NEC4NEOP – STUDY SYNOPSIS

Study Title	A multicenter, single-arm, phase II study of neoadjuvant enfortumab vedotin in patients with untreated borderline resectable pancreatic cancer
Short Title	NEC4NEOP
Principal Investigators	Adrian Seifert, MD, Department for Visceral, Thoracic and Vascular Surgery, University Hospital Carl Gustav Carus Dresden, Technische Universität Dresden, Fetscherstr. 74, 01307 Dresden Email: adrian.seifert@ukdd.de Lena Seifert, MD, Department for Visceral, Thoracic and Vascular Surgery, University Hospital Carl Gustav Carus Dresden, Technische Universität Dresden, Fetscherstr. 74, 01307 Dresden Email: lena.seifert@ukdd.de
Co-Principal Investigators	Ulrike Ubbelohde, MD, Department of Medicine I, University Hospital Carl Gustav Carus Dresden, Technische Universität Dresden, Fetscherstr. 74, 01307 Dresden Gunnar Folprecht, MD, Department of Medicine I, University Hospital Carl Gustav Carus Dresden, Technische Universität Dresden, Fetscherstr. 74, 01307 Dresden Jürgen Weitz, MD, Department for Visceral, Thoracic and Vascular Surgery, University Hospital Carl Gustav Carus Dresden, Technische Universität Dresden, Fetscherstr. 74, 01307 Dresden
Protocol Number	NA
Version/Date	5/12/25
Study Phase	Phase II
Indication	Untreated borderline resectable pancreatic cancer
Investigational Product	Enfortumab Vedotin (EV)

OBJECTIVES

Primary Objective:

- To evaluate the pathologic response of neoadjuvant Enfortumab Vedotin.

Secondary Objectives:

- To evaluate the resection rate of neoadjuvant Enfortumab Vedotin.
- To evaluate the R0 resection margin rate of neoadjuvant Enfortumab Vedotin.
- To evaluate the safety of neoadjuvant Enfortumab Vedotin.
- To evaluate the biochemical response of neoadjuvant Enfortumab Vedotin.
- To evaluate the postoperative complication rate of neoadjuvant Enfortumab Vedotin.
- To evaluate the postoperative mortality rate of neoadjuvant Enfortumab Vedotin.
- To evaluate the effect of neoadjuvant Enfortumab Vedotin on event-free survival.

ENDPOINTS

Primary Endpoint:

- The primary endpoint is the rate of pathologic response after neoadjuvant Enfortumab Vedotin.

Secondary Endpoints:

- The proportion of subjects considered eligible for surgical exploration per protocol-defined criteria
- Proportion of all subjects in whom R0 or R1 resection is achieved
- Feasibility and safety of Enfortumab Vedotin as neoadjuvant treatment (Common Terminology Criteria for Adverse Events, grade 3-5, dose reduction, dose delay)
- Mean change from baseline during the treatment period in CA19-9
- Progression-free survival (PFS), defined as the time from start of treatment until objective tumor progression or death (whichever occurs first) at 18 months
- Change in Patient Reported Outcomes (PROs) as measured by:
    - − Mean change from baseline during the treatment period in physical function by EORTC-QLQ-C30
    - − Mean change from baseline during the treatment period in abdominal pain by NCI-PRO-CTCAE
    - − Mean change from baseline during the treatment period in fatigue by NCI-PRO-CTCAE
- Overall survival (OS), defined as the time from start of treatment to death due to any cause
- Event-Free Survival Endpoint: The EFS endpoint would be a composite time-to-event endpoint, the event being ‘treatment failure’ defined as the earliest occurrence of:
    - − Failure to achieve disease-free status locally after completion of neoadjuvant treatment and/or after surgery (i.e., resection failure or progression that precludes surgery)
    - − Local or distant recurrence, or
    - − Death

Exploratory Endpoints:

- Difference in OS between resected and non-resected subjects
- RECIST 1.1 at EOT: proportion of patients with partial response (PR), complete response (CR), or stable disease (SD)
- Histological analysis of tumor tissues collected at biopsies and resection
- Evaluation of immune cells, ctDNA, other selected protein and nucleic acid markers in blood and/or tumor samples

STUDY DESIGN

This is a multicenter, single-arm, phase II study of neoadjuvant Enfortumab Vedotin (EV) in patients with untreated borderline resectable pancreatic cancer. Approximately 27 subjects will be enrolled.

