Clinical trial results:
NGR007: A phase II study of NGR-hTNF administered in combination with doxorubicin every 3 weeks in patients affected by advanced or metastatic small cell lung carcinoma (SCLC) previously treated with at least one therapeutic regimen.

Summary

EudraCT number	2006-005700-14
Trial protocol	IT
Global end of trial date	18 November 2015

Results information

Result version number	v1 (current)
This version publication date	05 May 2019
First version publication date	05 May 2019

Trial information

Trial identification

Sponsor protocol code	NGR007

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00483509
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	MolMed S.p.A.
Sponsor organisation address	Via Olgettina, 58, Milano, Italy, 20132
Public contact	Clinical Operations, MolMed S.p.A., 0039 02212771, clinical.operations@molmed.com
Scientific contact	Clinical Operations, MolMed S.p.A., 0039 02212771, clinical.operations@molmed.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	05 December 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 November 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Antitumour activity defined as progression free survival (PFS).

Protection of trial subjects:

The responsible investigator will ensure that this study is conducted in full conformance with either the principles of the "Declaration of Helsinki" (as amended in Tokyo, Venice, Hong Kong, South Africa and Edinburgh) or the laws and regulations of the country in which the study was conducted, whichever affords the greater protection to the individual.
The protocol has been written and the study will be conducted in conformity to the "Guideline for Good Clinical Practice" (recommended for adoption at step 4 of the ICH process on 1 May 1996 and on 10 June 1996 by the ICH Steering Committee and acknowledged as ministerial decree, on 15 July 1997, by the Italian Ministry of Health).
The study descriptions were submitted to the IEC before study start.
All patient received all the information about the study and they gave their written acceptance through informed consent signature.
Sponsor provided a full insurance coverage. All personal data complied with local law for privacy protection. All data recorded has been coded.

Background therapy:

Patients previously treated with at least one therapeutic regimen (including treatment with doxorubicin, radiotherapy, chemotherapy).

Evidence for comparator: -

Actual start date of recruitment	14 February 2007
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 28
Worldwide total number of subjects	28
EEA total number of subjects	28

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0

Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	16
From 65 to 84 years	12
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study period: 14 February 2007 (first enrollment); 17 May 2011 (LPLV). Between 14 February 2007 and 16 October 2007, 9 patients had previously been enrolled and treated with NGR-hTNF in monotherapy. Due to lack of monotherapy efficacy, this patient cohort was closed to accrual (data presented for descriptive purpose only). 5 clinical sites in Italy

Pre-assignment

Screening details:

Planned sample size: 27 patients; Patients screened n.: 28; Patients screening failure n.: 0.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	NGR-hTNF plus doxorubicin

Arm description:

Patients will receive NGR-hTNF at dose of 0.8 µg/m² by a 60 minutes iv infusion in combination with doxorubicin 75 mg/m2 as slow infusion of 15 minutes starting 60 minutes after the end of NGR-hTNF infusion, every 3 weeks.

Arm type	Experimental
Investigational medicinal product name	NGR-hTNF
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients will receive NGR-hTNF at dose of 0.8 µg/m² by a 60 minutes iv infusion, every 3 weeks. Before infusion to patients, NGR-hTNF in phosphate buffered saline (PBS) will be diluted to the appropriate concentration with 0.9% NaCl containing human serum albumin (HSA).

Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Doxorubicin 75 mg/m2 will be administrated as slow infusion of 15 minutes starting 60 minutes after the end of NGR-hTNF infusion

Number of subjects in period 1	NGR-hTNF plus doxorubicin
Started	28
Completed	28

Baseline characteristics

Reporting groups	
Reporting group title	NGR-hTNF plus doxorubicin
Reporting group description:	
Patients will receive NGR-hTNF at dose of 0.8 µg/m² by a 60 minutes iv infusion in combination with doxorubicin 75 mg/m2 as slow infusion of 15 minutes starting 60 minutes after the end of NGR-hTNF infusion, every 3 weeks.	

Reporting group values	NGR-hTNF plus doxorubicin	Total	
Number of subjects	28	28	
Age categorical			
Patients >18 years affected by SCLC previously treated with at least one therapeutic regimen (including doxorubicin).			
Units: Subjects			
Adults (18-64 years)	16	16	
From 65-84 years	12	12	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	62.5		
full range (min-max)	41.0 to 76.0	-	
Gender categorical			
Units: Subjects			
Female	9	9	
Male	19	19	

End points

End points reporting groups

Reporting group title	NGR-hTNF plus doxorubicin

Reporting group description:

Patients will receive NGR-hTNF at dose of 0.8 µg/m² by a 60 minutes iv infusion in combination with doxorubicin 75 mg/m2 as slow infusion of 15 minutes starting 60 minutes after the end of NGR-hTNF infusion, every 3 weeks.

Primary: progression free survival (PFS)

End point title	progression free survival (PFS)[1]

End point description:

Progression-free survival was defined as the time from the baseline CT scan to the first observation of disease progression, or death due to any cause, whichever occurred earlier, or the last date the patient was known to be progression free and alive. The proportion of Progression Free survivors at 18 weeks, will be computed on all registered patients, on
an ITT basis.

