Clinical trial results:
NGR012: A phase II study of NGR-hTNF administered in combination with doxorubicin every 3 weeks in patients affected by advanced or metastatic ovarian cancer

Summary

EudraCT number	2007-000004-33
Trial protocol	IT
Global end of trial date	17 December 2015

Results information

Result version number	v1 (current)
This version publication date	26 January 2020
First version publication date	26 January 2020

Trial information

Trial identification

Sponsor protocol code	NGR012

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	MolMed S.p.A.
Sponsor organisation address	Via Olgettina, 58, Milan, Italy, 20132
Public contact	MolMed S.p.A., Clinical Development, 0039 0221277234, clinical.operations@molmed.com
Scientific contact	MolMed S.p.A., Clinical Development, 0039 0221277234, 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	12 December 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 December 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Antitumor activity defined as response rate according to RECIST criteria

Protection of trial subjects:

The study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki. The study was performed in compliance with Good Clinical Practices (CPMP/ICH/135/95), and the essential documents are archived as required by the applicable regulatory requirements. The study and any amendments were reviewed by an Independent Ethics Committees or Institutional Review Boards.

Background therapy:

Patients affected by advanced or metastatic ovarian cancer previously treated with platinum regimens (cis or carboplatin) plus paclitaxel and with documented progression disease within 6 months from last chemotherapy administered (refractory/resistant population) or in progression disease after 6 months from last chemotherapy (platinum regimens plus paclitaxel) administered.

Evidence for comparator:

-

Actual start date of recruitment	01 December 2008
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: 37
Worldwide total number of subjects	37
EEA total number of subjects	37

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)	17
From 65 to 84 years	20
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study period: First patient enrolled: 01 December 2008; Last patient completed: 17 December 2015; Study centres: 2 investigational study sites in Italy.

Pre-assignment

Screening details:

Totally 37 consented and screened patients received at least one dose of study medication and were included in the Safety population (SAF set).

Period 1

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

Arms

Arm title	NGR-hTNF + doxorubicin

Arm description:

Patients received 60 minutes intravenous NGR-hTNF infusion every 3 weeks at dose of 0.8 µg/m2 before of a dose of doxorubicin 60 mg/m2 as 15 minutes infusion. At reaching of a cumulative dose of doxorubicin of 550 mg/m2, a continuation of treatment (if patient was showing an objective response or is in stable disease) with single agent NGR-hTNF at dose of 0.8 µg/m2 every 3 weeks was allowed.

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 received 60 minutes intravenous NGR-hTNF infusion every 3 weeks at dose of 0.8 µg/m2 before of a dose of doxorubicin 60 mg/m2 as 15 minutes infusion. At reaching of a cumulative dose of doxorubicin of 550 mg/m2, a continuation of treatment (if patient was showing an objective response or is in stable disease) with single agent NGR-hTNF at dose of 0.8 µg/m2 every 3 weeks was allowed.

Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients received 60 minutes intravenous NGR-hTNF infusion every 3 weeks at dose of 0.8 µg/m2 before of a dose of doxorubicin 60 mg/m2 as 15 minutes infusion. At reaching of a cumulative dose of doxorubicin of 550 mg/m2, a continuation of treatment (if patient was showing an objective response or is in stable disease) with single agent NGR-hTNF at dose of 0.8 µg/m2 every 3 weeks was allowed.

Number of subjects in period 1	NGR-hTNF + doxorubicin
Started	37
Completed	26
Not completed	11
Consent withdrawn by subject	8
Physician decision	2
Adverse event, non-fatal	1

Baseline characteristics

Reporting groups	
Reporting group title	NGR-hTNF + doxorubicin

Reporting group description:

Patients received 60 minutes intravenous NGR-hTNF infusion every 3 weeks at dose of 0.8 µg/m2 before of a dose of doxorubicin 60 mg/m2 as 15 minutes infusion. At reaching of a cumulative dose of doxorubicin of 550 mg/m2, a continuation of treatment (if patient was showing an objective response or is in stable disease) with single agent NGR-hTNF at dose of 0.8 µg/m2 every 3 weeks was allowed.

Reporting group values	NGR-hTNF + doxorubicin	Total	
Number of subjects	37	37	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	17	17	
From 65-84 years	20	20	
85 years and over	0	0	
Age continuous			
Units: years			
median	57.0		
full range (min-max)	35 to 72	-	
Gender categorical			
Units: Subjects			
Female	37	37	
Male	0	0	

End points

End points reporting groups

Reporting group title	NGR-hTNF + doxorubicin

Reporting group description:

Patients received 60 minutes intravenous NGR-hTNF infusion every 3 weeks at dose of 0.8 µg/m2 before of a dose of doxorubicin 60 mg/m2 as 15 minutes infusion. At reaching of a cumulative dose of doxorubicin of 550 mg/m2, a continuation of treatment (if patient was showing an objective response or is in stable disease) with single agent NGR-hTNF at dose of 0.8 µg/m2 every 3 weeks was allowed.

Primary: Response rate (RR)

End point title	Response rate (RR)[1]

End point description:

The primary endpoint of the study was antitumor activity defined as response rate according to RECIST criteria. Response rate was defined as the percentage of patients having as best response throughout the study a CR or a PR: (CR + PR)/n. of patients in ENR population.

