:13.

Figure 17. Applicant - VPC of Final Population PK Model for part 2 of MCLA-128-CL01, Stratified by Dose.

Observed data (black dots); Within each bin: observed median (blue line), observed 5th and 95th percentiles (dashed blue lines), 95% interval of simulated median (yellow ribbon), 95% interval of simulated 5th and 95th percentiles (green ribbons).

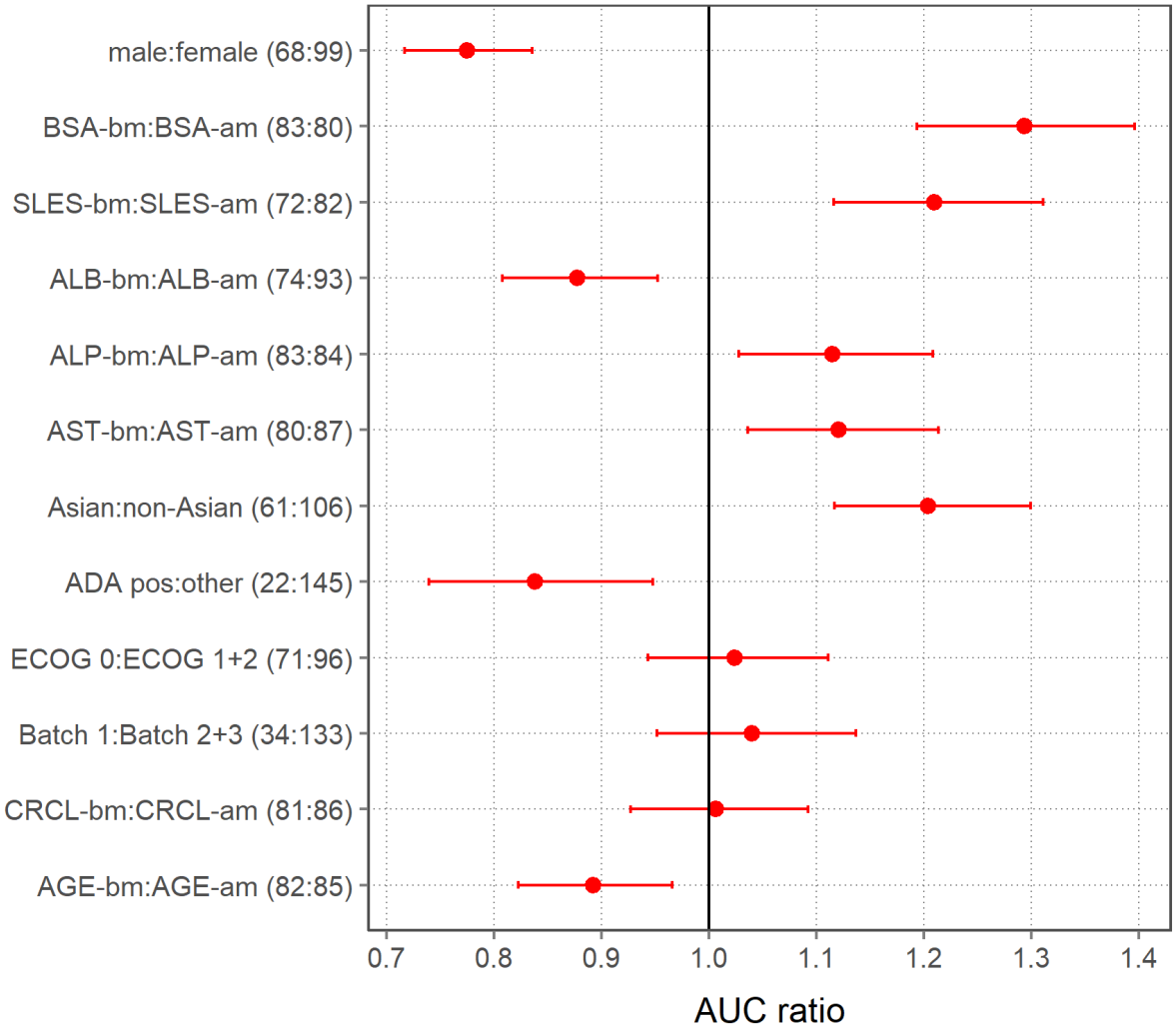


Source: Final Report Population PK Analysis, 13DEC2023, Figure 7.2:19.

Figure 18. Applicant - Impact of Significant Covariates on Exposure.

Forest plot of geometric mean AUC0−2week,ss ratios for the NRG1 subpopulation derived from the final population PK model of zenocutuzumab by dichotomized covariate of interest. Red dot and bar are the median and 90%CI, respectively, of the ratio by dichotomized variable of AUC0−2week,ss geometric means.

This median and CI was obtained by sampling 10000 replicate trials based on the individual AUC values with replacement, per group. AUC0−2week,ss were derived via simulation: each subject (individual parameters) was subjected to 750 mg Q2W dosing up to 200 weeks. Values between brackets represent the number of individuals with PK information in the dataset (and thus in each replicate trial) per category. For continuous covariates, patients were grouped below (bm) and above (am) the median observed covariate.



Source: Final Report Population PK Analysis, 13DEC2023, Figure 7.2:30.

The FDA's Assessment:

The final popPK model was determined to be reasonably well describe the observed PK profile of zenocutuzumab. None of the tested covariates were considered to be clinically meaningful to warrant dosing adjustment for application of zenocutuzumab.

No clinically significant differences in the pharmacokinetics of zenocutuzumab were observed based on age (22 to 88 years), sex, race [White or Asian], body weight (38 to 126 kg), albumin level (20 to 49 g/L), mild or moderate renal impairment (creatinine clearance (CLcr) 30 to 89 mL/min), and mild hepatic impairment (total bilirubin >1 to 1.5 times ULN or AST > ULN).

Black patients were removed from the race group as insufficient number of black patients were included in the popPK model. Zenocutuzumab PK was studied and compared in limited number of cancer types. Therefore, data are not sufficient to support the statement of no effect of tumor type on exposure.

19.4.2. Exposure-Response Analysis

19.4.2.1. ER (efficacy) Executive Summary

The FDA's Assessment:

Efficacy:

- The Cavg,ss could not be identified as a significant predictor for the duration of response (DOR) per central assessment. Per local assessment, the Cavg,ss was found to be a borderline significant predictor for the duration of response: after one year of treatment, more than 50% of the patients in the upper two Cavg,ss quartiles were still responders, while this was lower than 25% for the lower two Cavg,ss quartiles.
- The response was found to be significantly higher for pancreatic ductal adenocarcinoma (PDAC) patients versus patients with tumor types other than PDAC and non-small cell lung cancer (NSCLC) (overall response rate (ORR) central and local), and for eastern cooperative oncology group performance status (ECOG) 0 patients.
- For ORR central endpoint, it was found that the ER relationship is partially driven by early drop out patients who received only a few doses and thus did not reach their potential Cavg,ss or timepoint of first imaging assessment. Additionally, an ER relationship was also observed with individual clearance as a predictor. It is thus expected that the ER

relationship for efficacy endpoints may be confounded by interaction between patient health factors, antibody clearance, and response status. It was anticipated that severely ill patients, with an unfavorable prognosis, could have a faster drug clearance on average. In the present analysis, patients with a higher clearance were associated with a low albumin-to-alkaline phosphatase ratio, which was reported as a potential biomarker for poor prognosis and tumor recurrence. Therefore, interpretation of efficacy ER relationship should be cautious due to confounding and data limitation from one dose level.

19.4.2.2. ER (efficacy) Assessment Summary

The Applicant's Position:

Exposure-response analyses for overall response, clinical benefit rate, duration of response and maximum percentage decrease from baseline in sum of diameters of target lesions supported that a fixed dose of 750 mg Q2W is an adequate dose for clinical use of zenocutuzumab in NRG1+ cancer patients. Please see section 6.3.2.1 for a summary of the key results.

General Information		
Goal of ER analysis		The objective of this analysis was to perform an E-R analysis for safety and efficacy dependent variables of interest. Different individual exposure metrics derived from the final population PK model for zenocutuzumab were evaluated as predictors of response, together with other, compound-independent, intrinsic and extrinsic factors. A formal E-R analysis plan describing the analysis steps was established prior to receiving the final locked dataset.
Study Included		MCLA-128-CL01.
Endpoint		Primary:overall response rate (ORR), clinical benefit rate (CBR), duration of response (DOR) and maximum percentage decreasae from baseline in sum of diameters of target lesions (sum of lesions nadir). For each endpoint the local and central assessment was evaluated.
No. of Patients (total, and with individual PK)		129 patients, all with individual PK.
Population Characteristics (Table 57and Table 58)	General	Population characteristics were summarized for the total population, consisting of the safety and efficacy population. Age 61 (21 - 88) years. Weight 67 (38.4 – 125.5)kg 132 (40%) male, 198 (60%) female 238 (72%) caucasian, 67 (20%) Asian, 12 (3.6%) not reported, 7 (2.1%) other, 6 (1.8%) black or African Amerian.

	Pediatrics (if any)	Not included	
Dose(s) Included		750 mg Q2W	
Exposure Metrics Explored (range)		Average serum concentration at steady state ($C_{avg,ss}$). Median 99.9 (range 35.9 – 174) µg/mL.	
Covariates Evaluated		Age, sex, baseline bodyweight, race, ECOG status, liver enzyme category, tumour tpe, sum of target lesion diameters, presence of visceral lesions, number of organs involved, number of previous lines of therapy.	
Final Model Parameters		**Summary**	**Acceptability [FDA's comments]**
Model Structure		For ORR and CBR a logistic regression model was applied: $logit(P) = log_e\left(\frac{P}{1-P}\right) \approx intercept + slope \cdot exposure$ where P is the predicted probability of response, intercept is the estimated proability of response when the exposure metric is zero, and the slope is the estimated slope of the linear relationship with exposure. For DOR a Kaplan-Meier evaluation was performed. For sum of lesions nadir a linear regression model was applied: $DV \approx intercept + slope \cdot exposure$ where intercept is the estimated sum of lesions when exposure metric is zero and slope is the estimated slope of the linear relationship with exposure.	**Acceptable**
Model Parameter Estimates		ORR & CBR:Table 59 Sum of lesions nadir: Table 60	Acceptable (CBR and Sum of lesions nadir are NOT primary clinical endpoints and are NOT assessed.)
Model Evaluation		For **ORR**, **CBR** and **sum of lesions nadir**, assessed central and locally, the relationship with	Acceptable (CBR and

	$C_{avg,ss}$ was significant in univariate analyses and maintained significance in multivariate analyses. For **central** assessed **DOR** $C_{avg,ss}$ was not found a significant predictor, and for **locally** assessed **DOR** $C_{avg,ss}$ was found to be a borderline significant predictor.	Sum of lesions nadir are NOT primary clinical endpoints and are NOT assessed.)
Covariates and Clinical Relevance	The probability for **central** and **locally** assessed **ORR** was slightly higher for PDAC patients vs patients with tumor types other than PDAC and NSCLC. The probability for **central** assessed **CBR** was higher for males vs females, patients with ECOG 0 and PDAC vs ECOG 1 or 2 and other than PDAC tumor patients. For **locally** assessed **CBR** the same effects of sex and tumor types were observed, but the effect of ECOG was not significant. For **central** and **locally** assessed **DOR** covariates other than exposure were not considered. The decrease in **central** and **locally** assessed **sum of lesions nadir** is higher in PDAC patients versus patients with tumours other than PDAC and NSCLC, and lower for patients with four or more prior lines of therapy vs 2-3 therapies. In addition, for **locally** assessed **sum of lesions nadir**, males were found to have a higher effect.	Acceptable (CBR and Sum of lesions nadir are NOT primary clinical endpoints and are NOT assessed.)
Simulation for Specific Population	Not applicable	Acceptable
Visualization of E-R relationships	Figure 18 and Figure 19	Acceptable
Overall Clinical Relevance for ER	Higher exposure is associated with higher ORR, CBR and sum of lesions nadir. In additional analysis, an ER relationship was also observed with individual clearance (independent of the individual dosing history) as a predictor. These positive trends for E-R would indicate the possibility of achieving higher benefit with higher Q2W exposures, although there were limitations in	Acceptable (CBR and Sum of lesions nadir are NOT primary clinical endpoints and are NOT assessed.)

	interpreting these analyses because of potential confounding by patient health factors.	
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.2 Pharmacodynamics	The exposure-response relationship and time-course of pharmacodynamic response for the effectiveness of zenocutuzumab have not been fully characterized.	

Table 80. Applicant - Summary of continuous Baseline Characteristics in the Dataset, for the total population (safety and efficacy, n=330).

Covariate	Minimum	Q1	Median	Q3	Maximum	n Missing
Age (y) (AGE)	21.0	52.0	61	69.0	88.0	0
Baseline body weight (kg) (WT)	38.4	56.0	67	78.1	125.5	0
Sum of target lesion diameters (mm) (SLES)	10.0	42.5	71	107.5	277.0	27
Number of organs involved (NORG)	1.0	2.0	2	3.0	8.0	31

Source: Final Report E-R Analysis, 18DEC2023, Table 7.1:3.

Table 81. Applicant - Summary of categorical Baseline Characteristics and Laboratory Values in the Dataset, for the total population (safety and efficacy, n=330).

