KURZPROTOKOLL
NintNivo (AIO-TRK-0117)

Öffentlicher Titel	Phase I Studie zu Nintedanib und Nivolumab bei vorbehandelte, fortgeschrittenem oder metastasiertem nicht-kleinzelligem Lungenkarzinom
Wissenschaftl. Titel	Machbarkeit und Sicherheit von Nintedanib in Kombination mit Nivolumab bei vorbehandelten Patienten mit fortgeschrittenem oder metastasiertem nicht-kleinzelligem Lungenkarzinom (NSCLC) mit Adenokarzinom-Histologie - Eine AIO-Phase-Ib-Studie
Kurztitel	NintNivo (AIO-TRK-0117)
Studienart	multizentrisch, prospektiv, Therapiestudie, offen/unverblindet, einarmig
Studienphase	Phase I
Erkrankung	Lunge: Lungenkrebs: Nicht kleinzelliges Lungenkarzinom (NSCLC) - Zweitlinie oder höher
Einschlusskriterien	- Written informed consent and any locally-required authorization (EU Data Privacy Directive in the EU) obtained from the subject prior to performing any protocol-related procedures, including screening evaluations. - Subject is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow up. - Age >= 18 years at time of study entry. - Histologically confirmed adenocarcinoma of the lung stage IIIB/IV according to UICC7 - One previous line of systemic chemotherapy including maintenance for advanced or metastatic NSCLC. Patients should be offered standard chemotherapy regimens as recommended by current local Clinical Practice Guidelines. Neo-adjuvant and adjuvant therapies are permitted, provided that disease progression/relapse occurred more than 6 months after cessation of therapy. - ECOG performance status 0-1. - Expected life expectancy of at least 3 months. - Patients with measurable disease (at least one uni-dimensionally measurable target lesion by CT-scan or MRI) according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1) are eligible. If a potential target lesion has been irradated previously, clear evidence of progression at target site must be documented. - A formalin fixed, paraffin-embedded (FFPE) tumor tissue block (archival or recent) or a approx. of 10-15 unstained slides of tumor sample (slices must be recent and collected on slides provided by the sponsor) must be available for PD L1 and other biomarker evaluation. Biopsy should be excisional, incisional or core needle. Fine needle aspiration is insufficient - Prior therapies and surgeries are allowed if completed 2 weeks (for minor surgery) or 4 weeks (palliative radiotherapy for bone pain; major surgeries with complete wound healing), respectively prior to start of treatment and patient recovered from toxic effects. - Adequate blood count, liver-enzymes, and renal function (obtained no later than 14 days prior to start of treatment): - -> WBC >= 2000/MüL - -> Neutrophils >= 1500/MüL - -> Platelets >= 100 x103/MüL - -> Hemoglobin > 9.0 g/dL - -> Serum creatinine <= 1.5 x ULN or creatinine clearance (CrCl) >= 40 mL/min (if using the Cockcroft-Gault formula) - -> AST/ALT <= 1.5 x ULN (< 3 ULN in case of liver metastases) - -> Total Bilirubin <= 1.5 x ULN

- Women of childbearing potential (WOCBP) must use appropriate method(s) of contraception. WOCBP should use an adequate method to avoid pregnancy for 5 months (30 days plus the time required for nivolumab to undergo five half-lives) after the last dose of nivolumab. Since the effect of nintedanib on the metabolism and efficacy of contraceptives has not been investigated, barrier methods should be applied as a second form of contraception, to avoid pregnancy.
- Women of childbearing potential must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study treatment and monthly throughout treatment until 5 months after last dose of IMP.
- Men who are sexually active with WOCBP must use any contraceptive method with a failure rate of less than 1% per year. Men receiving nivolumab and who are sexually active with WOCBP will be instructed to adhere to contraception for a period of 7 months after the last dose of investigational product. Women who are not of childbearing potential (ie, who are postmenopausal or surgically sterile) as well as azoospermic men do not require contraception.