End point type	Primary

End point timeframe:

The response rate was measured during the whole study.

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: The study was conducted using Simon’s two-stage design method for the primary efficacy end point. Since 7 responses (complete or partial) were observed among the 37 patients, the study was to be considered to have a positive result.

End point values	NGR-hTNF + doxorubicin			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: Percentage of patients				
number (confidence interval 95%)	18.9 (8.0 to 35.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival (PFS)

End point title	Progression-free survival (PFS)

End point description:

Progression-free survival (PFS), defined as the time from baseline CT-scan date until the first observation of disease progression, or death due to any cause, or the last date the patient was known to be progression free or alive.

End point type	Secondary

End point timeframe:

Progression-free survival (PFS) was measured during the whole study/at each cycle.

End point values	NGR-hTNF + doxorubicin			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: months				
median (confidence interval 95%)	4.7 (3.1 to 6.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival

End point description:

Overall Survival (OS), defined as the time from baseline until the date of death from any cause or the last date the patient was known to be alive.

End point type	Secondary

End point timeframe:

Patiens were followed for survival after documented disease progression or after discontinuation before disease progression (every 12 weeks)

End point values	NGR-hTNF + doxorubicin			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: Months				
median (confidence interval 95%)	13.9 (9.3 to 17.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Tumor marker CA125 detection

End point title	Tumor marker CA125 detection

End point description:

Changes from baseline of tumor marker CA125.

End point type	Secondary

End point timeframe:

The level of tumor marker CA125 was measured before the treatment (within 14 days prior treatment) and during the treatment (every 2 cycles).

End point values	NGR-hTNF + doxorubicin			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: U/ml				
median (full range (min-max))	1.8 (-1833.8 to 745.8)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events and serious adverse events occurring after initiation of trial treatment will be recorded for 28 days after completion of the last treatment cycle. All serious adverse events related to the study drug will be recorded indefinitely.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	NGR-hTNF + doxorubicin

Reporting group description:

Patients received 60 minutes intravenous NGR-hTNF infusion every 3 weeks at dose of 0.8 µg/m2 before of a dose of doxorubicin 60 mg/m2 as 15 minutes infusion. At reaching of a cumulative dose of doxorubicin of 550 mg/m2, a continuation of treatment (if patient was showing an objective response or is in stable disease) with single agent NGR-hTNF at dose of 0.8 µg/m2 every 3 weeks was allowed.

Serious adverse events	NGR-hTNF + doxorubicin		
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 37 (18.92%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Infusion Site Extravasation			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea			

subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Pelvic Pain			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary Embolism			
subjects affected / exposed	1 / 37 (2.70%)		
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 + doxorubicin		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	37 / 37 (100.00%)		
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	4 / 37 (10.81%)		
occurrences (all)	4		
Aspartate Aminotransferase Increased			
subjects affected / exposed	3 / 37 (8.11%)		
occurrences (all)	3		
Gamma-Glutamyltransferase Increased			
subjects affected / exposed	3 / 37 (8.11%)		
occurrences (all)	3		
Nervous system disorders			
Paraesthesia			
subjects affected / exposed	15 / 37 (40.54%)		
occurrences (all)	18		
Headache			

subjects affected / exposed occurrences (all)	8 / 37 (21.62%) 12		
Blood and lymphatic system disorders Leukopenia subjects affected / exposed occurrences (all) Anaemia subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all) Thrombocytosis subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all)	 31 / 37 (83.78%) 84 29 / 37 (78.38%) 34 29 / 37 (78.38%) 73 8 / 37 (21.62%) 8 5 / 37 (13.51%) 8		
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) Chills subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all)	 33 / 37 (89.19%) 37 24 / 37 (64.86%) 40 4 / 37 (10.81%) 5		
Immune system disorders Contrast Media Allergy subjects affected / exposed occurrences (all)	 2 / 37 (5.41%) 2		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	 29 / 37 (78.38%) 45		

Vomiting subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Stomatitis subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all)	24 / 37 (64.86%) 43 23 / 37 (62.16%) 32 19 / 37 (51.35%) 19 7 / 37 (18.92%) 8		
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all) Cough subjects affected / exposed occurrences (all)	 3 / 37 (8.11%) 3 2 / 37 (5.41%) 2		
Infections and infestations Urinary Tract Infection subjects affected / exposed occurrences (all) Herpes Zoster subjects affected / exposed occurrences (all)	 3 / 37 (8.11%) 3 2 / 37 (5.41%) 2		
Metabolism and nutrition disorders Hypoalbuminaemia subjects affected / exposed occurrences (all) Hypocalcaemia subjects affected / exposed occurrences (all)	 3 / 37 (8.11%) 3 3 / 37 (8.11%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 May 2008	Summary of changes: - The reference name of the sponsor was changed; - The introduction was modified according to the availability of results of new studies; - The production process of the study drug has been changed, and therefore the protocol has been modified for the sections regarding pharmaceutical form, labelling, mode of dispensing and returning, and other details on study drug; - Plan of visits schedule of assessments has been changed; - Criteria for evaluation of relationship of adverse events have been modified; - Other minor changes.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported