A phase Ib/II, open-label, multicenter trial with oral cMET inhibitor INC280 alone and in combination with erlotinib versus platinum/pemetrexed in adult patients with EGFR mutated, cMET-amplified, locally advanced/metastatic non-small cell lung cancer (NSCLC) with acquired resistance to prior EGFR tyrosine kinase inhibitor (EGFR TKI)

Published: 29-09-2015
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Primary phase 1: To determine MTD and/or RP2D of INC280 incombination with erlotinibPrimary phase 2: To compare the antitumor activity of INC280 alone, and INC280 in combination with erlotinib, vs platinum with pemetrexed, as measured by Progression...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Respiratory and mediastinal neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON42451

Source
ToetsingOnline

Brief title
CINC280B2201

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified
- Respiratory disorders NEC

Synonym
non-small cell lung cancer; lung cancer

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Novartis Pharma BV

Intervention

Keyword: cMET amplification, EGFR mutation, erlotinib, INC280

Outcome measures

Primary outcome

Phase I: MTD and/or RP2D

Phase II: PFS.

Secondary outcome

Phase I: MTD and/or RP2D DOR, ORR, DCR, PFS, adverse events, PK parameters.

Phase II: DOR, ORR, DCR, PFS, OS, adverse events, PK parameters.

Study description

Background summary

INC280 is a highly potent and selective cMET inhibitor in biochemical and cellular assays and capable of blocking cMET activation.
Erlotinib is an approved EGFR tyrosine kinase inhibitor (TKI).
Currently approved EGFR TKIs are effective in activated EGFR mutant non-small cell lung cancer (NSCLC), however nearly all patients develop resistance, and platinum-based chemotherapy is considered standard of care after failure of first line EGFR TKI.
An important mechanism of acquired resistance to EGFR TKIs in NSCLC is cMET amplification that accounts for approximately 15-20% of cases and is mutually exclusive with the EGFRT790M mutation.
Overall, preclinical and clinical data suggests that INC280 in combination with an EGFR TKI may have a favorable benefit-risk ratio for the treatment of cMET-amplified, EGFR mutated and known to be associated with EGFR TKI drug sensitivity (L858R and/or ex19del), EGFRT790M negative, locally advanced or metastatic NSCLC with acquired resistance to prior EGFR TKI. This study aims to further explore the benefit-risk ratio of the combination of INC280 tablet formulation with erlotinib in this patient population.
This study has two parts:
* a dose escalation part (part 1, phase Ib) in order to determine the maximum tolerated dose (MTD) or recommended phase II dose (RP2D) of the combination of INC280 and (fixed-dose) erlotinib.
* A dose expansion part (part 2, phase 2) in order to assess safety and efficacy of this part 1 dose in comparison with INC280 alone and standard chemotherapy of platinum plus pemetrexed.
The Netherlands will only participate in part 2. This ABR-form will therefore only address part 2.

Study objective

Primary phase 1: To determine MTD and/or RP2D of INC280 in combination with erlotinib

Primary phase 2:
To compare the antitumor activity of INC280 alone, and INC280 in combination with erlotinib, vs platinum with pemetrexed, as measured by Progression Free Survival (PFS) per investigator*s assessment
Secondary:
Duration of response (DOR), overall response rate (ORR), disease control rate (DCR), overall survival (OS), safety and tolerability, PK profiles.

Study design

Multicenter phase I/II open-label study. Prescreening for CMET amplification and EGFRT790M mutation.

Phase I: INC280 tablets until MTD or RP2D BID plus erlotinib 150 mg QD.

Continuous dosing.
Treatment period until disease progression or unacceptable side effects.
Follow-up for survival (and if relevant for disease progression).
Approx. 15 patients.

Phase II: Randomization (1:1:1) to treatment with
* INC280 tablets 400 mg BID. Continuous dosing.
* INC280 tablets MTD or RP2D BID plus erlotinib 150 mg QD. Continuous dosing.
* Pemetrexed 500 mg/m2 plus (investigator*s choice) cisplatin 75 mg/m2 or carboplatin AUC 5 or 6. On day 1 of up to 6 cycles.
Cycles of 3 weeks.
Treatment period until disease progression or unacceptable side effects.
Follow-up for survival (and if relevant for disease progression).
Approx. 120 patients.

