KURZPROTOKOLL
CanStem111P

Öffentlicher Titel	Phase III Studie zu BBI-608 plus nab-Paclitaxel und Gemcitabin bei metastasiertem Pankreasadenokarzinom
Wissenschaftl. Titel	A Phase III Study of BBI-608 plus nab-Paclitaxel with Gemcitabine in Adult Patients with Metastatic Pancreatic Adenocarcinoma
Kurztitel	CanStem111P
Studienart	multizentrisch, prospektiv, Therapiestudie, randomisiert, offen/unverblindet, Pharma-Studie, zweiarmig
Studienphase	Phase III
Erkrankung	Verdauung: Bauchspeicheldrüsenkrebs (Pankreaskarzinom): Erstlinie
Einschlusskriterien	- Written, signed consent for trial participation must be obtained from the patient appropriately in accordance with applicable ICH guidelines and local and regulatory requirements prior to the performance of any study specific procedure. - Must have histologically or cytologically confirmed advanced PDAC that is metastatic. The definitive diagnosis of metastatic PDAC will be made by integrating the histopathological data within the context of the clinical and radiographic data. Patients with islet cell neoplasms are excluded. - Must not have previously received chemotherapy or any investigational agent for the treatment of metastatic PDAC. (A fluoropyrimidine or gemcitabine administered as a radiation sensitizer in the adjuvant setting is allowed for as long as last dose was administered > 6 months prior to randomization and no lingering toxicities are present) - Nab-paclitaxel with gemcitabine therapy is appropriate for the patient and recommended by the Investigator. - Patient has one or more metastatic tumors evaluable by CT scan with contrast (or MRI, if patient is allergic to CT contrast media) per RECIST 1.1. Imaging investigations including CT/MRI of chest/abdomen/pelvis or other scans as necessary to document all sites of disease must be performed within 14 days prior to randomization. Qualifying scans performed as part of standard of care prior to patient signature of the study informed consent will be acceptable as baseline scanning as long as scanning is performed < 14 days prior to randomization. - Must have ECOG Performance Status of 0 or 1, assessed within 14 days prior to randomization. Two observers qualified to perform assessment of the performance status will be required to perform this assessment. If discrepant, the one with the most deteriorated performance status will be considered true. CanStem111P Protocol Date: 2017-JUN-16 Amendment #2: a) Patients must not require any help with activities of daily living (ADLs), including eating, dressing, washing or using the toilet; b) Patients must not need to stay in bed or chair for 50% or more of waking hours; c) Patients with factors that limit accurate assessment of performance status will not be eligible for the study. This includes but is not limited to patients with pre-existing conditions preventing them from full mobility (including but not limited to spinal or orthopedic conditions, amputees, morbid obesity defined by BMI > 40). - Must have life-expectancy of > 12 weeks. - Must be >= 18 years of age. (Due to increased risk of sepsis in patients >80 years old, candidate patients in this age group should be thoroughly evaluated prior to study randomization to ensure they are fit to receive chemotherapy. In addition to all of the inclusion/exclusion criteria listed, clinical judgment should be used regarding patients' susceptibility to infection (including but not limited to presence of ascites or diabetes mellitus increasing risk of infection). Furthermore, the expected stability of their performance status while receiving repeat weekly chemotherapy cycles should be given special attention. Patients in this age group should not be randomized on the study should there be any hesitation on any of these considerations.)