Covariate	Level	n	%
SEX	Female	198	60
	Male	132	40
RACE	Caucasian	238	72
	Asian	67	20
	Not reported	12	3.6
	Other	7	2.1
	Black or African American	6	1.8
TTYP	Other	177	54
	NSCLC	113	34
	PDAC	40	12
ECOG	1	189	57
	0	133	40
	2	8	2.4
CBILI	$\leq 3 \times$ ULN	329	99.7
	$> 3 \times$ ULN	1	0.3
LEC	AST and ALT $\leq 3 \times$ ULN	319	96.7
	AST or ALT $> 3 \times$ ULN	9	2.7
	AST or ALT $\geq 5 \times$ ULN	2	0.6
NPTC1	2-3 prior therapies	135	41
	>3 prior therapies	107	32
	1 prior therapy	74	22
	0 prior therapy	14	4.2
NPTC2	>1 prior therapies	242	73
	1 prior therapy	74	22
	0 prior therapy	14	4.2
VISL	Visceral lesions	274	83
	No visceral lesions	54	16
	Missing covariate data	2	0.6

Source: Final Report E-R Analysis, 18DEC2023, Table 7.1:4.

Table 82. Applicant - Parameter Estimates from Final ER Models of overall response rate (ORR) and clinical benefit rate (CBR).

Endpoint	Parameter Estimates
ORR central	Type Name Estimate S.E. Slope p-value glm (Intercept) -20.3468 5.6016 - ECOG 0 11.6162 7.3372 0.113377 log(CavgSS) 3.9383 1.1774 0.000823 log(CavgSS):ECOG 0 -2.2971 1.5592 0.140677 TTYP NSCLC 0.7350 0.6386 0.249725 TTYP PDAC 1.5969 0.7034 0.023204
ORR local	Type Name Estimate S.E. Slope p-value glm (Intercept) -25.4247 6.7866 - ECOG 0 15.7919 8.2934 0.056889 log(CavgSS) 4.9093 1.4110 0.000503 log(CavgSS):ECOG 0 -3.0648 1.7494 0.079782 TTYP NSCLC 0.9662 0.6513 0.137935 TTYP PDAC 1.9574 0.7343 0.007682
CBR 24w central	Type Name Estimate S.E. Slope p-value glm (Intercept) -19.9750 4.1367 - ECOG 0 1.2040 0.5157 0.01956 log(CavgSS) 3.9258 0.8744 7.13e-06 SEX Male 1.3399 0.5086 0.00842 TTYP NSCLC 1.1994 0.6530 0.06626 TTYP PDAC 2.0643 0.7447 0.00557
CBR 24 w local	Type Name Estimate S.E. Slope p-value glm (Intercept) -16.4687 4.2136 - ECOG 0 1.0228 0.5253 0.051540 log(CavgSS) 3.4746 0.9004 0.000114 NORG -0.3022 0.1524 0.047347 NPTC1 0-1 prior therapies 0.3147 0.5057 0.533677 NPTC1 4 or more prior therapies -1.3000 0.7331 0.076192 SEX Male 1.4741 0.5392 0.006255 TTYP NSCLC 0.6062 0.6687 0.364627 TTYP PDAC 2.0672 0.7849 0.008448

Source: Final Report E-R Analysis, 18DEC2023, Table 7.10:16 (ORR central), Table 7.11:19 (ORR local), Table 7.12:22 (CBR central), Table 7.13:25 (CBR local).

Table 83. Applicant - Parameter Estimates from Final ER Models of and Sum of lesions nadir.

Endpoint	Parameter Estimates
Sum of lesions nadir central	

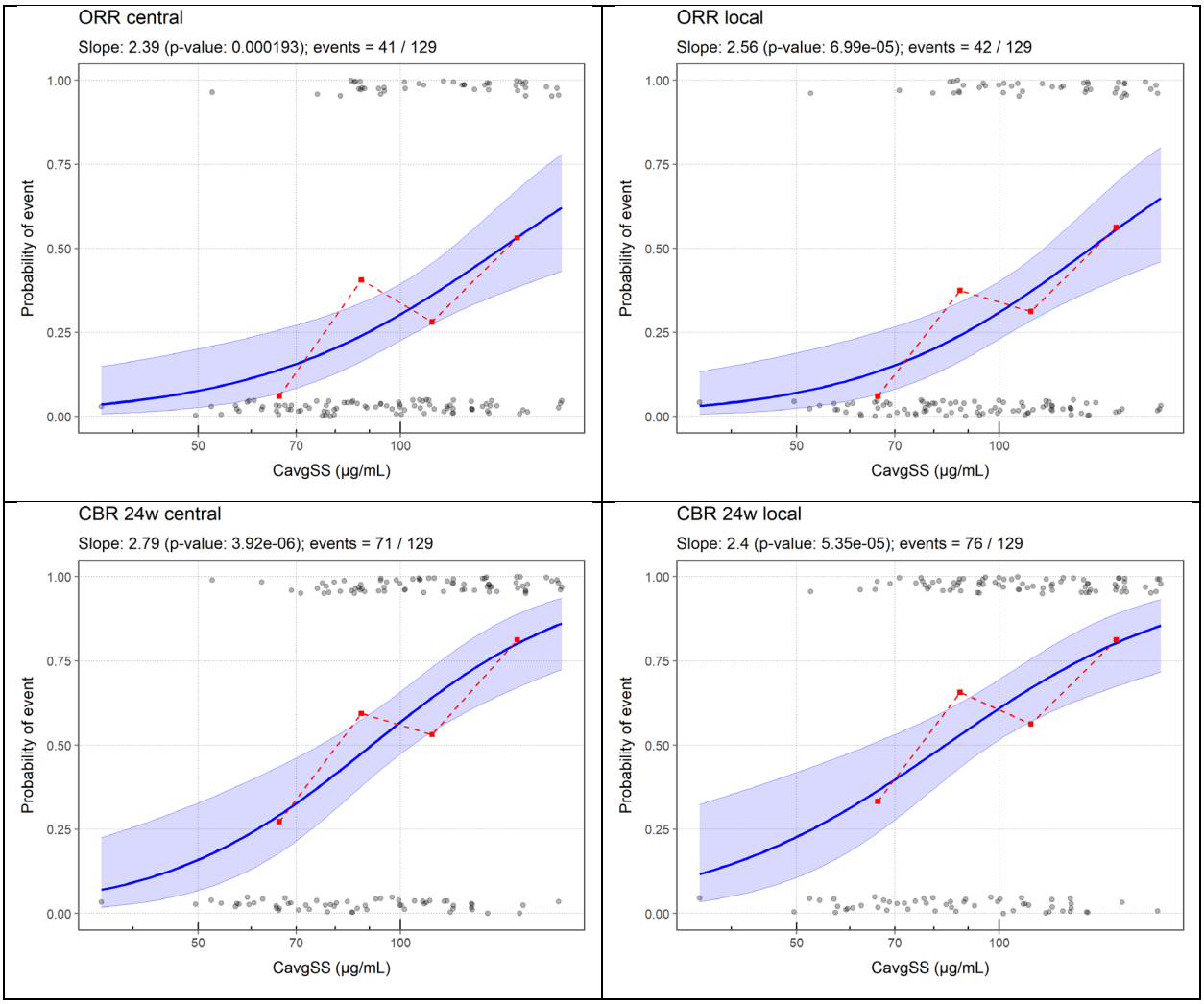
Type	Name	Estimate	S.E.	Slope p-value
lm	(Intercept)	-9.1866	24.0345	-
	CavgSS	-0.4485	0.1103	8.87e-05
	log(SLES)	7.5027	4.6548	0.1098
	NORG	3.2350	2.1603	0.1371
	NPTC1 0-1 prior therapies	-2.5181	6.8164	0.7125
	NPTC1 4 or more prior therapies	19.7592	9.5344	0.0405
	SEX Male	-10.1125	6.5513	0.1255
	TTYP NSCLC	-0.1640	8.3724	0.9844
	TTYP PDAC	-18.1293	9.1401	0.0498

