CASE STUDY
Randomized, Double-Blind, Phase III Trial of NES-822 plus AMO-1002 vs. AMO-1002 alone as first-line therapy in patients with advanced pancreatic cancer

This is a multicenter, randomized Phase III study in patients with surgically incurable locally advanced or metastatic pancreatic cancer, that will be conducted at approximately 100 sites in the United States, Australia, Austria, Belgium, Canada, France, Germany, India, Ireland, Italy, Japan, Korea, Netherlands, Russian Federation, Singapore, South Africa, Spain, Sweden, Switzerland, and the United Kingdom

Planned enrollment
630 randomized subjects. At total of 596 evaluable patients and 460 events are required for a log rank test to have an overall 1 sided significance level of 0.025 and power of 0.90.

Objectives
The objective of this study is to determine the efficacy of NES-822 plus AMO-1002 in the first-line treatment of patients with locally advanced, unresectable or metastatic pancreatic cancer.

Primary Endpoint
The primary endpoint is overall survival, measured as the time in weeks from randomization to date of death due to any cause.

Secondary endpoints include:

- Progression Free Survival (PFS) – investigator-determined; measured as time in weeks from randomization to the first documentation of objective tumor progression or death due to any cause (baseline until disease progression or at least one year after the randomization of the last participant)
- Percentage of participants with objective response (OR) – confirmed CR or PR according to RECIST criteria. Duration of Response (DR) – measured as time in weeks from the first documentation of objective tumor response to objective tumor progression or death due to any cause.
- Change From Baseline in European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire Core-30 (EORTC QLQ- C30) Score [Time Frame: Baseline, Day 1 (D1) of each cycle up to 28 days after the last dose (follow-up) or early withdrawal]
- Change From Baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Pancreatic 26 (EORTC QLQ- PAN26) Score [Time Frame: Baseline, Day 1 (D1) of each cycle up to 28 days after the last dose (follow-up) or early withdrawal]
- Safety and tolerability of ABC-123 plus Drug AMO-1002.

Study Arms

Patients will be stratified by center, performance status (Eastern Cooperative Oncology Group [ECOG] 0 or 1 v 2), and stage (locally advanced v metastatic) and assigned 1:1 to receive AMO-1002 plus NES-822 or AMO-1002 plus placebo. Patients, investigators, and the trial sponsor will be blinded to treatment assignments.

Study Drugs
AMO-1002 is approved as first-line therapy for patients with locally advanced or metastatic adenocarcinoma of the pancreas. NES-822 is an unapproved, small-molecule kinase inhibitor in clinical trials for a variety of tumor types. The combination appeared to have benefit in a single-arm phase II trial (1.9 month improvement in progression-free survival).

Dosing
Arm A: Subjects will receive AMO-1002 at a dose of 1000 mg/m^2 administered by IV infusion on day 1, day 8 and day 15 every 4 weeks and NES-822 at 5 mg twice daily [BID] every day for the four week cycle until unacceptable toxicity or tumor progression

Arm B: Subjects will receive AMO-1002 at a dose of 1000 mg/m^2 administered by IV infusion on day 1, day 8 and day 15 every 4 weeks and placebo matched to NES-822 at 5 mg twice daily [BID] every day for the four week cycle until unacceptable toxicity or tumor progression

Patients may receive treatment until there is progression of disease, intolerable toxicity, the patient refuses to continue or the Investigator decides to discontinue treatment.

Doses of NES-822 or AMO-1002 may be reduced or delayed (no more than 20 days) to allow recovery from toxicity. Patients who develop either neutropenic fever requiring antibiotic therapy or bleeding associated with thrombocytopenia should receive a 25% dose reduction of Drug AMO-1002 for subsequent cycles.

Drug NES-822 or placebo will be administered orally with food at a starting dose of 5 mg twice a day, which may be dose-titrated up to 10 mg twice daily if well tolerated.

Subjects will record the date, time, and quantity of each NES-822 /placebo dose (or the reason a dose was missed) in an electronic subject diary, and compliance with dosing will be evaluated during clinic visits.

Study Drug
Study drug should be stored protected from light, at room temperature.

Data Monitoring Committee
An Independent Data Monitoring Committee (IDMC) will be formed to assure subject safety in this clinical trial. The IDMC will also evaluate efficacy data at the time of the pre-specified interim analysis and make a recommendation about early termination."

Target subject population
Male or female patients ≥ 18 years of age, with histologically or cytologically confirmed, metastatic or locally advanced pancreatic adenocarcinoma; High-quality contrast-enhanced CT scanning is required to evaluate resectability. Subjects must have measurable disease according to RECIST and ECOG performance status of 0 through 2. Patients must have adequate renal and liver function as defined by serum creatinine and total bilirubin levels of no greater than 1.5 times the upper limits of normal (UNL) and transaminase (i.e., SGOT or SGPT) levels no higher than 2.5 times the institution's UNL. Patients must have adequate bone marrow function as defined by an absolute neutrophil count (ANC) of ≥ 1,500/mm^3 and platelet count of ≥ 100,000/mm^3. Patients must sign an informed consent form, indicating that they are aware of the investigational nature of this study that is in keeping with the policies of the institution.

