A Phase I open-label dose escalation study with expansion to assess the safety and tolerability of INC280 in patients with c-MET dependent advanced solid tumors

Published: 09-01-2013
Last updated: 24-04-2024

Primary objective: To determine the MTD/highest studied dose determined to be safe, the safety and tolerability of INC280 as a single agent when administered orally to adult patients with c-MET dependent advanced solid malignancies.Secondary…

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Miscellaneous and site unspecified neoplasms benign
Study type	Interventional

Summary

ID

NL-OMON43929

Source
ToetsingOnline

Brief title
A phase I study with INC280 in c-MET dependent solid tumors

Condition

- Miscellaneous and site unspecified neoplasms benign

Synonym
c-MET dependend solid tumors

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: c-MET, INC280, phase I, solid tumors

Outcome measures

Primary outcome

Escalation: Incidence, frequency, and category of DLT during the first cycle of

INC280 treatment.

Expansion: Safety by monitoring the frequency, duration, and severity of AEs,

changes in clinical laboratory findings, physical examinations, vital

signs, ECGs, EEGs and Brain MRI.

Expansion cohort NSCLC patients EGFRwt with high c-MET expression: Progression

free survival (PFS), duration of response (DOR), disease

control rate (DCR), and overall survival (OS)

Secondary outcome

Objective response.

Type, frequency, and severity of AEs, changes in hematology and blood chemistry

values, assessment of physical examinations, vital signs,

EEGs, ECGs, brain MRIs.

c-MET signaling inhibitory activity

Study description

Background summary

INC280 possesses potent inhibitory activity against the c-MET kinase.
The c-MET pathway is one of the most frequently dysregulated pathways implicated in human cancers. Inappropriate signaling through the c-MET RTK pathway occurs in multiple types of human cancers due to receptor overexpression, gene amplification, gene mutation and/or ligand-dependent activation and contributes to malignant progression through increased cell proliferation, survival, invasion and metastasis. Aberrant c-MET signaling has been documented in various tumor types, including most carcinomas and sarcomas, as well as in many hematological malignancies. Using animal models, c-MET has been shown to play a pivotal role in the development, maintenance and dissemination of malignancies. Currently, several HGF and c-MET targeted agents are being evaluated in clinical trials. These inhibitors have shown evidence of early clinical benefit (e.g., objective responses, durable stable disease) in various human cancers including lung, renal, breast, liver and gastric, underscoring the potential of these agents in cancer treatment.

Study objective

Primary objective: To determine the MTD/highest studied dose determined to be safe, the safety and tolerability of INC280 as a single agent when administered orally to adult patients with c-MET dependent advanced solid malignancies.
Secondary objective: Preliminary anti-tumor activity of INC280, safety and tolerability, c-MET inhibition and anti-tumor effect of INC280 by paired pre-treatment and post-treatment tumor biopsies, PK.

Study design

Open-label phase I dose escalation and dose expansion study. Approximately 90 patients (max. 100).
Screening for c-MET mutation.
Determination of the MTD/highest studied dose of INC280. Cohorts of 3-6 patients. Cycles of 4 weeks. Dose-escalation decision after 1 cycle. Starting dose 100 mg BID.
After the MTD/highest studied dose been determined, patients will be enrolled to be treated with this dose.
Treatment until progression or unacceptable toxicity.

Protocol amendment 6: additional group in expansion cohort NSCLC patients

EGFRwt with high c-MET expression

Intervention

INC280 capsules for oral administration.
Strenght: 10 mg and 50 mg
Dosing schedule BID or QD
The starting dose for this study will be 100 mg BID

Protocol Amendment 5:
INC280 tablets 50mg and 100mg available and will replace INC280 hard gelatin apsules

Study burden and risks

Risk: Adverse events of study medication.