End point type	Primary

End point timeframe:

Progression free survival (PFS) at 18 weeks.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This is a single-arm study therefore a "comparison group" is not applicable. The PFS at 18 weeks, was computed on all registered patients, on an ITT basis. Kaplan-Meier curve of PFS, defined as the time from the baseline CT scan until the first observation of disease progression, or death due to any cause, whichever occurred earlier, or the last date the patient was known to be progression free or alive, was provided for descriptive purposes

End point values	NGR-hTNF plus doxorubicin			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: months	13			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Serious Adverse Events (SAE), related or not to the protocol treatment, occurring during the trial and within 30 days after the last treatment administration, were reported by MolMed S.p.A. within 24 hours of the initial observation of the event.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22

Reporting groups

Reporting group title	NGR-hTNF plus Doxorubicin

Reporting group description: -

Serious adverse events	NGR-hTNF plus Doxorubicin		
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 28 (25.00%)		
number of deaths (all causes)	28		
number of deaths resulting from adverse events			
Nervous system disorders			
Seizure			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Anaemia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

General disorders and administration site conditions			
Infectious fever	Additional description: Pirexia		
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Mucosal Inflammation	Additional description: Mucositis		
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Enteritis			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Stomatitis	Additional description: Oral mucositis		
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism	Additional description: Bilateral Acute Pulmonary Embolism		
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Muscular weakness	Additional description: Inferior Leg Hypostenia		
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Wound infection	Additional description: Wound Infection With Grade 4 Neutropenia		
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia	Additional description: Bilateral Pneumonia		

subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	NGR-hTNF plus Doxorubicin		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 28 (100.00%)		
Vascular disorders			
Flushing			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Hypertension			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Hypotension			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Phlebitis			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	5 / 28 (17.86%)		
occurrences (all)	6		
Chills			
subjects affected / exposed	15 / 28 (53.57%)		
occurrences (all)	20		
Extravasation			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	13 / 28 (46.43%)		
occurrences (all)	14		

Feeling cold			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	3		
Injection site pain			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Injection site reaction			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Mucosal inflammation			
subjects affected / exposed	6 / 28 (21.43%)		
occurrences (all)	9		
Oedema peripheral			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	8 / 28 (28.57%)		
occurrences (all)	8		
Wound infection			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 28 (14.29%)		
occurrences (all)	4		
Dyspnoea			
subjects affected / exposed	5 / 28 (17.86%)		
occurrences (all)	6		
Hiccups			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Hypoxia			

subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Increased bronchial secretion			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Pulmonary embolism			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Rhinorrhoea			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Psychiatric disorders			
Confusional state			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Depression			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Insomnia			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Blood bilirubin increased			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Blood uric acid increased			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	2		
Electrocardiogram abnormal			

subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Injury, poisoning and procedural complications			
Allergic transfusion reaction			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Injury			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Cardiac disorders			
Aortic valve incompetence			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Aortic valve sclerosis			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Atrial fibrillation			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Atrial hypertrophy			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Bundle branch block bilateral			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Bundle branch block right			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Mitral valve incompetence			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Pericardial effusion			

subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Sinus tachycardia			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	3		
Nervous system disorders			
Convulsion			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Dizziness			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Headache			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Hypotonia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Paraesthesia			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	3		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	16 / 28 (57.14%)		
occurrences (all)	17		
Febrile neutropenia			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Leukopenia			
subjects affected / exposed	18 / 28 (64.29%)		
occurrences (all)	42		
Lymphopenia			
subjects affected / exposed	12 / 28 (42.86%)		
occurrences (all)	15		
Neutropenia			

subjects affected / exposed	17 / 28 (60.71%)		
occurrences (all)	38		
Thrombocytopenia			
subjects affected / exposed	10 / 28 (35.71%)		
occurrences (all)	20		
Eye disorders			
Conjunctivitis			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	4		
Eyelid ptosis			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	5 / 28 (17.86%)		
occurrences (all)	5		
Diarrhoea			
subjects affected / exposed	4 / 28 (14.29%)		
occurrences (all)	7		
Enteritis			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Gastritis			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Glossodynia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	12 / 28 (42.86%)		
occurrences (all)	14		
Regurgitation			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Vomiting			

subjects affected / exposed	5 / 28 (17.86%)		
occurrences (all)	8		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	3		
Dry skin			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	3		
Nail disorder			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Pruritus			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	5		
Skin exfoliation			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	3		
Skin hyperpigmentation			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Bone pain			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Monarthritis			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Neck pain			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Osteoarthritis			

subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Oral candidiasis			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Pneumonia			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Respiratory tract infection			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	3		
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	10 / 28 (35.71%)		
occurrences (all)	11		
Hyperuricaemia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Hypocalcaemia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Hypokalaemia			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Hyponatraemia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Metabolic acidosis			

subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 July 2007	- The treatment with NGR-hTNF in monotherapy was replaced by the combination of NGR-hTNF plus doxorubicin. - The collection and analysis of Circulating tumor cells (CTCs) and circulating endothelial cells (CECs) was suspended. - Evaluation of adaptative immune response was deleted.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported