A Phase I/II Study with NAMI-A a Novel Ruthenium Anticancer Agent, and Gemcitabine Combination Second-Line Therapy in NSCLC Patients

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The primary objectives of the study are:- to establish the optimal dose of the combination for second-line therapy with NAMI-A and Gemcitabine (Phase I part)- to assess the response rate according to RECIST criteria (Phase II part) in advanced NSCLC...

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

Summary

ID

NL-OMON31433

Source
ToetsingOnline

Brief title
NRA study

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

Synonym
advanced NSCLC

Research involving
Human

Sponsors and support

Primary sponsor: Universita degli Studi di Trieste

Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Gemcitabine, NAMI-A, NSCLC., second line

Outcome measures

Primary outcome

To establish the optimal dose of the combination for second-line therapy with

NAMI-A and Gemcitabine (Phase I part) and

to assess the response rate according to RECIST criteria (Phase II part) in

advanced NSCLC and

to determine the profile of adverse events (both Phase I and Phase II part).

Secondary outcome

to assess the time to disease progression.

Study description

Background summary

Preclinical pharmacological studies with NAMI-A showed selective activity against lung metastases of murine tumors (7, 8, 13, 15) and a relatively low toxicity in mice and dogs (10, 16, 17). Preclinical toxicological studies revealed primarily alteration of kidney, liver, and gastrointestinal function (17).

For first-line treatment of advanced NSCLC patients with a good performance status, the accepted standard of care is a platinum agent combined with gemcitabine, docetaxel, paclitaxel, vinorelbine or irinotecan (19).

In a preclinical study the toxicity of NAMI-A administered in combination with Gemcitabine was characterized. NAMI-A was administered once a week for three weeks and Gemcitabine was administered the day after NAMI-A administration once a week for three weeks. Both NAMI-A and Gemcitabine were admistered by intravenous route in mouse and a dose level free of toxicity under these conditions was established. Two dose levels of NAMI-A were evaluated (35 mg/kg

and 90 mg/kg) in combination with a single dose level of Gemcitabine (200 mg/kg). The effect of this association on body weight, haematological parameters, clinical chemistry, absolute organ weight, relative organ weight, organ histopathology and mortality were studied. Under these experimental conditions, the drug combination was well tolerated at both dose levels even if NAMI- A 35 mg/kg and Gemcitabine 200 mg/kg appeared not to be effective with respect to histopathology analysis (20).

As NAMI-A has an important activity against lung metastases formation and growth in different kind of induced solid tumor in mice, we may hypothesize that the administration of NAMI-A in combination with Gemcitabine could have a great therapeutic effect against NSCLC. This tumor has shown to have a high rate of metastasis. NAMI-A could inhibit metastasis formation and growth. It is very interesting that this activity was reported to be independent on both the type of primary tumor and the stage of growth of the metastasis (7, 8, 9) in preclinical studies. For this reason patients bearing NSCLC at late stages could be putative to be treated with this drug association.

Study objective

The primary objectives of the study are:
- to establish the optimal dose of the combination for second-line therapy with NAMI-A and Gemcitabine (Phase I part)
- to assess the response rate according to RECIST criteria (Phase II part) in advanced NSCLC
- to determine the profile of adverse events (both Phase I and Phase II part)

- to establish the pharmacokinetic profile of the combination of NAMI-A and gemcitabine

The secondary objective of the study is:
- to assess the time to disease progression

Study design

The study is designed in two stages:Stage AAll eligible patients will be treated with the combination of NAMI-A and Gemcitabine. This part of the study aims to establish the best tolerated dose of the combination therapy. Stage BStage B will be performed only if the combination therapy assessed in stage A will be well tolerated. This part of the study aims to collect activity data (response rate, time to disease progression) and further information about the profile of adverse events.

Intervention

NAMI-A will be administered at day 1, 8 and 15 while Gemcitabine will be administered at day 2, 9 and 16, for a 28-day cycle up to progressive disease or intolerance or patient refusal to continue therapy.
The dose levels of NAMI-A will be 300, 450, 600 and 750 mg/m2. Therapy will be administered as an i.v. infusion over 3h.
Gemcitabine will be administered at the dose of 1000 mg/m2. Therapy will be administered as an i.v. infusion over 30 min

Study burden and risks

The toxicity of different doses of NAMI-A was studied in a phase I clinical trial in the Netherlands Cancer Institute (reached dose: 500 mg/m2/day) (18). The results from this study showed that NAMI-A was in general well tolerated when administered as an intravenous infusion over three hours for 5 days every three weeks. Main toxicities, possibly or probably related to study medication, were phlebitis, hypersensivity reactions and the formation of blisters.
On the basis of this study, we aim to investigate four possible treatment groups: NAMI-A administered at the dose of 300, 450, 600 and 750 mg/m2, once a week for 3 weeks in a 28-days cycle up to progressive disease or intolerance or patient refusal to continue therapy.
The safety profile of Gemcitabine is known. The risks associated with th estudy procedures are low. For most people, needle punctures for blood samples do not cause any serious problems. However, this procedure may cause bleeding, bruising, discomfort, infections and or pain at the needle site.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Inclusion Criteria:
- age >= 18 years
- documented diagnosis of advanced NSCLC
- presence of metastases (M1 or higher)
- previous treatment with cisplatin or carboplatin
- previous anticancer chemotherapy discontinued for at least 4 weeks before entry into the study
- radiotherapy discontinued for at least 4 weeks
- WHO performance status of 0-2
- Adequate renal function (creatinine £ 120 uM or creatinine clearance > 50 mL/min calculated by Cockcroft Gault formula) and adequate hepatic function (total bilirubin <= 25 mM, AST and ALT less or equal to twice normal upper limit, but in case of liver metastases these values have to be <= 5 times the normal upper limit)
- Life expectancy of at least 16 weeks, necessary to cover 3 courses of treatment and 4 weeks of follow-up
- Written informed consent

Exclusion criteria

Exclusion criteria:- Breast feeding or pregnancy or inadequate use of contraception- concomitant acute infection or inflammatory disease (e.g. rheumatoid arthritis)- clinical evidence of hearing loss (>=CTC grade 2) - prior treatment with ruthenium complexes- current participation in other clinical trials in oncology

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	31-07-2008
Enrollment:	45
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Gemzar
Generic name:	Gemcitabine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Nami-A
Generic name:	na

Ethics review

Approved WMO Date:	15-10-2007
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	19-05-2008
Application type:	First submission

Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	09-10-2008
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	25-02-2010
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	19-05-2010
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
EudraCT	EUCTR2007-004996-20-NL
CCMO	NL19999.031.07