# NGR015: Randomised double-blind phase III study of NGR-hTNF plus best investigator's choice (BIC) versus placebo plus BIC in previously treated patients with advanced malignant pleural mesothelioma (MPM)

Published: 13-12-2011
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Primary:• To compare overall survival (OS) in patientsrandomized to NGR-hTNF plus BIC versuspatients randomized to placebo plus BICSecondary:• To compare progression-free survival (PFS)• To compare disease control rate (DCR, defined asthe percentage...

| | |
|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Mesotheliomas |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON37673

**Source**
ToetsingOnline

**Brief title**
NGR015

### Condition

- Mesotheliomas

**Synonym**
Pleural Tumor / advanced malignant pleural mesothelioma

**Research involving**

Human

## Sponsors and support

**Primary sponsor:** COMPANY IS INNOPHARMA S.R.L, ITALY
**Source(s) of monetary or material Support:** MolMed S.p.A.

## Intervention

**Keyword:** malignant pleural mesothelioma

## Outcome measures

### Primary outcome

Primary variable:

• Overall Survival (OS) is defined as the time from the

date of randomization until the date of death due to any

cause.

### Secondary outcome

Secondary variables:

• Progression-free survival (PFS) is defined as the time

from the date of randomization until disease

progression, or death due to any cause.

• Disease control rate (DCR) is defined as the percentage

of patients who have a best-response rating of

complete response, partial response, or stable disease.

The tumor thickness perpendicular to the chest wall or

mediastinum will be assessed according to modified

RECIST criteria for MPM. All other measurable

lesions will be measured unidimensionally as per

standard RECIST criteria.

• Complete remission (CR): Disappearance of all target lesions. Any pathological lymph nodes must have reduction in short axis to <10 mm.

• Partial remission (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

• Stable Disease (SD): neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest sum diameters while on study.

• Progressive disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

• Duration of disease control: In the subset of patients who achieve disease control, the duration of disease control will be measured from the date of randomization until disease progression, or death due

to any cause.

# Study description

**Background summary**

Tumor Necrosis Factor (TNF) was first identified by Carswell et al. in the serum of Bacillus Calmette-Guerin sensitized animals, treated with an endotoxin which caused the release of a factor able to induce hemorrhagic necrosis of murine tumors. Based on these initial findings two distinct molecules have been recognized, TNF-α, produced by macrophages and monocytes, and TNF-β, mainly produced by lymphocytes.1-3
Although TNF-β shows similar, but not identical, biological profile to TNF-α, in general the term TNF refers only to TNF-α and not to TNF-β, considering that the overwhelming majority of reports published to date on the therapeutic use of TNF describe the use of TNF-α.4
In in vitro experiment TNF has been shown to have cytostatic and cytotoxic effects against a wide range of human tumor cells but have no such effects against normal human fibroblast.5 Anti-tumor effects have been demonstrated in both syngeneic murine tumors and human tumor xenografts in nude mice.6 In addiction to the well known cytostatic/cytotoxic properties, TNF has a broad spectrum of immunomodulatory activities.7 Like interferon (INF), TNF has shown antiviral activity and in some cell lines promotes 2-5A synthetase activity, an enzyme that is strongly induced by INFs. 8, 9
Furthermore, TNF enhances the expression of Class I major histocompatibility antigens on human endothelial cells, dermal fibroblasts and human tumor cell lines10,11 and the expression of Class II major histocompatibility antigens on human T cells and tumor cells.12 TNF has been demonstrated to be an effector molecule involved in monocyte cytotoxicity,13,14 a cell-associated molecule able to kill TNF-sensitive target cells on direct contact in the absence of any measurable secreted TNF15 and an enhancer of in vivo and in vitro macrophage tumoricidal activity using

peritoneal exudates
macrophages.16 Like IFN-γ, IFN-β and interleukin-2 (IL-2), TNF increases
urinary neopterin
levels,17 a monocyte product. Moreover, TNF has multiple actions on natural
killer cells, including
an enhancement of HLA-DR antigens, IL-2 receptors and IL-2 effects.18 Finally,
TNF has positive
effects on granulocyte function, including chemotaxis activity19, increased
phagocytosis and
enhanced antibody-dependent cellular cytotoxicity.20,21
TNF exerts its effects by binding to two types of receptor, TNF-R1 and TNF-R2,
which are present
on nearly all mammalians cells and in soluble form in the circulation.22
Several lines of evidence suggest that the anti-tumor activity of TNF depends
on indirect
mechanisms associated with selective obstruction and damage of tumor-associated
blood vessels
and on activation of immune mechanisms rather than a direct toxic effect on
tumor cells.23
Although numerous pre-clinical studies have demonstrated that TNF has notable
anti-tumor
activity,1,6,16,24 early trials in humans showed that its clinical use is
limited by severe systemic
toxicity.5,7,25-27
However, loco-regional therapy by isolated limb perfusion using high doses of
TNF in combination
with chemotherapy led to high response rates in patients with melanoma or
sarcoma of the
extremities,28-30 regression of bulky hepatic cancers confined to the liver31
and peritoneal
carcinomas.32 The clinical results obtained with these treatments indicate that
TNF can induce
tumor regression, provided that high concentrations of the cytokine are
achieved at tumor level.