Burden:
Cycles of 4 weeks.
Screening visit, 6 visits during cycle 1, 4 during cycle 2. Thereafter 1 visit per cycle. Duration 1-4 h. 2 visits with duration of 8-10 h (PK samples). 2 end of treatment/study visits.
Blood tests 7-50 ml/occasion.
Screening: Physical examination, blood tests, pregnancy test, ECG, MRI brain, EEG, tumor measurements, tumor biopsy, skin biopsy.
Cycle 1: 5 x physical examination, 4 x blood tests, 2 long PK measurement days 0-24 h (8 samples per day of 3 ml), 3x ECG, 1x tumor biopsy, 1 x skin biopsy.
Cycle 2: 4 x physical examination, 4 x blood tests, MRI brain.
Following courses: Physical examination, blood tests, pregnancy test, tumor measurements every 8 weeks, MRI brain (cycle 4).
End of treatment visit: Physical examination, blood tests, pregnancy test, ECG, MRI brain, EEG, tumor measurements (unless performed <30 days).

Contacts

Public
Novartis Pharma

Raapopseweg 1 1
Arnhem 6824 DP
NL
Scientific
Novartis Pharma

Raapopseweg 1 1
Arnhem 6824 DP
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Advanced solid tumors with confirmed c-MET dysregulation and for whom no currently available therapy excists
- Previous anti-cancer and investigational therapy must be discontinued for at least 28 days before start study treatment, (6 weeks for GBM patients that received nitrosoureas), previous anti-body therapy for at least 60 days before start of study treatment and must have recovered fully from the adverse effects of such treatment before start study treatment.
- ECOG performance status <= 2
- Laboratory values:
Hemoglobin > 9 g/dL (5,58 mmol/l) without transfusion support or growth factors within 10 days of starting INC280
Platelet count >= 75 x 109/L
Absolute neutrophil count (ANC) >= 1.2 x 109/L without growth factor support
Total bilirubin <= 2 x upper limit of normal (ULN)
AST/SGOT and/or ALT/SGPT <= 2.5 x upper limit of normal (ULN) or <= 5.0 ULN if HCC is primary disease or liver metastases are present
Serum creatinine <= 2 x ULN
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
Serum lipase <= ULN
Fasting serum triglyceride level <= 500 mg/dL
-Patients with GBM must have radiographic evidence of recurrent tumor and must be at least 12 weeks post radiation therapy (XRT).;Additional inclusion criteria for NSCLC patients EGFRwt with high c-MET expression:

a. Written documentation of EGFRwt NSCLC.
b. c-MET positivity as defined by c-MET IHC intensity score +3 in >= 50% of tumor cells performed through a Novartis designated central laboratory.
c.No more than three prior lines of antineoplastic therapy for NSCLC.;Other protocol-defined inclusion citeria may apply. See protocol page 49

Exclusion criteria

- HCC with liver dysfunction greater than Child-Pugh A.
- Previous treatment with a c-MET inhibitor or HGF-targeting therapy.
- Symptomatic CNS metastases that are neurologically unstable or requiring increasing doses of steroids to control their CNS disease.
- Any CNS deficits. For patients with GBM, CNS symptoms grade 2 or greater.
- Receiving anti-epileptic drugs that are known to be strong inducers of CYP3A4.
- Prior or current anti-angiogenic therapy for patients with GBM.
- Radiation therapy within <= 4 weeks (<12 for GBM) or limited field radiotherapy within <=2 weeks (<12 weeks GBM) prior to the start of study treatment. Any persistent side effect of prior radiotherapy must be resolved to <= Grade 1 prior to the first dose of study drug.
;Additional exclusion criteria for patients of the expansion group with NSCLC EGFRwt and high c-MET expression :
a. Any unresolved toxicity (CTCAE grade > 1) from previous anti-cancer therapy or radiotherapy, except alopecia.
b. Anti-cancer therapies within the following time frames prior to the first dose of study treatment:
• Conventional cytotoxic chemotherapy: <=4 weeks (<=6 weeks for nitrosoureas and mitomycin-C)
• Biologic therapy (e.g., antibodies): <=4 weeks
• Non-cytotoxic small molecule therapeutics: <=5 half-lives or <=2 weeks (whichever is longer)
• Other investigational agents: <=4 weeks
• Radiation therapy (palliative setting is allowed.): <=4 weeks
• Major surgery: <=2 weeks;Other protocol-defined exclusion criteria may apply. See protocol page 50-51