- For male or female patients of child producing potential: Must agree to use contraception or take measures to avoid pregnancy during the study and for 180 days after the final dose of nab-paclitaxel and gemcitabine or for 30 days for female patients and for 90 days for male patients, after the final BBI-608 dose if nab-paclitaxel and gemcitabine were not administered. Adequate contraception is defined as follows: 1. Complete true abstinence: when this is in line with the preferred and usual lifestyle of the subject; 2. Consistent and correct use of one of the following methods of birth control: a) male partner who is sterile prior to the female subjects entry into the study and is the sole sexual partner for that female subject; or b) implants of levonorgesterol; or c) injectable progestagen; or d) any intrauterine device (IUD) with a documented failure rate of less than 1% per year; or e) any intrauterine hormone-releasing system (IUS) with a documented failure rate of less than 1% per year; or f) oral contraceptive pill (either combined or progesterone only); or g) one barrier method, for example diaphragm with spermicide or condom with spermicide in combination with either implants of levonorgesterol or injectable progestagen, any intrauterine device (IUD) or intrauterine hormone-releasing system (IUS) with a documented failure rate of less than 1% per year, or oral contraceptive pill (either combined or progesterone only).
- Women of child bearing potential (WOCBP) must have a negative serum or urine pregnancy test within 5 days prior to randomization. The minimum sensitivity of the pregnancy test must be 25 IU/L or equivalent units of human chorionic gonadotropin (HCG). WOCBP include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhoea > 12 consecutive months; or women on hormone replacement therapy (HRT) with documented serum follicle stimulating hormone (FSH) level > 35 mIU/mL). Even women who are using oral, implanted or injectable contraceptive hormones or mechanical products such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides) to prevent pregnancy or practicing abstinence or where partner is sterile (e.g. vasectomy), should be considered to be of child bearing potential.
- Patient has adequate biological parameters as demonstrated by the following blood counts at baseline (obtained < 14 days prior to randomization; laboratory testing performed as part of standard of care prior to patient signature of informed consent for the study will be acceptable as baseline laboratory work as long as testing is performed < 14 days prior to randomization): a) Absolute neutrophil count (ANC) > 1.5 x 10^9/L; b) Platelet count > 100,000/mm^3 (100 x 10^9/L). Must not have required transfusion of platelets within 1 week of baseline platelet count assessment; c) Hemoglobin (Hgb) > 9 g/dL. Must not have required transfusion of red blood cells within 1 week of baseline Hgb assessment.
- Patient has the following blood chemistry levels at baseline (obtained < 14 days prior to randomization; laboratory testing performed as part of standard of care prior to patient signature of informed consent for the study will be acceptable as baseline laboratory work as long as testing is performed < 14 days prior to randomization): a) AST (SGOT) and ALT (SGPT) <= 2.5 × institutional upper limit of normal (ULN) [<= 5 × ULN in presence of liver metastases]; b) Total bilirubin <= 1.5 x institutional ULN. If total bilirubin is > ULN, it must be non-rising for at least 7 days; c) Serum creatinine within normal limits or calculated clearance > 60 mL/min/1.73 m^2 for patients with serum creatinine levels above or below the institutional normal value. If using creatinine clearance, actual body weight should be used for calculating creatinine clearance (eg. Using the Cockroft-Gault formula). For patients with a Body Mass Index (BMI) > 30 kg/m^2, lean body weight should be used instead.

- Patient not on anticoagulation has acceptable coagulation studies (obtained < 14 days prior to randomization; laboratory testing performed as part of standard of care prior to patient signature of informed consent for the study will be acceptable as baseline laboratory work as long as testing is performed < 14 days prior to randomization) as demonstrated by prothrombin time (PT) and partial thromboplastin time (PTT) within normal limits (+15%). Patients on anticoagulation must have coagulation values within the therapeutic range appropriate for the anti-coagulation indication.
- Patient has no clinically significant abnormalities on urinalysis results (obtained < 14 days prior to randomization; laboratory testing performed as part of standard of care prior to patient signature of informed consent for the study will be acceptable as baseline laboratory work as long as testing is performed < 14 days prior to randomization).
- Patient must have adequate nutritional status with Body Mass Index (BMI) > 18 kg/m^2 and body weight of > 40 kg with serum albumin > 3 g/dL.
- Baseline laboratory evaluations must be done within 14 days prior to randomization and some must be repeated < 72 hours prior to randomization, as listed in Section 5.0.
- Patients requiring biliary stent placement must have biliary stent placed > 7 days prior to screening.
- Pain symptoms should be stable (of tolerable Grade 2 or less).
- Only patients with available archival tumor tissue must consent to provision of, and Investigator(s) must confirm access to and agree to submit a representative formalin fixed paraffin block of tumor tissue in order that the specific correlative marker assays proscribed in Section 13.6 (Correlative Studies) of this protocol may be conducted. Submission of the tissue does not have to occur prior to randomization. Where local center regulations prohibit submission of blocks of tumor tissue, two 2 mm cores of tumor from the block and 5-20 unstained slides of whole sections of representative tumor tissue are preferred. Where it is not possible to obtain two 2 mm cores of tumor from the block, 5-20 unstained slides of representative tumor tissue are also acceptable. Where no previously resected or biopsied tumor tissue exists or is available, on the approval of the Sponsor/designated CRO, the patient may still be considered eligible for the study.
- Patient must consent to provision of a sample of blood in order that the specific correlative marker assays proscribed in Section 13.6 (Correlative Studies) may be conducted.
- Patients must be accessible for treatment and follow-up. Patients registered on this trial must receive protocol treatment and be followed at the participating center. This implies there must be reasonable geographical limits placed on patients being considered for this trial. Investigators must ensure that the patients randomized on this trial will be available for complete documentation of the treatment, response assessment, adverse events, and follow-up.
- Protocol treatment is to begin within 2 calendar days of patient randomization for patients randomized to Arm 1. Patients randomized to Arm 2 must begin protocol treatment within 7 calendar days of randomization.
- The patient is not receiving therapy in a concurrent clinical study and the patient agrees not to participate in other interventional clinical studies during their participation in this trial while on study treatment. Patients participating in surveys or observational studies are eligible to participate in this study.

Ausschlusskriterien

- Patients with no evidence of metastatic disease as well as patients with a local recurrence following surgical resection of primary lesion.
- Patient has experienced a decline in ECOG performance status between Baseline visit and within 72 hours prior to randomization.