Intervention

Phase I: INC280 plus erlotinib or chemotherapy

Phase II: Treatment with INC280 alone, INC280 plus erlotinib or chemotherapy with platinum and pemetrexed.

Study burden and risks

Risk: Adverse effects of INC280, INC280 plus erlotinib or standard chemotherapy.
Burden: Cycles of 3 weeks. Cycle 1-2: 3 visits, cycle 3 onwards 1 visit.
Duration mostly 1-4 hours. Day 1 and 15 of cycle 1 take 8 hour with an additional visit 24 hour later (only phase 1)
Up to 6 cycles with i.v. chemotherapy in one of the arms. However chemotherapy is currently the standard treatment (only in phase 2)
Physical examination: Once per cycle.
Blood tests (5-25 ml/occasion): Once per cycle (cycle 1 twice). PK on 3 occasions (2 samples in 2 h twice, one sample once). Day 1 and 15 of cycle 1 have 7 samples with an additional sample 24 hour later (only phase 1)

Pregnancy test (if relevant): at screening and end of treatment (blood mandatory) plus once per cycle (urine or blood).
Urine test once.
ECG: 5 visits in total.
CT-/MRI-scan: every 6 weeks.
Optional tumor biopsies: 2.
Optional storage and use of the remaining blood and tissue for future research.

Contacts

Public
Novartis

Raapopseweg 1
Arnhem 6824 DP
NL
Scientific
Novartis

Raapopseweg 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

* * 18 years of age.
* Stage IIIB or IV NSCLC other than predominantly squamous cell histology, harboring EGFR mutation exon 19 deletion or L858R.
* Acquired resistance to EGFR TKI of the 1st or 2nd generation. See protocol page 15 for details.
* One prior line of treatment is defined as:
o Only one prior line of 1st or 2nd generation EGFR TKI for the treatment of locally advanced or metastatic NSCLC
o No prior chemotherapy is allowed. Exceptions: see protocol page 15 for details.
* Molecular pre-screening assessment:
o cMET-amplification (GCN * 6) on a newly obtained tumor biopsy (preferred) or an archival tumor sample obtained at or any time after the progression on prior 1st or 2nd generation

EGFR TKI.
o EGFRT790M negative status assessed from a biopsy or an archival tumor sample collected after the progression on prior 1st or 2nd generation EGFR TKI.
* Presence of at least one measurable lesion. See protocol page 15 for details.
* ECOG performance status 0 or 1.
* Life expectancy at least 3 months.

Exclusion criteria

* Prior treatment with crizotinib, or any other cMET or HGF inhibitor, concomitant EGFR TKI and platinum based chemotherapy or platinum-based as first line regimen.
* Prior treatment with any 3rd generation EGFR TKI.
* Symptomatic CNS metastases.
* Presence or history of interstitial lung disease or interstitial pneumonitis.
* Presence of clinically significant ophthalmologic abnormalities.
* Clinically significant, uncontrolled heart diseases. See protocol page 44 for details.
* Strong inhibitors of CYP3A4, moderate and strong inducers of CYP3A4, strong inhibitors or inducers of CYP1A2, proton pump inhibitors within 1 week prior to the start of INC280 and during treatment.
* Pregnancy, lactation, insufficient contraception for females of childbearing potential.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	26-01-2016
Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Alimta
Generic name:	Pemetrexed
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Carboplatin
Generic name:	Carboplatin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Cisplatin
Generic name:	Cisplatin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	INC280
Generic name:	capmatinib
Product type:	Medicine
Brand name:	Tarceva
Generic name:	Erlotinib
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	29-09-2015
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	01-12-2015
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO	

Date:	07-01-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	12-01-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	26-01-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	12-02-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	25-05-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	15-07-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	10-01-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	11-05-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van

	Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	19-10-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	27-10-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

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
Other	clinicaltrials.gov; NCT02468661
EudraCT	EUCTR2015-001241-84-NL
CCMO	NL54344.031.15