The coupling of murine TNF (mTNF) with the peptide NGR
(asparagine-glycine-arginine), an aminopeptidase N (CD13) ligand capable of
binding to tumor blood vessels, demonstrated therapeutic properties superior to
those of mTNF in animal
models. Considering a potential therapeutic use, a modified human TNF (hTNF)
containing the
cyclic CNGRC peptide sequence was subsequently prepared using recombinant DNA
techniques.
The resulting NGR-hTNF will enable targeted delivery of TNF to tumor vessels in
humans.

## Study objective

Primary:
• To compare overall survival (OS) in patients randomized to NGR-hTNF plus BIC versus patients randomized to placebo plus BIC
Secondary:
• To compare progression-free survival (PFS)
• To compare disease control rate (DCR, defined as the percentage of patients who have a bestresponse rating of complete or partial response or stable disease, according to MPM-modified RECIST criteria)
• To compare duration of disease control
• To evaluate safety and toxicity profile related to NGR-hTNF
• To assess changes in quality of life (QoL) in the two treatment arms
• To evaluate medical care utilization in the two treatment arms

## Study design

This is a multicenter, double-blind, placebo-controlled, randomized, 2-arm (1:1 ratio), phase III study with a comparison of NGR-hTNF plus BIC versus placebo plus BIC in patients with advanced malignant pleural mesothelioma previously treated with a pemetrexed-based chemotherapy regimen for advanced or metastatic disease. Best investigator*s choice (BIC) includes either best supportive care alone or combined with a single-agent chemotherapy (doxorubicin, gemcitabine, or vinorelbine). Before randomization, the physician has to decide for each patient if he/she is candidate to either best supportive care (BSC) alone or combined with single-agent chemotherapy. Patients will be randomly assigned to the treatment group through a centralized randomization system using the following stratification factors: candidate for chemotherapy (yes vs no and, if yes, for type of chemotherapy ) and ECOG performance status (0 vs 1-2). The experimental group A will receive NGR-hTNF plus the current treatment option (best supportive care with or without single-agent chemotherapy).
The control group B will receive placebo plus the current treatment option (best supportive care with or without single-agent chemotherapy).

Arm A (experimental group = NGR-hTNF + BSC ± single-agent chemotherapy)
• NGR-hTNF: 0.8 µg/m² as 60-minute intravenous infusion every week until confirmed evidence of disease progression.
• Best Supportive Care: where applicable and as appropriate according to Institutional clinical practice and literature guidelines
• Investigator*s Choice: At Investigator discretion, one of the following single-agent chemotherapy might be administered in combination:
a) Doxorubicin: 60-75 mg/m2 iv every 3 weeks, for a maximum of 6 cycles, OR
b) Gemcitabine: 1,000-1,250 mg/m2 iv on days 1 and 8, every 3 weeks, for a maximum of 6 cycles, OR
c) According to results of sub-study:
Vinorelbine: 25mg/m2 iv on days 1 and 8 every 3 weeks, for a maximum of 6 cycles (or weekly for 12 weeks) or, if approved in the Country, 60 mg/m2 per os on days 1 and 8 every 3 weeks for a maximum of 6 cycles (or weekly for 12 weeks).
Arm B (control group = Placebo + BSC ± single-agent chemotherapy)
• Placebo: 0.8 µg/m² as 60-minute intravenous infusion every week until confirmed evidence of disease progression or unacceptable toxicity occurs.
• Best Supportive Care: as above
• Investigator*s Choice: as above.

**Intervention**

The experimental group A will receive NGR-hTNF plus the current treatment option (best supportive care with or without single-agent chemotherapy).
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Arm B (control group = Placebo + BSC ± single-agent chemotherapy)
• Placebo: 0.8 µg/m² as 60-minute intravenous infusion every week until confirmed evidence of disease progression or unacceptable toxicity occurs.
• Best Supportive Care: as above
• Investigator*s Choice: as above.

**Study burden and risks**

At the screening visit patient will be given a full clinical examination, blood will be drawn for laboratory tests and radiological evaluation will be performed to establish the general overall state of health. Other procedures foreseen at screening visit 12-lead electrocardiogram (EKC) and if r treatment will include doxorubicin, echocardiogram or a Multi Gated Acquisition (MUGA) scan.
Patient will be asked to complete a quality of life questionnaire at this visit and after every 6 weeks.
Treatment Phase:
Patient will be and treated once per week, receiving either treatment according to treatment arm A (NGR-hTNF) or treatment arm B (Placebo) for entire study. Before each chemotherapy treatment a blood sample will be taken and also a physical examination is foreseen.
Every 6 weeks a 12-lead EKG and radiological evaluation will be performed. Chemotherapy will be administered for a maximum of 6 cycles, while the treatment with NGR-hTNF/placebo will be continued weekly in monotherapy, until evidence of progressive disease.
Follow up phase:
Every 6 weeks (only before evidence of Progressive Disease): radiological evaluation, collection of information about subsequent anticancer therapies
Every 12 weeks: survival follow up
Benefits
Benefits cannot guarantee the outcome of the treatment, since the effective action of this therapy is not quantifiable at this stage of the study. However, this clinical trial will provide precious indications, thus leading to improvements in treatment and to helping other patients in the future.