Prior radiotherapy for local disease is allowed provided disease progression is documented, and treatment completed at least 4 weeks before random assignment. Prior chemotherapy is not permitted, except for fluorouracil or gemcitabine given concurrently as a radiosensitizer.

Patients meeting the following criteria will be excluded: current or recent bleeding; History of cerebrovascular accident (CVA), pulmonary embolism or untreated deep venous thrombosis (DVT) within the past 6 months; use of a thrombolytic agent; pre-existing uncontrolled blood pressure as defined by 2 consecutive baseline blood pressure readings of > 140 / 90; History of any one of more of the following cardiovascular conditions within the past 6 months: Cardiac angioplasty or stenting; myocardial infarction; unstable angina; symptomatic peripheral vascular disease; Class III or IV congestive heart failure as defined by the New York Heart Association; Any serious and/or unstable pre-existing medical, psychiatric, or other condition that could interfere with patient's safety, provision of informed consent, or compliance to study procedures; inability to take oral medication; known brain metastases.

Study schedule
Patients will be screened for eligibility over an up to 4-week period including medical and pancreatic cancer history, physical exam, vital signs, clinical laboratory measurements, ECOG performance status, EKG, and CT scan. Following the screening period (of up to 28 days), eligible patients will be randomized. Subject eligibility must be centrally confirmed before the investigator will be permitted to randomize the subject in the IVRS. Women of childbearing potential must have a negative serum or urine pregnancy test within 3 days prior to treatment.

Clinical laboratory assessments (including hematology, chemistry, and urinalysis) will be performed within 14 days before treatment start; during Cycle 1 at Day 1 (pre-dose), and Day 8, 15 and 22, during Cycle 2 - Cycle 4 at Day 1 and 15; during Cycle 5 and later on Day 1, and at early termination or end of treatment. ECOG scores will be performed prior to initiating each course of treatment and at the end of treatment. Physical examination and vitals will performed at screening, baseline (Day 1 of Cycle 1), and every 4 weeks thereafter. BP will be measured daily at home by subjects. Three consecutive ECGs will be completed at screening, baseline

(Day1), week 4 and at the end of treatment. If mean QTc interval is prolonged (> 500 msec) on repeat ECGs, then subject should discontinue treatment.

Response to therapy will be assessed after every 2 cycles using the Response Evaluation Criteria in Solid Tumors (RECIST) criteria until tumor progression or death. Follow-up for survival will be completed every 6 months after end of treatment and will continue for at least 1 year after the randomization of the last subject on study.

Adverse events (AEs) will be assessed at each study visit, by asking an open ended question to the patient, prior to treatment or disease assessment procedures, as appropriate, and again after procedures are completed. AEs will be reported according to severity grade and relationship to study agents using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4 as the grading scale. Serious adverse events will be reported for 28 days following the subject's last dose, regardless of initiation of other anticancer therapy.

Withdrawal:
Subjects may withdraw from the trial at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety or other appropriate reasons. If a subject does not return for a scheduled visit, at least three documented efforts should be made to contact them.

If PD is confirmed based on RECIST, the subject must be withdrawn from study treatment unless continuation of treatment has clinical benefit, in the opinion of the investigator and the study medical monitor, and no new lesions are identified. Any disease progression requiring other forms of specific anticancer therapy will be cause for discontinuation from study treatment. If study treatment is permanently discontinued, the investigator must update the subject status in the IVRS system within 2 calendar days.

Statistical methods:
Patients must have completed two cycles of study therapy to be considered evaluable for response unless there is clear evidence of clinical progression. To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed at least 4 weeks after the criteria for response are first met, even if the patient is removed from the study.

Demographic data and baseline disease characteristics will be displayed, and summary statistics (e.g., mean, median, standard deviation, percentages and frequency counts) will be used to describe each of the study populations. Survival analyses will be performed on all randomly assigned patients as per the intent-to-treat principle. The trial is powered to detect a hazard ratio (HR) of 0.90 between patients randomly assigned to AMO-1002 plus NES-822 or AMO-1002 plus placebo. A Cochran-Mantel-Haenszel test will be used compare response rates, adjusting for stratification factors at baseline. Fisher's exact tests will be used to compare the toxicities between treatment groups, when appropriate. Patients' quality of life

response distributions will be categorized based on change scores from their own baseline, and will be analyzed between treatment groups using $\chi 2$ tests followed by Mantel-Haenszel $\chi 2$ tests for trend. A change in score of 10 points will be considered clinically relevant.

Safety: Safety data will be tabulated for all patients who received any amount of study medication and include vital signs, laboratory parameters and adverse events. Adverse events will be evaluated according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0.