KURZPROTOKOLL
CINC280A2201

Öffentlicher Titel	Phase II Studie zu oraler Gabe des cMET Inhibitors INC280 bei Patienten mit fortgeschrittenem NSCLC und EGFR wt in Zweitlinie oder höher
Wissenschaftl. Titel	A phase II, multicenter, three-cohort study of oral cMET inhibitor INC280 in adult patients with EGFR wild-type (wt), advanced non-small cell lung cancer (NSCLC) who have received one or two prior lines of systemic therapy for advanced/metastatic disease
Kurztitel	CINC280A2201
Studienart	multizentrisch, prospektiv, offen/unverblindet, mehrarmig
Studienphase	Phase II
Erkrankung	Lunge: Lungenkrebs: Nicht kleinzelliges Lungenkarzinom (NSCLC) - Erstlinie
Einschlusskriterien	- Written informed consent must be obtained prior to any screening procedures - Age >= 18 years - Stage IIIB or IV NSCLC (any histology) at the time of study entry - Histologically or cytologically confirmed diagnosis of NSCLC that is: - 1. EGFR wt. This should have been assessed as part of the patient standard of care by a validated test for EGFR mutations, as per the Molecular Testing Guideline for selection of Lung Cancer Patients for EGFR and ALK Tyrosine Kinase Inhibitors from College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology (Lindeman et al 2013). The EGFR wt status (for exon 19 deletions and exon 21 L858R substitution mutations) must be documented in the patient source documents before the patient can be consented for pre-screening for cMET amplification and cMET mutation status (except for patients who are treatment-naïve potentially eligible for Sub-Cohort 5a, 5b and Cohort 7 or if molecular pre-screening will be performed by NGS and local status is not available). Patients with NSCLC of pure squamous cell histology can enter prescreening without EGFR mutation testing or result, however patients with pure squamous cell histology and are known to have EGFR mutations in exons 19 or 21 will be excluded, - 2. AND ALK rearrangement -negative. This should have been assessed as part of the patient standard of care by a validated test. The ALK rearrangement-negative status must be documented in the patient source documents before the patient can be consented for pre-screening for cMET amplification and cMET mutation status, except for patients who are treatment-naïve potentially eligible for Sub-Cohorts 5a, 5b and Cohort 7; if local ALK testing is not available, patient status will be determined centrally along with the cMET status. Patients with NSCLC of pure squamous cell histology can enter pre-screening without ALK testing or result, however patients with pure squamous cell histology that are known to have ALK rearrangement will be excluded. - 3. AND (as determined by central assessment at a Novartis designated laboratory) either: - a. Cohort 1: Pre-treated patients with cMET GCN >= 6, including: - aa. Sub-cohort 1a: Patients with cMET GCN of >= 10, or - bb. Sub-cohort 1b: Patients with cMET GCN of >= 6 and < 10, or - b. Cohort 2: Pre-treated patients with cMET GCN >= 4 and < 6, or - c. Cohort 3: Pre-treated patients with cMET GCN < 4, or - d. Cohort 4: Pre-treated patients with cMET mutations regardless of cMET GCN, or - e. Cohort 5: Treatment-naïve patients with cMET dysregulation, including: - aa. Sub-cohort 5a: Patients with cMET GCN of >= 10, or - bb. Sub-cohort 5b: Patients with cMET mutations regardless of cMET GCN, or - f. Cohort 6: Pre-treated patients with either cMET GCN 10 without cMET mutations or cMET mutations regardless of cMET GCN, or