- Patient has a > 20% decrease in serum albumin level between Baseline visit and within 72 hours prior to randomization.
- Patient has a > 10% decrease in weight between Baseline visit and within 72 hours prior to randomization.
- Any prior anti-cancer chemotherapy, biologic or investigational therapy for PDAC. a) Patients receiving immunotherapy for non-cancer related treatment within < 4 weeks of first planned dose of study treatment will be excluded; b) A fluoropyrimidine or gemcitabine administered as a radiation sensitizer in the adjuvant setting is allowed for as long as last dose was administered > 6 months prior to randomization.
- Major surgery within 4 weeks prior to randomization.
- Any known brain or leptomeningeal metastases are excluded, even if treated.
- Patients with clinically significant ascites.
- Women who are pregnant or breastfeeding. Women should not breastfeed while taking study treatment and for 4 weeks after the last dose of BBI-608 or while undergoing treatment with nab-paclitaxel and gemcitabine and for 180 days after the last dose of nab-paclitaxel and gemcitabine.
- Gastrointestinal disorder(s) which, in the opinion of the Principal Investigator, would significantly impede the absorption of an oral agent (e.g. active Crohn’s disease, ulcerative colitis, extensive gastric and small intestine resection).
- Unable or unwilling to swallow BBI-608 capsules daily.
- Uncontrolled inter-current illness including, but not limited to, ongoing or active infection, clinically significant non-healing or healing wounds, symptomatic congestive heart failure, unstable angina pectoris, clinically significant cardiac arrhythmia, significant pulmonary disease (shortness of breath at rest or mild exertion), uncontrolled infection or psychiatric illness/social situations that would limit compliance with study requirements. a) History of cardiac disease: congestive heart failure (CHF) > NYHA Class II; active coronary artery disease, myocardial infarction or coronary stenting within 6 months prior to randomization; unevaluated new onset angina within 3 months or unstable angina (angina symptoms at rest) or cardiac arrhythmias requiring anti-arrhythmic therapy (beta blockers or digoxin are permitted); b) Current uncontrolled hypertension (systolic blood pressure [BP] > 150 mmHg or diastolic pressure > 90 mmHg despite optimal medical management) as well as prior history of hypertensive crisis or hypertensive encephalopathy; c) Significant vascular disease (e.g., aortic aneurysm, aortic dissection, symptomatic peripheral vascular disease including claudication, Leo Buerger’s disease). Treated peripheral vascular disease that is stable for at least 6 months is allowed; d) Evidence of bleeding diathesis or clinically significant coagulopathy; e) Major surgical procedure (including open biopsy, significant traumatic injury, etc.) within 28 days, or anticipation of the need for major surgical procedure during the course of the study as well as minor surgical procedure (excluding placement of a vascular access device or bone marrow biopsy) within 7 days prior to randomization; f) Patients with clinically significant abnormalities on urinalysis at < 14 days prior to randomization; g) History of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 6 months prior to randomization; h) Ongoing serious, non-healing wound, ulcer, or bone fracture; i) Known infection with Human Immunodeficiency Virus (HIV), and/or active infection with hepatitis B or hepatitis C; j) History of interstitial lung disease, history of slowly progressive dyspnea and unproductive cough, sarcoidosis, silicosis, idiopathic pulmonary fibrosis, pulmonary hypersensitivity pneumonitis or multiple allergies; k) History of hemolytic-uremic syndrome; l) History of connective tissue disorders (eg, lupus, scleroderma, arteritis nodosa); m) Serious medical risk factors involving any of the major organ systems, or serious psychiatric disorders that could compromise the patient’s safety or the study data integrity.

	- Known hypersensitivity to gemcitabine, taxanes or any of their excipients, or the patient exhibits any of the events outlined in the Contraindications or Special Warnings and Precautions sections of the product or comparator SmPC or Prescribing Information. - Neurosensory neuropathy > grade 2 at baseline. - Uncontrolled chronic diarrhea > grade 2 at baseline. - Patients being treated with Warfarin. - Patients with active, uncontrolled bacterial, viral or fungal infection(s) requiring systemic therapy - Patients with a history of other malignancies except: adequately treated non-melanoma skin cancer, curatively treated in-situ cancer of the cervix, or other solid tumors curatively treated by surgery alone or surgery plus radiotherapy with no evidence of disease continuously for > 5 years. - Any active disease condition which would render the protocol treatment dangerous or impair the ability of the patient to receive protocol therapy. - Any condition (e.g. psychological, geographical, etc.) that does not permit compliance with the protocol, including patients with history of poor compliance or history of drug/alcohol abuse, or excessive alcohol beverage consumption that would interfere with the ability to comply with the study protocol. Patients planning to take a vacation for 14 or more consecutive days during the course of the study are ineligible.
Alter	18 Jahre und älter
Prüfzentren	**Krankenhaus Nordwest GmbH** (Rekrutierung beendet) Institut für klinisch-onkologische Forschung Steinbacher Hohl 2-26 60488 Frankfurt am Main Prof. Dr. med. Salah-Eddin Al-Batran Tel: 069 7601 4420 albatran.salah@khnw.de
Sponsor	Boston Biomedical
Registrierung in anderen Studienregistern	ClinicalTrials.gov NCT02993731 EudraCT 2016-004359-57