Sum of lesions nadir local

Type	Name	Estimate	S.E.	Slope p-value
lm	(Intercept)	43.2330	12.0343	-
	CavgSS	-0.5616	0.0908	1.06e-08
	NPTC1 0-1 prior therapies	4.8251	5.7696	0.40479
	NPTC1 4 or more prior therapies	20.7984	7.9753	0.01036
	SEX Male	-13.8237	5.6080	0.01523
	TTYP NSCLC	-3.0091	7.1918	0.67646
	TTYP PDAC	-20.9887	7.9199	0.00922

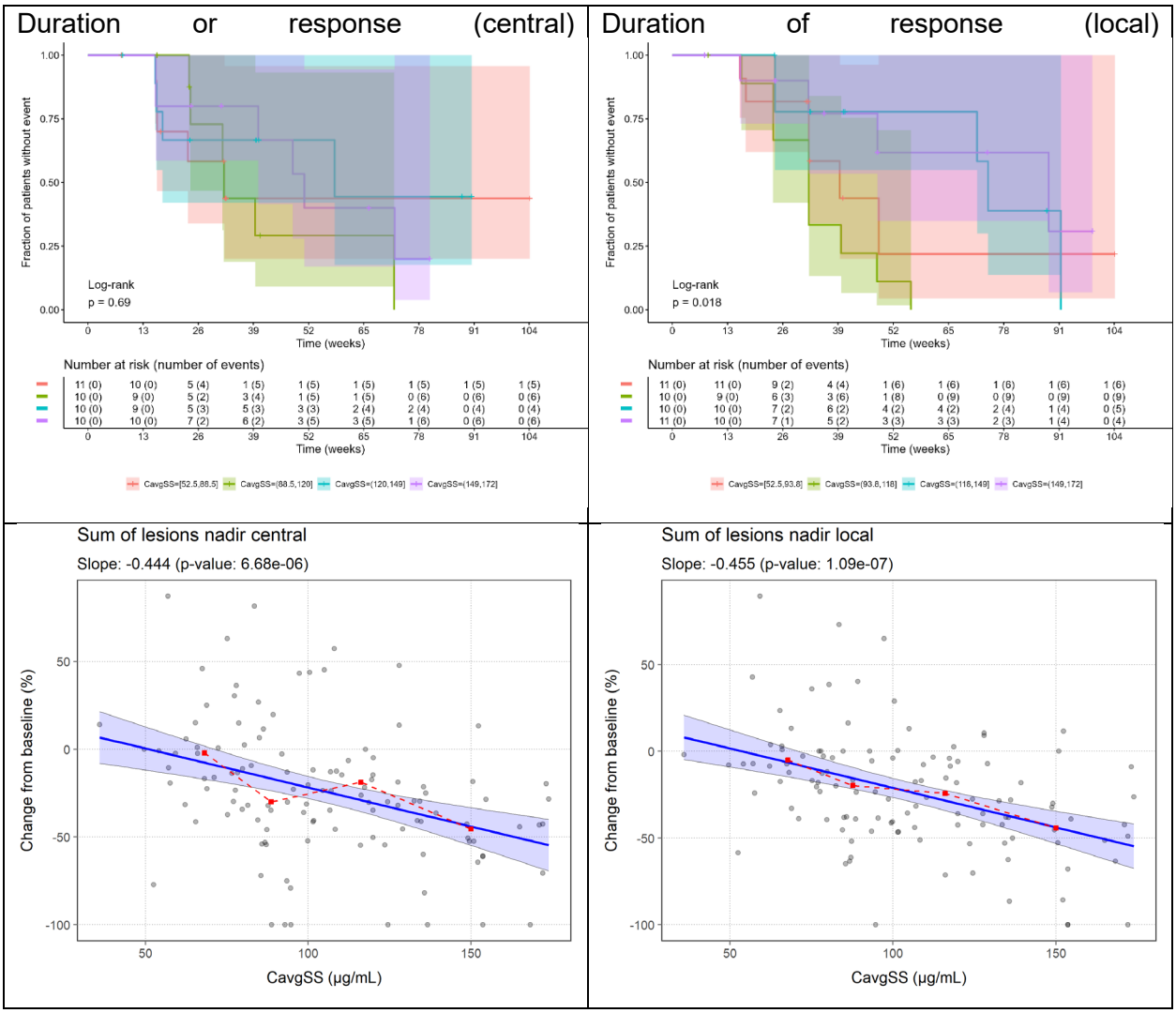
Source: Final Report E-R Analysis, 18DEC2023 Table 7.16:28 (Sum of lesions nadir central), Table 7.17:31 (Sum of lesions nadir local).

Figure 19. Applicant - ER Curves of ORR (top row) and CBR (bottom row) vs $C_{avg,ss}$ in 129 Patients, according to central assessment (left column) and local assessment (right column).



Source: Final Report E-R Analysis, 18DEC2023: Figure 7.10:20 (ORR central), Figure 7.11:22 (ORR local), Figure 7.12:24 (CBR central) and Figure 7.13:26 (CBR local).

Figure 20. Applicant - ER Curves of DOR (top row) and sum of lesions nadir (bottom row) vs $C_{avg,ss}$ in 129 Patients, according to central assessment (left column) and local assessment (right column).



Source: Final Report E-R Analysis, 18DEC2023Figure 7.14:29 (DOR central), Figure 7.15:30 (DOR local), Figure 7.16:31 (sum of lesions nadir central) and Figure 7.17:35 (sum of lesions nadir local).

19.4.2.3. ER (safety) Executive Summary

The FDA's Assessment:

Safety:

None of the exposure metrics (average concentration under steady state (Cavg,ss) and maximum concentration under steady state (Cmax,ss) (log and not transformed) were significant predictors for the occurrence of treatment related adverse event (TRAE) grade ≥3, TRAE any grade, diarrhea and left ventricular ejection fraction (LVEF) reduction.

The Cavg,ss was found to be a significant predictor for the occurrence of Any AE grade ≥3 whereby the probability of this event decreased with increasing Cavg,ss. A Kaplan-Meier (KM) analysis was performed for the time to first occurrence of this event. In this analysis, the Cavg,ss and the dosing interval were found to be significant predictors for the time to this event. In line with the trends observed in the logistic regression analysis, within the first year, the strongest drop in fraction of patients without this event was observed for the patients with a Cavg,ss below the median of the population.

For infusion related reaction (IRR) of the first dose, the planned analysis was considered not to be informative, because the occurrence of this event triggered the interruption of the infusion, thus leading to a lower Cmax,1st on average by design.

The Cavg,ss and Cmax,ss quartiles, and the dosing interval were found to be significant predictors for the time to first occurrence of a dose interruption. However, the causal relationship for this observation remains unclear, since dose interruption directly leads to a lower exposure.

19.4.2.4 ER (safety) Assessment Summary

The Applicant's Position:

Exposure-response analyses for occurrence of a treatment related adverse event of grade 3 or higher, occurrence of an adverse event irrespective of causality of grade 3 or higher, occurrence of any treatment related adverse event, occurrence of an infusion related reaction after the first dose, occurrence of diarrhea and occurrence of clinically significant left ventricular ejection fraction reduction showed no or a negative relationship with exposure to zenocutuzumab. Please see section 6.3.2.1 for a summary of the key results.

General Information	
Goal of ER analysis	The objective of this analysis was to perform an E-R analysis for safety and efficacy dependent variables of interest. Different individual exposure metrics derived from the final population PK model for zenocutuzumab were

		evaluated as predictors of response, together with other, compound-independent, intrinsic and extrinsic factors. A formal E-R analysis plan describing the analysis steps was established prior to receiving the final locked dataset.
Study Included		MCLA-128-CL01
Population Included		All patients that received at least one dose of zenocutuzumab in study MCLA-128-CL01.
Endpoint		• Occurrence of a treatment related adverse event of grade 3 or higher (TRAE grade ≥3) • Occurrence of an adverse event irrespective of causality of grade 3 or higher (Any AE grade ≥3) • Occurrence of any treatment related adverse event (TRAE any grade) • Occurrence of an infusion related reaction after the first dose (IRR first dose) • Occurrence of diarhea (Diarrhea) • Occurrence of clinically significant left ventricular ejection fraction reduction (LVEF reduction) • Time after first dose to first occurrence of an adverse event irrespective of causality of grade 3 or higher (time to Any AE grade ≥3) • Time after the first dose to first occurrence of a dose interruption (time to dose interruption)
No. of Patients (total, and with individual PK)		330, all with individual PK.
Population Characteristics (Table 57)	General	Age 61 (21 - 88) years. Weight 67 (38.4 – 125.5)kg 132 (40%) male, 198 (60%) female 238 (72%) caucasian, 67 (20%) Asian, 12 (3.6%) not reported, 7 (2.1%) other, 6 (1.8%) black or African Amerian.
	Organ impairment	ALB: median 39.0 (range 20.0-49.0) g/L AST: 27.0 (11.0-206) IU/L ALP: 108 (35.0-1062) IU/L ALT: 19.0 (4.00-226) IU/L BILI: 8.55 (2.22-30.8) µM CREAT: 67.2 (31.8-153) µmol/L
	Pediatrics (if any)	Not included
	Geriatrics (if any)	Not included
Dose(s) Included		Part 1: 40 to 900 mg Q3W

	Part 2: 750 mg Q3W, 400 mg Q1W (800 mg loading dose) and 750 mg Q2W	
Exposure Metrics Explored (range)	$C_{avg,ss}$: median 74.1 (range 1.05- 174) µg/mL. $C_{max\ after\ first\ dose}$: median 223 (range 13.1 - 456) µg/mL. $C_{max\ at\ steady\ state}$: median 243 (range 13.1 – 554) µg/mL.	
Covariates Evaluated	Age, sex, baseline bodyweight, race, ECOG status, liver enzyme category, tumour tpe, sum of target lesion diameters, presence of visceral lesions, number of organs involved, number of previous lines of therapy, dosing regimen and study part and dosing regimen.	
Final Model Parameters	**Summary**	**Acceptability [FDA's comments]**
Model Structure	For TRAE grade ≥3, Any AE grade ≥3, TRAE any grade, IRR first dose, Diarrhea and LVEF reduction a logistic regression model was applied: $logit(P) = log_e\left(\frac{P}{1-P}\right) \approx intercept + slope \cdot exposure$ where P is the predicted probability of response, intercept is the estimated proability of response when the exposure metric is zero, and the slope is the estimated slope of the linear relationship with exposure. For time to Any AE grade ≥3 and time to dose interruption a Kaplan-Meier evaluation was performed.	**Acceptable**
Model Parameter Estimates	Table 61	**Acceptable**
Model Evaluation	For TRAE grade ≥3, TRAE any grade, Diarrhea and LVEF reduction no significant relationship with exposure was identified. Probabilitiy for Any AE grade ≥3 and IRR after the first dose were found to decrease with increasing exposure.	**Acceptable**
Covariates and Clinical Relevance	• TRAE grade ≥3, TRAE any grade, Diarrhea and LVEF reduction: no significant relationship with exposure, therefore multivariate analysis including covariates could not be performed. • Any AE grade ≥3: decreasing probability with increasing $C_{avg,ss}$. In addition, significant effects of number of organs involved, number of previous lines of therapy and Asian patients, where patients with 2-3 therapies and non-Asian patients had a higher probability for this event. • IRR first dose: decreasing probability with increasing C_{max1st}.	**Acceptable**
Simulation for Specific Population	Not applicable	**Acceptable**

Visualization of E-R relationships	Figure 20, Figure 21 and Figure 22.	**Acceptable**
Overall Clinical Relevance for ER	No relationship between exposure and TRAE grade ≥3, TRAE any grade, Diarrhea and LVEF reduction was identified. A negative relationship between Any AE grade ≥3 and exposure may possibly be because of early dropout of patients before reaching their potential $C_{avg,ss}$. For infusion-related reactions (IRRs) after the first dose, the planned analysis was considered not to be informative, because the occurrence of this event triggered the interruption of the infusion, thus leading to a lower Cmax,1st on average by design.	**Acceptable**
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.2 Pharmacodynamics	(b) (4)	**Acceptable**

Table 84. Applicant - Parameter Estimates from Final ER Models of overall response rate (ORR) and clinical benefit rate (CBR).

Adverse Event

Parameter Estimates

TRAE grade ≥3

Exposure Metric	LRT p-value	Slope	Slope p-value	AIC	BIC	n
log(CavgSS)	0.475	-0.219	0.454	148.852	156.450	330
CmaxSS	0.667	0.001	0.667	149.177	156.775	330
log(CmaxSS)	0.888	-0.070	0.887	149.341	156.940	330
CavgSS	0.938	0.000	0.938	149.355	156.953	330
Null model	NA	NA	NA	147.361	151.160	330

Any AE grade ≥3

Type	Name	Estimate	S.E.	Slope p-value
glm	(Intercept)	1.4604	0.9506	-
	CavgSS	-0.0179	0.0066	0.00622
	CavgSS:log(NORG)	0.0108	0.0067	0.10555
	log(NORG)	-2.3549	0.9997	0.01849
	NORG	0.7038	0.3154	0.02563
	NPTC1 0-1 prior therapies	-0.6787	0.3188	0.03329
	NPTC1 4 or more prior therapies	-0.6771	0.2842	0.01720
	RACE Asian	-0.7853	0.3627	0.03038
	SLES	0.0047	0.0028	0.09289
	WT	-0.0138	0.0081	0.09039

TRAE any grade

Exposure Metric	LRT p-value	Slope	Slope p-value	AIC	BIC	n
log(CmaxSS)	0.165	-0.360	0.178	435.793	443.391	330
CmaxSS	0.289	-0.001	0.290	436.599	444.197	330
log(CavgSS)	0.638	-0.078	0.640	437.503	445.101	330
CavgSS	0.819	0.001	0.819	437.672	445.270	330
Null model	NA	NA	NA	435.724	439.523	330

IRR first dose

Type	Name	Estimate	S.E.	Slope p-value
glm	(Intercept)	0.2091	0.5264	-
	Cmax1st	-0.0076	0.0023	0.00119
	ECOG 0	-0.5127	0.3324	0.12306
	VISL No visceral lesions	-0.7142	0.5043	0.15669

Diarrhea

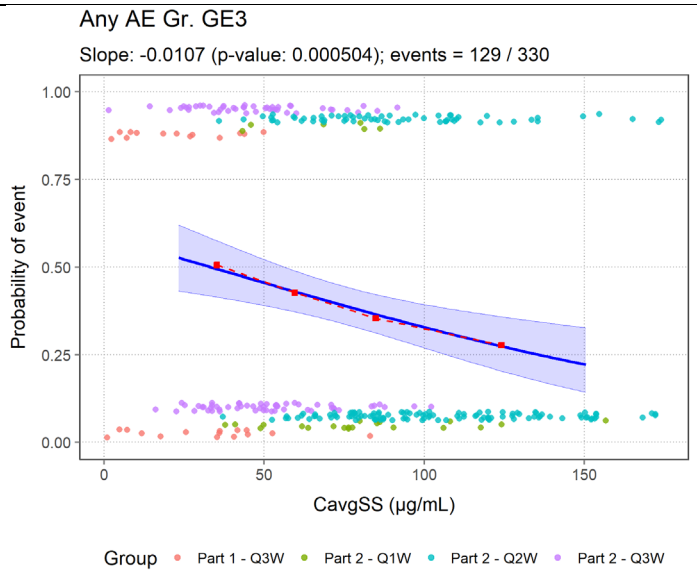
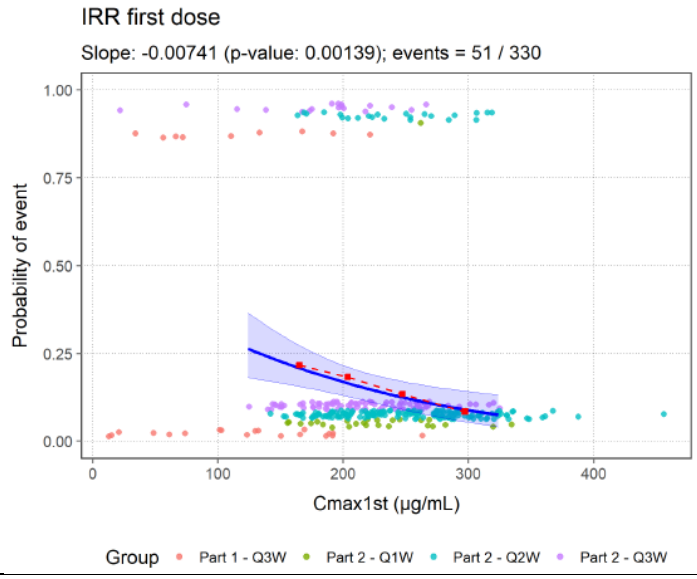
Endpoint	Exposure Metric	LRT p-value	Slope	Slope p-value	AIC	BIC	n
Diarrhea	CavgSS	0.519	0.002	0.519	408.436	416.034	330
	log(CavgSS)	0.575	0.099	0.579	408.536	416.134	330
	log(CmaxSS)	0.682	-0.105	0.680	408.683	416.281	330
	CmaxSS	0.690	-0.001	0.690	408.691	416.289	330
	Null model	NA	NA	NA	406.851	410.650	330

LVEF reduction

Exposure Metric	LRT p-value	Slope	Slope p-value	AIC	BIC	n
log(CmaxSS)	0.425	1.141	0.469	46.618	54.216	330
CmaxSS	0.553	0.003	0.549	46.901	54.499	330
log(CavgSS)	0.585	0.473	0.613	46.955	54.554	330
CavgSS	0.789	0.003	0.787	47.182	54.780	330
Null model	NA	NA	NA	45.254	49.053	330

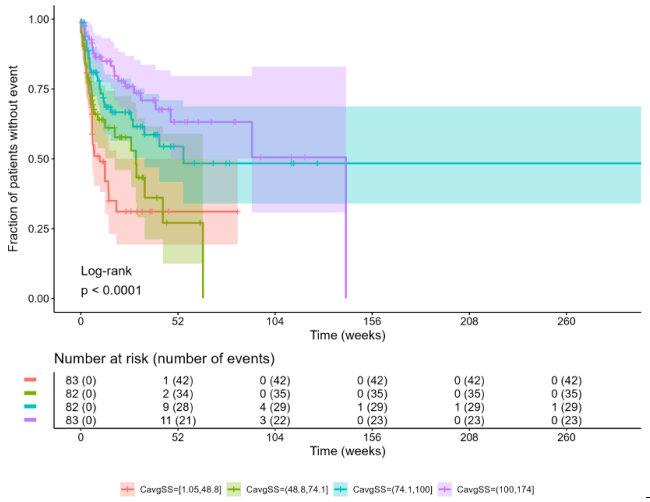
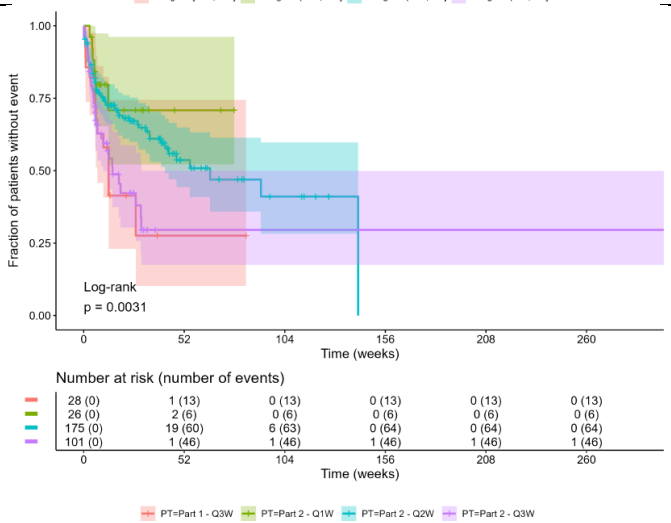
Source: Final Report E-R Analysis, 18DEC2023: Table 7.3:5 (TRAE grade ≥3), Table 7.3:7 (Any AE grade ≥3), Table 7.4:9 (TRAE any grade), Table 7.5:11 (IRR first dose), Table 7.6:13 (Diarrhea) and Table 7.7:14.