- g. Cohort 7: Treatment-naïve patients with cMET mutations regardless of cMET GCN cMET (and ALK, if applicable) testing may be performed while patient is still receiving anti-cancer therapy. However, the patient can only be screened for the main study once the patient has discontinued the last prior systemic treatment due to either disease progression or intolerance.
- To be eligible for Cohorts 1-4, patients must have failed one or two prior lines of systemic therapy for advanced/metastatic disease (stage IIIB or IV NSCLC). To be eligible for Cohort 6, patients must have failed one prior line of systemic therapy for advanced/metastatic disease (stage IIIB or IV NSCLC). Treatment failure is defined as documented disease progression or intolerance to treatment. Maintenance therapy given after first line chemotherapy will be considered as part of the first line if given to patients with documented response or stable disease before starting the maintenance therapy. Neoadjuvant and adjuvant systematic therapies will count as one prior line of treatment if relapse occurred within 12 months from the end of the neo-adjuvant or adjuvant systemic therapy. To be eligible for Cohort 5 and 7, patients must not have received any systemic therapy for advanced/metastatic disease (stage IIIB or IV NSCLC). Neo-adjuvant and adjuvant systemic therapies will not count as one prior line of treatment if relapse occurred > 12 months from the end of the neo-adjuvant or adjuvant systemic therapy.
- At least one measurable lesion as defined by RECIST 1.1. A previously irradiated site lesion may only be counted as a target lesion if there is clear sign of progression since the irradiation.
- Patients must have recovered from all toxicities related to prior anticancer therapies to grade 1 (CTCAE v 4.03). Patients with any grade of alopecia are allowed to enter the study.
- Patients must have adequate organ function including the following laboratory values at the screening visit:
- 1. Absolute neutrophil count (ANC) >= 1.5 x 109/L without growth factor support
- 2. Platelets >= 75 x 109/L
- 3. Hemoglobin (Hgb) > 9 g/dL
- 4. Calculated creatinine clearance (using Cockcroft-Gault formula) 45 mL/min
- 5. Total bilirubin <= 1.5 x ULN
- 6. Aspartate transaminase (AST) 3 x ULN, except for patients with liver metastasis, who may only be included if AST 5 x ULN
- 7. Alanine transaminase (ALT) <= 3 x ULN, except for patients with liver metastasis, who may only be included if ALT <= 5 x ULN
- 8. Alkaline phosphatase (ALP) <= 5 x ULN
- 9. Asymptomatic serum amylase <= grade 2. Patients with grade 1 or grade 2 serum amylase at the beginning of the study must be confirmed to have no signs and/or symptoms suggesting pancreatitis or pancreatic injury (e.g., elevated P-amylase, abnormal imaging findings of pancreas, etc.)
- 10. Serum lipase <= ULN
- 11. Fasting plasma glucose <= 175 mg/dL (<= 9.7 mmol/L)
- 12. Patients must have the following laboratory values within the laboratory normal limits or corrected to within normal limits with supplements during screening:
- a. Potassium
- b. Magnesium
- c. Phosphorus
- 13. Total calcium (corrected for serum albumin)
- ECOG performance status (PS) of 0 or 1.

- Willing and able to comply with scheduled visits, treatment plan and laboratory tests.

Ausschlusskriterien

- Prior treatment with crizotinib, or any other cMET or HGF inhibitor
- Patients with known hypersensitivity to any of the excipients of INC280 (crospovidone, mannitol, microcrystalline cellulose, povidone, sodium lauryl sulfate, magnesium stearate, colloidal silicon dioxide, and various coating premixes).
- Patients with characterized EGFR mutations that predict sensitivity to EGFR therapy, including, but not limited to exon 19 deletions and exon 21 mutations.
- Patients with characterized ALK-positive rearrangement.
- Patients with symptomatic central nervous system (CNS) metastases who are neurologically unstable or have required increasing doses of steroids within the 2 weeks prior to study entry to manage CNS symptoms
- Presence or history of carcinomatous meningitis
- Presence or history of a malignant disease other than NSCLC that has been diagnosed and/or required therapy within the past 3 years. Exceptions to this exclusion include the following: completely resected basal cell and squamous cell skin cancers, and completely resected carcinoma in situ of any type
- Clinically significant, uncontrolled heart diseases:
- 1. Unstable angina within 6 months prior to screening
- 2. Myocardial infarction within 6 months prior to screening
- 3. History of documented congestive heart failure (New York Heart Association functional classification III-IV)
- 4. Uncontrolled hypertension defined by a Systolic Blood Pressure (SBP) >= 160 mm Hg and/or Diastolic Blood Pressure (DBP) >= 100 mm Hg, with or without antihypertensive medication. Initiation or adjustment of antihypertensive medication(s) is allowed prior to screening
- 5. Ventricular arrhythmias
- 6. Supraventricular and nodal arrhythmias not controlled with medication
- 7. Other cardiac arrhythmia not controlled with medication
- 8. QTcF >= 450 ms (male patients), >= 460 ms (female patients) on the screening ECG (as mean of triplicate ECG)
- Thoracic radiotherapy to lung fields <= 4 weeks prior to starting INC280 or patients who have not recovered from radiotherapy-related toxicities. For all other anatomic sites (including radiotherapy to thoracic vertebrae and ribs), radiotherapy <= 2 weeks prior to starting INC280 or patients who have not recovered from radiotherapy-related toxicities. Palliative radiotherapy for bone lesions <= 2 weeks prior to starting INC280 is allowed
- Major surgery (e.g., intra-thoracic, intra-abdominal or intra-pelvic) within 4 weeks prior (2 weeks for resection of brain metastases) to starting INC280 or who have not recovered from side effects of such procedure. Video-assisted thoracic surgery (VATS) and mediastinoscopy will not be counted as major surgery and patients can be enrolled in the study >= 1 week after the procedure
- Patients receiving treatment with medications that meet one of the following criteria and that cannot be discontinued at least 1 week prior to the start of treatment with INC280 and for the duration of the study: Strong inducers of CYP3A4
- Impairment of GI function or GI disease that may significantly alter the absorption of INC280 (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, or malabsorption syndrome)
- Unable or unwilling to swallow tablets as per dosing schedule

- Patients receiving unstable or increasing doses of corticosteroids. If patients are on corticosteroids for endocrine deficiencies or tumor-associated symptoms other than CNS related, dose must have been stabilized (or decreasing) for at least 5 days before first dose of INC280
- Patients receiving treatment with any enzyme-inducing anticonvulsant that cannot be discontinued at least 1 week before first dose of INC280, and for the duration of the study. Patients on non-enzyme-inducing anticonvulsants are eligible
- Applicable to Cohorts 1-4 and Cohort 6 only: Previous anti-cancer and investigational agents within 4 weeks or <= 5 x half-life of the agent (whichever is longer) before first dose of INC280. If previous treatment is a monoclonal antibody, then the treatment must be discontinued at least 4 weeks before first dose of INC280. If previous treatment is an oral targeted agent, then the treatment must be discontinued at least 5 x half-life of the agent before the first dose of INC280.
- Other severe, acute, or chronic medical or psychotic conditions or laboratory abnormalities that in the opinion of the investigator may increase the risk associated with study participation, or that may interfere with the interpretation of study results
- Any other condition that would, in the Investigator's judgment, contraindicate patient's participation in the clinical study due to safety concerns or compliance with clinical study procedures, e.g., infection (including active hepatitis B and C), inflammation, intestinal obstruction, unable to swallow medication, social/ psychological issues, etc.
- Pregnant or nursing (lactating) women
- Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 7 days after stopping treatment. Highly effective contraception methods include (Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential):
- 1. Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
- 2. Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
- 3. Male sterilization (at least 6 months prior to screening). The vasectomized male partner should be the sole partner for that subject
- 4. Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception. In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.
- Sexually active males unless they use a condom during intercourse while taking drug and for 7 days after stopping treatment and should not father a child in this period. A condom is required to be used also by vasectomized men as well as during intercourse with a male partner in order to prevent delivery of the drug via semen.
- Presence or history of interstitial lung disease or interstitial pneumonitis, including clinically significant radiation pneumonitis (i.e., affecting activities of daily living or requiring therapeutic intervention).

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Alter	18 Jahre und älter
Molekularer Marker	ALK wt EGFR wt
Fallzahl	276
Prüfzentren	**Innere Medizin 2** (Nachbeobachtung) Hämatologie / Medizinische Onkologie Theodor-Stern-Kai 7 60590 Frankfurt am Main Lena Schütz Tel: 069 6301-84497 Fax: 069 6301-83655 lena.schuetz@kgu.de **Universitätsklinikum Frankfurt** (Nachbeobachtung) Medizinische Klinik II, Hämatologie/Onkologie Theodor-Stern-Kai 7 60590 Frankfurt am Main Lena Schütz Tel: 069 6301-84497 Fax: 069 6301-83655 lena.schuetz@kgu.de
Sponsor	Novartis Pharma
Förderer	Novartis Pharma
Registrierung in anderen Studienregistern	ClinicalTrials.gov NCT02414139 EudraCT 2014-003850-15
Therapie	Experimental: cMET GCN 6 Patients with cMET GCN 6 treated with INC280 at 400mg BID Intervention: Drug: INC280 (capmatinib) Experimental: cMET GCN 4 and < 6 Patients with cMET GCN 4 and < 6 treated with INC280 at 400 mgBID Intervention: Drug: INC280 (capmatinib) Experimental: cMET GCN < 4 Patients with cMET GCN < 4 treated with INC280 at 400mg BID Intervention: Drug: INC280 (capmatinib) Experimental: cMET mutations Patients with cMET mutations regardless of cMET GCN treated with INC280 at 400mg BID Intervention: Drug: INC280 (capmatinib)
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