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled

Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	28-02-2012
Enrollment:	16
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	niet van toepassing
Generic name:	niet van toepassing

Ethics review

Approved WMO Date:	09-01-2013
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	24-05-2013
Application type:	First submission
Review commission:	PTC stichting Het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis
Approved WMO Date:	18-06-2013
Application type:	Amendment
Review commission:	PTC stichting Het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis
Approved WMO Date:	17-09-2013
Application type:	Amendment
Review commission:	PTC stichting Het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis

Approved WMO Date:	18-09-2013
Application type:	Amendment
Review commission:	PTC stichting Het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis
Approved WMO Date:	09-01-2014
Application type:	Amendment
Review commission:	PTC stichting Het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis
Approved WMO Date:	10-01-2014
Application type:	Amendment
Review commission:	PTC stichting Het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis
Approved WMO Date:	21-01-2014
Application type:	Amendment
Review commission:	PTC stichting Het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis
Approved WMO Date:	23-01-2014
Application type:	Amendment
Review commission:	PTC stichting Het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis
Approved WMO Date:	27-02-2014
Application type:	Amendment
Review commission:	PTC stichting Het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis
Approved WMO Date:	28-02-2014
Application type:	Amendment
Review commission:	PTC stichting Het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis
Approved WMO Date:	31-07-2014
Application type:	Amendment

Review commission:	PTC stichting Het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis
Approved WMO Date:	15-09-2014
Application type:	Amendment
Review commission:	PTC stichting Het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis
Approved WMO Date:	14-11-2014
Application type:	Amendment
Review commission:	PTC stichting Het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis
Approved WMO Date:	17-11-2014
Application type:	Amendment
Review commission:	PTC stichting Het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis
Approved WMO Date:	25-11-2014
Application type:	Amendment
Review commission:	PTC stichting Het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis
Approved WMO Date:	05-12-2014
Application type:	Amendment
Review commission:	PTC stichting Het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis
Approved WMO Date:	06-02-2015
Application type:	Amendment
Review commission:	PTC stichting Het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis
Approved WMO Date:	12-02-2015
Application type:	Amendment
Review commission:	PTC stichting Het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis
Approved WMO	

Date:	14-07-2015
Application type:	Amendment
Review commission:	PTC stichting Het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis

Approved WMO

Date:	29-07-2015
Application type:	Amendment
Review commission:	PTC stichting Het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis

Approved WMO

Date:	18-09-2015
Application type:	Amendment
Review commission:	PTC stichting Het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis

Approved WMO

Date:	09-10-2015
Application type:	Amendment
Review commission:	PTC stichting Het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis

Approved WMO

Date:	15-10-2015
Application type:	Amendment
Review commission:	PTC stichting Het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis

Approved WMO

Date:	21-01-2016
Application type:	Amendment
Review commission:	PTC stichting Het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis

Approved WMO

Date:	01-03-2016
Application type:	Amendment
Review commission:	PTC stichting Het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis

Approved WMO

Date:	15-03-2016
Application type:	Amendment
Review commission:	PTC stichting Het Nederlands Kanker Instituut - Antoni van

	Leeuwenhoekziekenhuis
Approved WMO Date:	15-07-2016
Application type:	Amendment
Review commission:	PTC stichting Het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis
Approved WMO Date:	01-12-2016
Application type:	Amendment
Review commission:	PTC stichting Het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis
Approved WMO Date:	10-01-2017
Application type:	Amendment
Review commission:	PTC stichting Het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2010-024101-12-NL
ClinicalTrials.gov	NCT01324479
CCMO	NL43000.031.12