STUDY PERIODS

Screening Period (up to 30 days):

Subjects will be evaluated per the protocol inclusion/exclusion criteria to determine eligibility for participation in this trial. During screening, a central review board will confirm, if subjects have borderline resectable disease prior to enrollment according to the ABC-criteria of the International Association of Pancreatology (IAP; see Appendix I). Trained radiologists will also review each subjects' baseline CT scan to determine the degree of superior mesenteric artery (SMA) and hepatic artery encasement, and whether or not they have unreconstructible disease. Trained radiologists will also review liver MRI to exclude liver metastases. Protocol assessments will be completed during screening visits in accordance with Schedule of Assessments (SOA) to establish a baseline profile, including demographics, medical history, clinical status, and disease stage for each subject. Subjects determined to be eligible for participation will be enrolled in the trial and receive study treatment.

Neoadjuvant Treatment Period (~6-10 weeks):

Subjects will receive 2 cycles of neoadjuvant Enfortumab Vedotin (EV) 1.25 mg/kg (up to maximum dose of 125mg) by IV infusion before surgery. Treatment will start within 2 weeks after biopsy proving histology of pancreatic ductal adenocarcinoma. Subjects' clinical status and safety will be regularly evaluated. Efficacy assessments will be performed routinely to evaluate subjects' quality of life and disease state. CT scans will be performed approximately 6-7 and 10-11 weeks after initiation after the start of neoadjuvant therapy and evaluated by central imaging. RECIST response will be evaluated by central radiology. CA 19-9 levels will be determined in serum from subjects after approximately 6 and 10 weeks ±1 week. If disease progression occurs during the neoadjuvant treatment period, subjects will be discontinued from study treatment and switch to another chemotherapeutic regimen as per standard of care (SOC) for each institution. In the first stage, 11 patients will be accrued. There will be a safety-stop if 6 or more subjects have progressive disease and are no longer deemed candidates for surgery at restaging according to RECIST 1.1 or display a ≥50% increase, but at least by 200U/mL in CA 19-9 levels. If there are 5 or fewer pathological responses are observed in these 11 patients, the study will be stopped. Otherwise, 16 additional patients will be accrued for a total of 27. The null hypothesis will be rejected if 17 or more pathological responses are observed in 27 patients. No more than 6 subjects at a time will be treated. Tumor tissue after neoadjuvant Enfortumab Vedotin will be compared for pathologic response (according to Le Scodan et al.) to a matched historical cohort with subjects, who received other neoadjuvant chemotherapeutic treatment. Dose-reduction of Enfortumab Vedotin will be in case of TRAE grade 2 to 1,0 mg/kg. In case of intolerance or TRAE grade 3 there will be a discontinuation of treatment with Enfortumab Vedotin and switch to another chemotherapeutic regimen as per standard of care (SOC) for each institution.

Safety Follow-up:

All subjects will have a safety follow-up visit approximately 30 days after the last dose of study treatment and a final safety follow-up phone call at 60 days post last dose. However, if the investigator becomes aware of any serious adverse event that may be possibly related to study treatment after this protocol-required reporting period, the investigator may report the event within 24 hours following the investigator's knowledge of the event.

<u>Eligibility Assessment for Surgical Exploration:</u>
Eligibility for surgical exploration will be evaluated for all subjects, who complete study treatment. To be considered eligible for surgical exploration a subject must meet the protocol-defined criteria and have no contraindication to surgery, as outlined below:

The protocol-defined criteria for surgical eligibility are:

- Partial response (PR), complete response (CR), or stable disease (SD) per RECIST 1.1
- Meet the definition of resectable or borderline resectable per NCCN® Version 2.2018 (see Appendix II)

Contraindications to surgical eligibility are:

- Development of distant metastases or local progression per RECIST 1.1
- Performance status of Karnofsky score ≤50
- Unreconstructible disease as determined by central radiological/surgical review
- Other conditions that are considered to be contraindications to surgery by PI or surgeon

The site will be required to provide information to the central review board following the subject's EOT visit (CT scan). The central review board will determine RECIST response, unreconstructible disease and NCCN status. The site will provide additional information to the central review board following the subject's Safety Follow-up Visit (i.e. subject performance status and a summary of any existing medical conditions/contraindications). Considering all the information provided, the central review board (to include radiologists, surgeons and oncologists) will then determine whether or not a subject is eligible for surgical exploration per protocol. The central review board will provide their assessment of surgical eligibility to the site (approximately 1 week after the Safety Follow-up Visit). After the recommendation from central review board is received at the site, the PI and surgeon will make the final decision as to whether or not a subject will undergo surgery. All instances of discordance between the determination of eligibility for surgical exploration by the central review board and the action taken by the site with regards to surgical exploration will be documented in the clinical database. Subjects, who undergo surgical exploration within the protocol specified window will be followed for outcomes per protocol. Tissue samples will be collected during resection and provided to central pathology and our research lab for further analysis. Subjects, who do not undergo surgical exploration (e.g. subjects, who did not complete treatment or do not meet any of the protocol defined criteria or had a contraindication to surgery) will continue in the Follow-up period and receive treatment as per standard of care (SOC) for each institution.