Figure 21. Applicant - ER Curves of Any AE grade ≥3 and IRR first dose vs $C_{avg,ss}$ in 330 Patients.

Adverse Event	Parameter Estimates
Any AE grade ≥3	
IRR first dose	

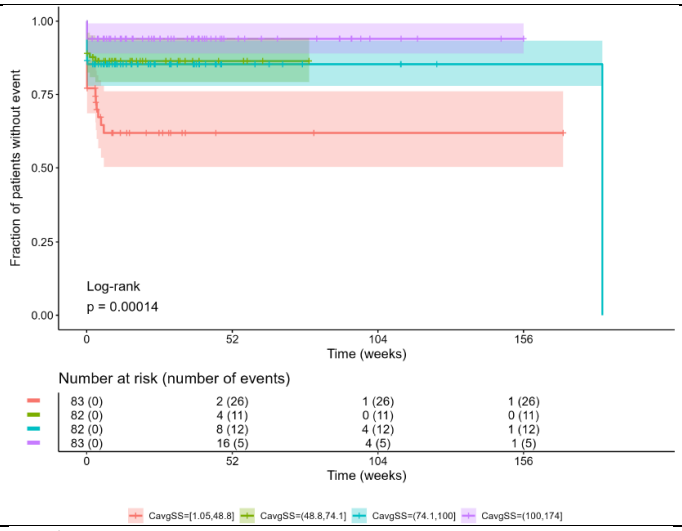
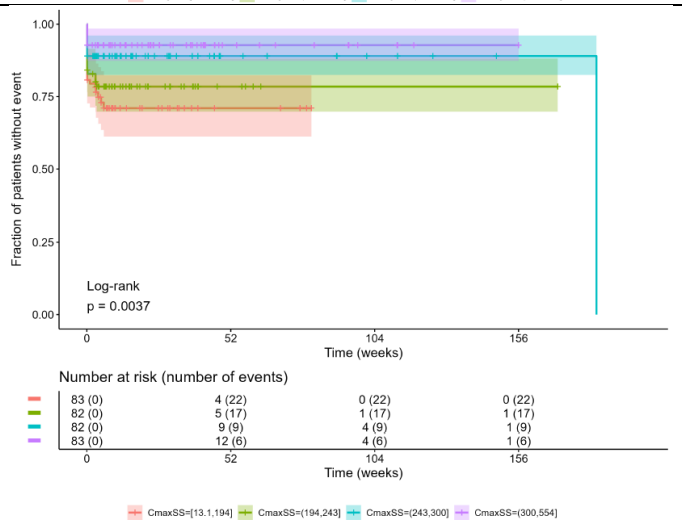
Source: Final Report E-R Analysis, 18DEC2023: Figure 7.3:6 (Any AE grade ≥3) and Figure 7.5:10 (IRR first dose).

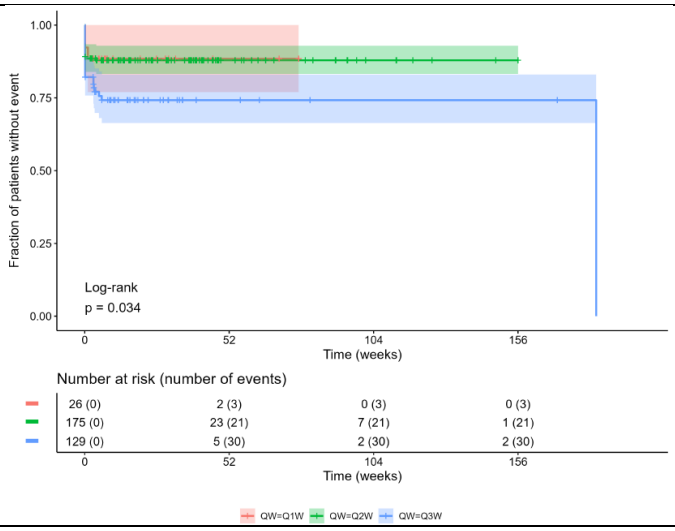
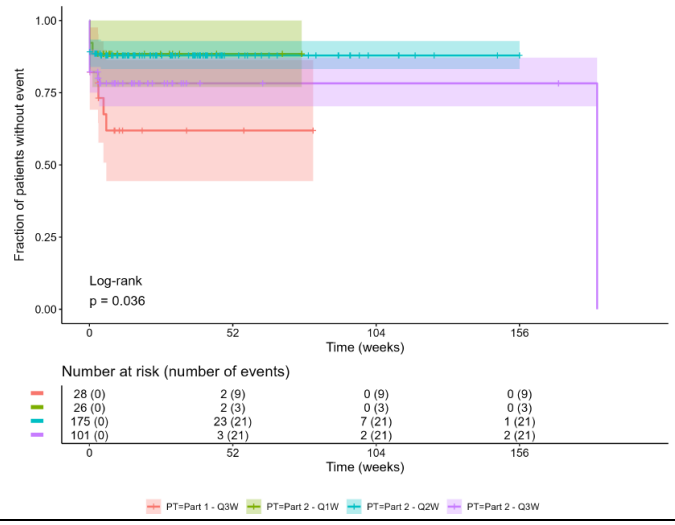
Figure 22. Applicant - Kaplan-Meier Curves of Time to Any AE grade ≥3.

Stratified by	Parameter Estimates
$C_{avg,ss}$ quartile	
Study part and dosing interval	

Source: Final Report E-R Analysis, 18DEC2023: Figure 7.8:12 (by Cavg,ss quartile) and Figure 7.8:15 (by study part and dosing interval).

Figure 23. Applicant - Kaplan-Meier Curves of Time to dose interruption.

Stratified by	Parameter Estimates
$C_{avg,ss}$ quartile	
$C_{max,ss}$ quartile	

Dosing interval	
Study part and dosing interval	

Source: Final Report E-R Analysis, 18DEC2023: Figure 7.9:16 (by $C_{avg,ss}$ quartile), Figure 7.9:17 (by $C_{max,ss}$ quartile), Figure 7.9:18 (by dosing interval) and Figure 7.9:19 (by study part and dosing interval).

19.4.2.7. Overall benefit-risk evaluation based on E-R analyses

The Applicant's Position:

The FDA's Assessment:

The benefit-risk profile of the proposed dosage of zenocutuzumab 750 mg IV Q2W is supported by the available data.

Positive trend for E-R relationship between exposure (Cavg, ss) and response (overall response rate & duration of response) was identified based on 129 patients from study MCLA-128-CL01 at one dose level at 750 mg. Interpretation should be cautious due to potential confounding issue and data limitation.

