An open-label, multi-center, phase I, dose finding study of oral TNO155 in adult patients with advanced solid tumors

Published: 18-01-2017
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This study has been transitioned to CTIS with ID 2023-508925-29-00 check the CTIS register for the current data. Primary: To characterize safety and tolerability of TNO155 and identify a recommended dose and regimen for future studies in adult...

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

Summary

ID

NL-OMON54714

Source
ToetsingOnline

Brief title
CTNO155X2101

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
head- and neckcancer and other solid tumors, Luncancer

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Head and Neck Cancer, Non-small Cell Lung Cancer, Solid tumor, Tyrosine kinase

Outcome measures

Primary outcome

Adverse effects. DLTs, dose interruptions/reductions.

Secondary outcome

Overall response rate, disease control rate, duration of response, progression

free survival, PK, changes from baseline of PD markers.

Study description

Background summary

Direct targeting of aberrantly activated RTKs (Receptor Tyrosine Kinase) leads to disease control in many human malignancies, but in advanced malignancies resistance to such therapies invariably occurs. In addition, some solid tumors harbor alterations in several different RTK signaling pathways, potentially limiting the efficacy of targeting any single RTK.

Targeting SHP2 (src-homology phosphatase 2) with TNO155 in advanced malignancies that are dependent upon RTK signaling is expected to result in anti-tumor efficacy; even in cases in which the oncogenic driver RTK has acquired a resistance mutation to a therapy as well as in cases in which the tumor is driven by multiple different RTK pathways. However, given the position of SHP2 in RTK signaling, upstream of RAS and BRAF, single agent TNO155 is not expected to have significant anti-tumor efficacy in malignancies driven by activating mutations in RAS molecules or BRAF.

The purpose of this Phase I study is to determine the maximum tolerated dose (MTD) and recommended dose (RD) and schedule of TNO155 monotherapy and combination therapy with TNO155 and nazartinib. And to evaluate the preliminary anti-tumor activity of TNO155 monotherapy and TNO155 and nazartinib combination

therapy in patients with advanced EGFR-mutant non-small cell lung cancer only and for patients with head and neck squamous cell carcinoma, gastrointestinal stromal tumor, or other advanced solid malignancies lacking activating RAS or BRAF mutations for TNO55 monotherapy.

Study objective

This study has been transitioned to CTIS with ID 2023-508925-29-00 check the CTIS register for the current data.

Primary:
To characterize safety and tolerability of TNO155 and identify a recommended dose and regimen for future studies in adult patients with advanced solid tumors. And a recommended dose of TNO155 in combination with nazartinib in patients with NSCLC with EGFR mutation.

Secondary:
Preliminary anti-tumor activity, pharmacokinetic profile, pharmacodynamic profile.

Study design

Multicenter phase I open-label dose finding study with a dose escalation part and a dose expansion part. Treatment with oral TNO155 possibly in combination with nazartinib until disease progression or unacceptable toxicity.
total number of patients worldwide: 255

Intervention

Treatment with oral TNO155 monotherapy or nazartinib in combination with TNO155. Several dosing schedule will be examined.

Study burden and risks

RISKS
Adverse effects of TNO155 and/or nazartinib and risks associated with the assessmetns as CT-scans - blood draw, tumor biopsy and skin biopsy.

BURDEN:
Visits: Cycles of 3 or 4 weeks. Cycle 1: 6 visits, cycle 2: 2 visits, thereafter 1 visit per cycle. Duration mostly 1-4 hours.
Physical examination: once per cycle.
Blood tests (15 ml/occasion, during dose escalation part occasionally fasting): every cycle (cycle 1: 4 times). Extra blood draws for PK (in total 50 ml) and biomarkers (in total 50 ml).
Urine testing during screening.

Pregnancy test: every cycle.
ECG: once per cycle (cycle 1: 4 times).
CT-/MRI scan: baseline, every 8 weeks thereafter.
MUGA scan (or echocardiography): during screening, once during cycle 1, twice during cycle 2 and onze during cycles 3, 4, 6 and 8. Thereafter every 3rd cycle.
Eye examinations (incl. OCT and fundoscopy with dilatation of the pupil): at the start and end of treatment.
3 tumor biopsies (incl. prescreening), 1 optional biopsy.
Food effect substudy in subset of subjects (20 ml extra blood in total, during dose expansion part only.