<u>Surgery:</u>
Surgery will occur at approximately 3-4 weeks after the last dose of Enfortumab Vedotin and only after receipt of the recommendation from the central review board with regards to surgical eligibility. Surgery will occur no longer than 6 weeks after the last dose. An outcome of R0 or R1 will be considered a 'Resection Achieved', while an outcome of R2 or partial resection will be considered a 'Resection Not Achieved'. Final surgical outcomes for all 'Resection Achieved' subjects will be determined by the central pathology lab. The sponsor/sites remain blinded to the central pathology lab assessments until their final analysis. If a subject undergoes surgical exploration, but the surgeon is unable to perform resection (e.g. due to identification of metastases or extensive vascular involvement), it will be considered a 'Resection Not Attempted'. Surgery will be performed in accordance with institutional standards and SOPs. Surgeons performing surgery for this study will be trained on the protocol, including criteria for surgical exploration. All subjects, who undergo surgical exploration, will be followed for surgical safety for 90 days (+/- 3 days) post discharge.

Follow-up Period:

Subjects will be followed for disease progression (if not previously detected) or recurrence following resection (local or distant recurrence). For subjects, who complete treatment without evidence of disease progression and do not undergo resection, CT scans will continue to be performed approximately every 12 weeks and evaluated by central imaging until progression is detected (per RECIST 1.1). For subjects, who undergo resection, follow-up CT scans to evaluate recurrence of disease will be evaluated by central imaging and performed approximately; every 3 months up to 2 years post-resection and every 6 months from 2 to 5 years post-resection. The investigator may perform an "off schedule" CT scan at any time post resection, if recurrence of disease is suspected clinically; these scans will be submitted to central imaging for review and confirmation of recurrence/disease progression. Subjects in follow-up will also be followed for any additional anti-cancer therapy received for their pancreatic cancer. All subjects will be followed for survival (until death) or until study closure (expected when the last subject to complete treatment reaches 18 months post-treatment).

SUBJECT ELIGIBILITY CRITERIA

Key Inclusion Criteria:

- Understand and sign informed consent; be willing to comply with study procedures, including surgery
- Age ≥18 years
- Histologically or cytologically proven diagnosis of pancreatic ductal adenocarcinoma (PDAC)
- Borderline resectable pancreatic cancer according to NCCN Guidelines® Version 2.2024 as determined by central imaging and the ABC-criteria of the International Association of Pancreatology, but CA19-9 <1000 U/mL
- Measurable disease as defined by Response Evaluation Criteria in Solid Tumors RECIST 1.1 criteria as determined by central imaging
- Planned neoadjuvant chemotherapy
- ECOG performance status of 0 or 1
- Adequate liver, bone marrow, and renal function
- Women of childbearing potential must have a negative urine or serum pregnancy test 7 days prior to initiating treatment.

Key Exclusion Criteria:

- Prior, current or anticipating use of other anti-neoplastic or investigational agents while participating in this study.
- Simultaneously enrolled in any other therapeutic clinical trial.
- Previous (within the past 3 years) or concurrent malignancy diagnosis.
- Subjects with a history of interstitial pneumonia, tuberculosis, HCV, HBV or HIV infection.
- Subjects with a known allergic reaction to any excipient contained in the study drugs formulation.
- Subjects who have been administered a live vaccine within 4 weeks prior to the first administration of therapy.
- Subjects with conditions requiring high doses of steroids (>10mg/day of prednisone or equivalent or other immunosuppressive medications.
- Subjects with uncontrolled diabetes (hemoglobin A1c >8% or HbA1c 7-8% with associated diabetes symptoms (polyuria or polydipsia) that are not otherwise explained.