No positive trend of exposure (Cavg,ss and Cmax,ss) for TRAE grade≥3, TRAE any grade, diarrhea and LVEF reduction was identified based on 330 patients from study MCLA-128-CL01.

19.5. Additional Safety Analyses Conducted by FDA

The FDA's Assessment:

N/A

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Kelie Reece, PhD	CDER/OOD/DHOT	Sections: 5, 19.1	_X_Authored _X_Approved
	Signature: Kelie M. Reece -S Digitally signed by Kelie M. Reece -S Date: 2024.10.18 12:08:04 -04'00'			
Nonclinical Supervisor	Claudia Miller, PhD	CDER/OOD/DHOT	Sections: 5, 19.1	_X_Authored _X_Approved
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Nonclinical Division Director (Acting)	Haleh Saber, PhD	CDER/OOD/DHOT	Sections: 5	__Authored _X_Approved
	Signature: Haleh Saber -S Digitally signed by Haleh Saber -S Date: 2024.12.03 14:21:57 -05'00'			
Clinical Pharmacology Reviewer	Om Anand, PhD	CDER/OTS/OCP/DCPII	Sections: Section 6	**Select one:** X__Authored __Approved
	Signature: Om Anand -S Digitally signed by Om Anand -S Date: 2024.10.18 11:03:23 -04'00'			
Clinical Pharmacology Team Leader	Jeanne Fourie-Zirkelbach, PhD	CDER/OTS/OCP/DCPII	Sections: 6, 19	**Select one:** __ Authored _x_ Approved
	Signature: Jeanne Fourie Zirkelbach -S Digitally signed by Jeanne Fourie Zirkelbach -S Date: 2024.10.18 11:11:29 -04'00'			
Pharmacometrics Reviewer	Hezhen Wang, PhD	CDER/OTS/OCP/DPM	Sections: 6.1, 19.4	**Select one:** _X_ __ Authored ____ Approved
	Signature: Hezhen Wang -S Digitally signed by Hezhen Wang -S Date: 2024.10.23 15:15:05 -04'00'			

Pharmacometrics Team Leader	Youwei Bi, PhD	CDER/OTS/OCP/DPM	Sections: 6.1, 19.4	**Select one:** X Authored X Approved
	Signature: Youwei Bi -S Digitally signed by Youwei Bi -S Date: 2024.10.18 14:14:28 -04'00'			
Genomics Team Leader	Sarah Dorff, PhD	CDER/OTS/OCP/DTPM	Sections: 6	**Select one:** X Authored X Approved
	Signature: Sarah E. Dorff -S Digitally signed by Sarah E. Dorff -S Date: 2024.10.18 11:08:20 -04'00'			
Genomics Reviewer	Javier Blanco, PhD	CDER/OTS/OCP/DTPM	Sections: 6	**Select one:** X Authored Approved
	Signature: Javier G. Blanco -S Digitally signed by Javier G. Blanco -S Date: 2024.10.18 10:57:53 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED / APPROVED
Clinical Pharmacology Division Director	NAM Atiqur Rahman	CDER/OTS/OCP/DCP II	Sections: 6, 19	**Select one:** Authored x Approved
	Signature: Stacy Shord -S Digitally signed by Stacy Shord -S Date: 2024.10.18 16:15:09 -04'00'			
Clinical Reviewer (DO2)	Kristin Wessel, MD	CDER/OOD/DO2	Sections: 1, 2, 3, 4, 7, 8, 9, 10, 12, 13	**Select one:** x Authored Approved
	Signature: Kristin M. Wessel -S Digitally signed by Kristin M. Wessel -S Date: 2024.10.22 17:02:44 -04'00'			
Clinical Reviewer (DO3)	Shruti Gandhy, MD, PhD	CDER/OOD/DO3	Sections: 2,3, 7, 8, 11, 13	**Select one:** X Authored Approved
	Signature: Shruti U. Gandhy -S Digitally signed by Shruti U. Gandhy -S Date: 2024.10.22 10:31:15 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	AUTHORED/ APPROVED	AUTHORED / APPROVED
Director, Division of Oncology 3 Office of Oncologic Diseases	Steven Lemery, M.D., M.H.S.	CDER/OND/OOD/DOIII	Sections:	**Select one:** ____ Authored __X__ Approved
	Signature: Steven J. Lemery -S Digitally signed by Steven J. Lemery -S Date: 2024.10.23 15:55:36 -04'00'			
Clinical Team Leader	Amy Barone, MD	CDER/OOD/DO2	Sections: see CTDL	**Select one:** X___ Authored X___ Approved
	Signature: see CDTL signature:			
Clinical Team Leader	Sandra J. Casak, MD	CDER/OOD/DO3	Sections: see CTDL	**Select one:** X___ Authored X___ Approved
	Signature: see CDTL signature:			
Clinical Team Leader	Sandra Casak, MD	CDER/OOD/DO3	Sections: see CTDL	**Select one:** X___ Authored X___ Approved
	Signature: see CDTL signature:			
Statistical Reviewer	Qingyu (Sophia) Chen, PhD	CDER/OTS/DBV	Sections: 1, 8	**Select one:** X__ Authored ___ Approved
	Signature: Qingyu Chen -S Digitally signed by Qingyu Chen -S Date: 2024.10.18 12:20:10 -04'00'			
Statistical Team Leader	Xiaoxue Li, PhD	CDER/OTS/DBV	Sections: 1,8	**Select one:** _X_ Authored X__ Approved
	Signature: Xiaoxue Li -S Digitally signed by Xiaoxue Li -S Date: 2024.10.18 12:05:12 -04'00'			
Division Director (OB/DBV)	Shenghui Tang	CDER/OTS/DBV	Sections: 1, 8	**Select one:** ___ Authored X__ Approved

	Signature: Shenghui Tang -S Digitally signed by Shenghui Tang -S Date: 2024.10.18 15:57:32 -04'00'			
Associate Director for Labeling (ADL)	Barbara Scepura, MSN, CRNP	CDER/OOD	Section: 11	**Select one:** X Authored ___ Approved
	Signature: Barbara A. Scepura -S Digitally signed by Barbara A. Scepura -S Date: 2024.10.21 13:57:08 -04'00'			
Cross-Disciplinary Team Leader (CDTL)	Amy Barone, MD	CDER/OOD/DO2	Sections: All	**Select one:** __x_Authored X__ Approved
	Signature: see DARRTS electronic signature			
Cross-Disciplinary Team Leader (CDTL)	Sandra Casak, MD			
	Signature: see DARRTS electronic signature			
Division Director (Clinical)	Nicole Drezner, MD	CDER/OOD/DO2	Sections: All	**Select one:** ___ Authored X___ Approved
	Signature: see DARRTS electronic signature:			

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/s/

AMY K BARONE
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SANDRA J CASAK
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PAUL G KLUETZ
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