Ausschlusskriterien

- More than one prior treatment line for advanced or metastatic NSCLC
- Subjects with active CNS metastases are excluded. Subjects are eligible if CNS metastases are adequately treated and subjects are neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment) for at least 4 weeks prior to enrollment. In addition, subjects must be either off corticosteroids, or on a stable or decreasing dose of <= 10 mg daily prednisone (or equivalent).)
- Leptomeningeal disease, carcinomatous meningitis, chronic diarrhea or short bowel syndrome
- Known activating EGFR mutation or a known ALK translocation
- Patients with symptomatic interstitial lung disease
- Any previous treatment with anti-tumor vaccines or other immuno-stimulatory antitumor agents, nintedanib or an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways
- Ongoing toxicities attributed to prior anti-cancer therapy other than alopecia and fatigue that have not resolved to grade 1 (NCI CTCAE version 4.03) or baseline before administration of study drug
- Major injuries and/or surgery within the past 4 weeks prior to start of study treatment with incomplete wound healing and/or planned surgery during the on-treatment study period
- Patients should be excluded if they have an active, known or suspected autoimmune disease. NOTE: Subjects are permitted to enroll if they have vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger
- Patients should be excluded if they have a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. NOTE: Inhaled or topical steroids and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.
- Positive test for HBV sAg or HCV RNA indicating acute or chronic infection OR positive HIV test
- History of severe hypersensitivity reactions to other monoclonal antibodies or any excipient. Known hypersensitivity to nintedanib, peanut, soya or to any of the excipients or contrast media.

- Radiotherapy to the target lesion within the past 3 months prior to baseline imaging. (see also inclusion criterion 8)
- Radiographic evidence of cavitary or necrotic tumors
- Centrally located tumors with radiographic evidence (CT or MRI) of local invasion of major blood vessels
- Therapeutic anticoagulation with drugs requiring INR monitoring (except low-dose heparin and/or heparin flush as needed for maintenance of an in-dwelling intravenous devise) or anti-platelet therapy (except for low-dose therapy with acetylsalicylic acid < 325mg per day)
- History of clinically significant hemorrhagic or thromboembolic event in the past 6 months
- Known inherited predisposition to bleeding or thrombosis
- Significant cardiovascular diseases (i.e. uncontrolled hypertension, unstable angina, history of infarction within the past 12 months prior to start of study treatment, congestive heart failure > NYHA II, serious cardiac arrhythmia, pericardial effusion)
- Active alcohol or drug abuse
- Significant weight loss (> 10% of BW) within past 6 months prior to inclusion into the trial
- Previous malignancy (other than NSCLC), which either progresses or requires active treatment
- Subjects with previous malignancies (except non-melanoma skin cancers, and the following in situ cancers: bladder, gastric, colon, cervical/dysplasia, endometrial, melanoma, or breast) are excluded unless a complete remission was achieved at least 2 years prior to study entry AND no additional therapy is required or anticipated to be required during the study period.
- Female subjects who are pregnant, breast-feeding or male or female patients of reproductive potential who are not employing an effective method of birth control (failure rate of less than 1% per year)
- Receipt of the last dose of anti-cancer therapy (chemotherapy, immunotherapy, endocrine therapy, targeted therapy, biologic therapy, tumor embolization, monoclonal antibodies, other investigational agent) <=28 days prior to the first dose of study treatment.
- Any other serious or uncontrolled medical disorder (e.g. active ulcers), active infection, physical exam finding, laboratory finding, altered mental status, or psychiatric condition that, in the opinion of the investigator, would limit a subject's ability to comply with the study requirements, substantially increase risk to the subject, or impact the interpretability of study results.
- Patient who might be dependent on the sponsor, site or the investigator.
- Patient who has been incarcerated or involuntarily institutionalized by court order or by the authorities § 40 Abs. 1 S. 3 Nr. 4 AMG.

Alter
18 Jahre und älter

Molekularer Marker
ALK wt

EGFR wt

Prüfzentren
Innere Medizin 2 (Rekrutierung beendet)
Hämatologie / Medizinische Onkologie
Theodor-Stern-Kai 7
60590 Frankfurt am Main
Christina Wabbels
Tel: 069 6301-80429
wabbels@med.uni-frankfurt.de

Sponsor
AIO-Studien GmbH (Hauptsponsor)

Förderer	AIO-Studien GmbH
Registrierung in anderen Studienregistern	EudraCT 2017-001723-45 (primäres Register)
Links	Studiendokumente zum Download (roXtra)