STUDY TREATMENT

Subjects will receive Enfortumab Vedotin (EV) as per protocol.
Dose and Mode of Administration:
Enfortumab Vedotin (EV) 1.25 mg/kg (up to maximum dose of 125mg) by IV infusion over 30 minutes on Days 1, 8 and 15 of each 28-day treatment cycle (with a total of 2 cycles).

Other Important Information:
Regular supportive care as clinically indicated is permitted during this trial.
Live vaccines are prohibited for subjects during the treatment period and for 3 months after the last dose of study therapy.
Female subjects of childbearing potential are required to use highly effective contraception methods during the conduct of the study and for 6 months after the last dose of study drug.
Male subjects with partners of childbearing potential are required to use highly effective contraception methods during the conduct of the study and for 6 months after the last dose of study drug.

STATISTICAL METHODS
Sample Size Calculations:
For the sample size calculation, the pathologic response (PR) of the historical cohort is taken to be 45%, and it is hypothesized that the PR after neoadjuvant treatment with Enfortumab Vedotin is equal to 70%. At least 27 patients need to be analyzed in order to achieve the power of 80% (5% significance level) in testing the hypothesized difference in PR. Simon's two-stage design (Simon, 1989) will be employed. The null hypothesis that the true pathological response rate is 45% will be tested against a one-sided alternative. In the first stage, 11 patients will be accrued. If there are 5 or fewer pathological responses are observed in these 11 patients, the study will be stopped. Otherwise, 16 additional patients will be accrued for a total of 27. The null hypothesis will be rejected if 17 or more pathological responses are observed in 27 patients. This design yields a type I error rate of 0.05 and power of 0.8 when the true response rate is 70%.
The patients who dropped out of the study will be accounted for as follows:

1. A patient who had an evaluable primary endpoint before droppping out will be counted as "success" or "failure" according to the definition of the primary endpoint.
2. A patient whose primary endpoint was not evaluable will be counted as "failure", that is, as no pathological response was achieved.

Statistical Analysis Methods:
Descriptive summaries will be reported using, as relevant: mean, standard deviations, medians, interquartile range for continuous outcomes, absolute and relative frequencies for discrete outcomes. Two-sided 95% confidence intervals will be included for the key efficacy parameters and odds ratios. For the primary endpoint, the null hypothesis of the difference in PR between the historical cohort and EV cohort will be tested using a binomial test, at two-sided significance level of 5%.
Differences for secondary endpoints will be assessed as:

- Proportion of subjects considered eligible for surgical exploration per protocol-defined criteria, proportion of all randomized subjects in whom R0 or R1 resection is achieved: descriptive.
- Feasibility of combining EV with neoadjuvant chemotherapy (Common Terminology Criteria for Adverse Events, grade 3-5, dose reduction, dose delay): descriptive.
- Complication rates after surgery (30 and 90 days, Dindo-Clavien and International Study Group of Pancreatic Surgery (ISGPS) classification systems): the chi-square test;
- Progression-free survival (PFS), defined as the time from randomization until objective tumor progression or death (whichever occurs first) at 18 months: Kaplan-

Meier estimator, log-rank test, Cox proportional hazards model adjusting for stratification factors and potential confounders;

• Mann-Whitney-U-Test and ANCOVA will be applied to Change in Patient Reported Outcomes (PROs) as measured by:

− Mean change from baseline during the treatment period in physical function by EORTC-QLQ-C30

− Mean change from baseline during the treatment period in abdominal pain by NCI-PRO-CTCAE

− Mean change from baseline during the treatment period in fatigue

• Kaplan-Meier estimator, log-rank test, Cox proportional hazards model adjusting for stratification factors and potential confounders will be applied to: Overall survival (OS), defined as the time from randomization to death due to any cause

Event-Free Survival Endpoint for Accelerated Approval:

• The EFS endpoint would be a composite time-to-event endpoint, the event being 'treatment failure' defined as the earliest occurrence of:

− Failure to achieve disease-free status locally after completion of neoadjuvant treatment and/or after surgery (i.e., resection failure or progression that precludes surgery)

− Local or distant recurrence, or

− Death

• Quality of life (EORTC QLQ-30): regression methods for longitudinal data, ANCOVA.

<u>Safety Analyses:</u>

Treatment-emergent adverse events (TEAEs) will be summarized. Treatment-emergent deaths, serious TEAEs, TEAEs with grade 3 or 4 per CTCAE criteria, and TEAEs leading to study or treatment discontinuation will be summarized separately. Surgical complications, clinically significant changes from baseline in vital signs, laboratory tests, and ECGs will be assessed.