Risks
The most common side effect are shivering that in majority of cases cleared up without any treatment and in other cases simply by taking paracetamol. Other common side effects are fever, high blood pressure and fatigue, which occurred in about 10 to 15 of 100 patients as well as feeling cold, nausea, vomiting, headache, low blood pressure and weakness, which occurred in about 2 to 7 of 100 patients.
Since NGR-hTNF is in the clinical development phase, it is not possible to exclude the appearance of other side effects, even unexpected, serious ones. Known toxicities that could occur following the administration of doxorubicin, gemcitabine and vinorelbine, drugs already on the market and widely used in clinical practice in combination treatments, include those of a gastrointestinal (diarrhea, nausea, vomiting and inflammation of the mouth), related to blood (decrease of the number in blood cells, such as the white blood cells and the platelets) and neurological (tingling/loss of sensitivity in the hands, lack of reflexes) nature, changes in kidney and/or liver function, as well as fatigue, reddening of the skin and hair loss.

# Contacts

**Public**
Selecteer

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**Scientific**
Selecteer

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# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

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

## Inclusion criteria

1.Age >= 18 years;
2. Histologically or cytological confirmed malignant pleural mesothelioma of any of the following subtype;
epithelial, sarcomatoid, mixed, or unknown;
3. Prior treatment with no more than one sistemic pemetrexed-based chemotherapy regimen administered;
for advanced or metastatic disease. Prior use of a biological agent in combination with a pemetrexed based;
regimen and prior administration of intrapleural cytotoxic agents are allowed. Patients who have previously received anthracyclines should not receive doxorubicin.;
4. ECOG Performance Status 0 - 2;
5. Life expectancy of >=12 weeks;
6. Adequate baseline bone marrow, hepatic and renal function, defined as follows;
a. Neutrophils >= 1.5 x 109/L; platelets >= 100 x 109/L; hemoglobin >= 9 g/dL;
b. Bilirubin <= 1.5 x ULN;
c. AST and/or ALT <= 2.5 x ULN in absence of liver metastasis or <= 5 x ULN in presence of liver metastasis;
d. Serum creatinine <1.5 x ULN;
7. Measurable or non-measurable disease according to MPM-modified RECIST criteria;
8. Patients may have had prior therapy providing the following conditions are met:;
a. Surgery: wash-out period of 14 days;
b. Systemic anti-tumor and radiation therapy: wash-out period of 28 days;
9. Patients must give written informed consent to participate in the study;

## Exclusion criteria

1. Patients must not receive any other investigational agents while on study;
2. Patients with myocardial infarction within the last six months, unstable angina, New York Heart association (NYHA) grade II or greater congestive heart failure, or serious cardiac arrhythmia requiring medication;
3. Uncontrolled hypertension;
4. QTc interval (congenital or acquired)> 450 ms;
5. History or evidence upon physical examination of CNS disease unless adequately treated (e.g., primary brain tumor, any brain metastasis, seizure not controlled with standard medical therapy, or history of stroke);
6. Patients with active or uncontrolled systemic disease/infections or with serious illness or

medical conditions, which is incompatible with the protocol;
7. Known hypersensitivity/allergic reaction to human albumin preparations or to any of the excipients;
8. Any psychological, familial, sociological or geographical condition potentially tampering compliance with the study protocol;
9. Pregnancy or lactation.

# Study design

## Design

| | |
|---|---|
| Study phase: | 3 |
| Study type: | Interventional |
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |
| Masking: | Double blinded (masking used) |
| Control: | Placebo |
| Primary purpose: | Treatment |

## Recruitment

NL

| | |
|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 21-06-2012 |
| Enrollment: | 45 |
| Type: | Actual |

## Medical products/devices used

| | |
|---|---|
| Product type: | Medicine |
| Brand name: | MolMed |
| Generic name: | NGR-hTNF / Placebo |

# Ethics review

Approved WMO

| | |
|---|---|
| Date: | 13-12-2011 |

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|---|---|
| Application type: | First submission |
| Review commission: | MEC-U: Medical Research Ethics Committees United (Nieuwegein) |
| Approved WMO Date: | 08-06-2012 |
| Application type: | First submission |
| Review commission: | MEC-U: Medical Research Ethics Committees United (Nieuwegein) |
| Approved WMO Date: | 18-10-2012 |
| Application type: | Amendment |
| Review commission: | MEC-U: Medical Research Ethics Committees United (Nieuwegein) |
| Approved WMO Date: | 26-10-2012 |
| Application type: | Amendment |
| Review commission: | MEC-U: Medical Research Ethics Committees United (Nieuwegein) |

# 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 | EUCTR2009-016879-29-NL |
| ClinicalTrials.gov | NCT01098266 |
| CCMO | NL38729.100.11 |