Contacts

Public
Novartis

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Scientific
Novartis

Haaksbergweg 16
Amsterdam 1101 BX
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1. >=18 years of age.

2. Site of disease amenable to biopsy.
3. ECOG performance status 0, 1, 2.
4. Presence of at least one measurable lesion (RECIST v1.1).
5. Dose escalation part:
• Advanced NSCLC (harbouring an activating EGFR mutation), advanced HNSCC, advanced GIST,KRASG12C mutant NSCLC, advanced oesophagol SCC and NRAS/BRAF WT melanoma who progressed after Standard of Care (SoC) or for whom no effective therapy exists) See protocol page 49 for details.
6. Dose expansion part:
• Group 1: advanced RAS/BRAF wild type NSCLC.
• Group 2: advanced RAS/BRAF wild type HNSCC.
• Group 3: advanced RAS/BRAF wild type other malignancies with RTK-dependency. Patients with NSCLC or HNSCC must have progressed on or after (or intolerant to), platinum-containing combination therapy.
• Group 4: advanced RAS/BRAF WT other solid malignancy (excl CRC), after progression on standard of care. Patients with NSCLC or HNSCC must have progressed on or after (or intolerant to), platinum-containing combination therapy.
For the first 4 groups the requirement for HRAS mutation testing may be waived following
documented discussion with Novartis when local testing for HRAS mutations is not feasible.
Group 5: Advanced KRAS G12C-mutant NSCLC, after progression on or after, or intolerance to SOC,
Group 6: advanced NRAS/BRAF WT melanoma, after progression on or after or intolerance to SOC immuno-oncologic therapy.
See protocol page 49-50 for more details.

Exclusion criteria

1. Tumors harbouring known activating KRAS, NRAS, HRAS, BRAF, or PTPN11 (SHP2) mutations, with the exception of KRAS G12C-mutant CRC in dose escalation and KRAS
G12C-mutant NSCLC in dose expansion.
2. Prior and concomitant anti-cancer therapies as radiotherapy, surgery, immunotherapy, cytotoxic agents, chemotherapy within half-live timelines as described in protocol page 38.
2A. No resolution of all clinically significant toxicity on prior systemicanti-cancer therapy (except where otherwise stated in the protocol and alopecia).
2B. Malignant disease, other than that being treated in this study. Exceptions to this exclusion
include the following: malignancies that were treated curatively and have not recurred within 2 years prior to study treatment; completely resected basal cell and squamous cell skin cancers;
3. History or current evidence of retinal vein occlusion (RVO) or current risk

factors for RVO.
4. Ongoing active diarrhoea requiring medication.
5. All primary central nervous system (CNS) tumors or symptomatic CNS metastases which are neurologically unstable or requiring increasing doses of steroids within the 4 weeks prior to study entry. See protocol page 38-39 for more details.
6. Clinically significant cardiac disease e.g. LVEF < 50% (or below institutional standard lower limit), uncontrolled hypertension, presence of significant arrhythmias, QTcF > 450 msec for males and >460 msec for females - See protocol page 39 for details.
7. Treatment with prohibited medication. See protocol appendix 2 for details. .
8. Insufficient bone marrow function, liver and kidney function defined by lab values. See protocol page 39 and 40 for details
9. The following labvalues must be within the lab normal ranges of the institution (and cannot be corrected with supplements): Potassium - magnesium - phosphorus - total calcium - fasting glucose
10. Pregnancy, lactation, insufficient contraception for females of childbearing potential. Males not using a condom.
11. Use of any live or live attenuated vaccines against infectious diseases within 4 weeks
prior to study treatment initiation.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	29-06-2017
Enrollment:	33
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	nvt
Generic name:	nazartinib

Ethics review

Approved WMO Date:	18-01-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-03-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	03-04-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-04-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-10-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-10-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	06-03-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-03-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-07-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-07-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-10-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-10-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-11-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-12-2018
Application type:	Amendment

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-04-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-05-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	31-12-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-01-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-04-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-07-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-12-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	18-03-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-04-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-05-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-10-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-10-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-02-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-03-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-04-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek

	(Assen)
Approved WMO Date:	23-07-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-08-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-10-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-01-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-01-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-07-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-07-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-12-2023

Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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
EU-CTR	CTIS2023-508925-29-00
EudraCT	EUCTR2016-001861-10-NL
ClinicalTrials.gov	NCT03114319
CCMO	NL60195.056.16