



Clinical trial results:

NGR014: Randomized phase II study of NGR-hTNF in combination with standard chemotherapy versus standard chemotherapy alone in previously untreated patients with advanced non-small cell lung cancer (NSCLC).

Summary

EudraCT number	2008-002703-20
Trial protocol	IT
Global end of trial date	30 March 2017

Results information

Result version number	v1 (current)
This version publication date	21 December 2019
First version publication date	21 December 2019

Trial information

Trial identification

Sponsor protocol code	NGR014
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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	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	24 July 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 March 2017
Global end of trial reached?	Yes
Global end of trial date	30 March 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effect on progression-free survival (PFS) of NGR-hTNF administered at low dose (0.8 µg/m²) in combination with standard chemotherapy as compared to standard chemotherapy alone.

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: -

Evidence for comparator: -

Actual start date of recruitment	24 July 2009
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: 121
Worldwide total number of subjects	121
EEA total number of subjects	121

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)	78
From 65 to 84 years	43

85 years and over	0
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Subject disposition

Recruitment

Recruitment details:

The study was performed in a total of 4 investigational study sites in Italy.

1. Department of Medical Oncology, Onco-Haematology Unit, San Raffaele Hospital, Milan, was the coordinator centre.
2. Istituto Nazionale dei Tumori (INT), Milan (IT)
3. A.O.U. San Martino (IST), Genoa (IT)
4. Istituto Europeo Oncologico (IEO), Milan (IT)

Pre-assignment

Screening details:

Overall, 121 consented and screened patients were enrolled.

62 patients were randomised to Arm A, whereas 59 were randomised to Arm B. 6 patients (2 in arm A and 4 in arm B) dropped out before receiving treatment for the following reasons: physician decision (n=2), withdrawal of ICF (n=2), death (n=1), poor compliance (n=1).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A (experimental arm = NGR-hTNF + standard chemotherapy)

Arm description:

In patients with squamous histology (including also generic diagnosis of NSCLC without further subtype classification) the following regimen was recommended:

- NGR-hTNF administered at 0.8 µg/m² intravenous (iv) infusion over 1 hour every 3 weeks until progression of disease, followed (1 hour after the end of NGR-hTNF infusion) by:
- Cisplatin 80 mg/m² iv infusion on day 1 every 3 weeks for a maximum of 6 cycles;
- Gemcitabine 1,250 mg/m² iv infusion on days 1 and 8 every 3 weeks for a maximum of 6 cycles.

In patients with nonsquamous histology (including adenocarcinoma and large-cell carcinoma) the following regimen was recommended:

- NGR-hTNF administered at 0.8 µg/m² iv infusion over 1 hour every 3 weeks until progression of disease, followed (1 hour after the end of NGR-hTNF infusion) by:
- Cisplatin 80 mg/m² iv infusion on day 1 every 3 weeks for a maximum of 6 cycles;
- Pemetrexed 500 mg/m² iv infusion on day 1 every 3 weeks for a maximum of 6 cycles.

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:

0.8 µg/m² iv infusion over 1 hour every 3 weeks for a maximum of 6 cycles

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

Dosage and administration details:

80 mg/m² iv infusion on day 1 every 3 weeks for a maximum of 6 cycles

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

Dosage and administration details:

1,250 mg/m² iv infusion (1 hour after the end of NGR-hTNF infusion) on days 1 and 8 every 3 weeks for a maximum of 6 cycles

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

Dosage and administration details:

500 mg/m² iv infusion (1 hour after the end of NGR-hTNF infusion) on day 1 every 3 weeks for a maximum of 6 cycles

Arm title	Arm B (control arm = standard chemotherapy)
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Arm description:

Patients with squamous histology (including also generic diagnosis of NSCLC without further subtype classification):

- Cisplatin 80 mg/m² iv infusion on day 1 every 3 weeks for a maximum of 6 cycles;
- Gemcitabine 1,250 mg/m² iv infusion on days 1 and 8 every 3 weeks for a maximum of 6 cycles.

Patients with nonsquamous histology (including adenocarcinoma and large-cell carcinoma):

- Cisplatin 80 mg/m² iv infusion on day 1 every 3 weeks for a maximum of 6 cycles;
- Pemetrexed 500 mg/m² iv infusion on day 1 every 3 weeks for a maximum of 6 cycles.

Arm type	control arm
Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

80 mg/m² iv infusion on day 1 every 3 weeks for a maximum of 6 cycles

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

Dosage and administration details:

1,250 mg/m² iv infusion on days 1 and 8 every 3 weeks for a maximum of 6 cycles

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

Dosage and administration details:

500 mg/m² iv infusion on day 1 every 3 weeks for a maximum of 6 cycles

Number of subjects in period 1^[1]	Arm A (experimental arm = NGR-hTNF + standard chemotherapy)	Arm B (control arm = standard chemotherapy)
Started	60	55
Completed	48	24
Not completed	12	31
Adverse event, serious fatal	2	2
Consent withdrawn by subject	1	1
Physician decision	5	5
Disease progression	-	15
Adverse event, non-fatal	3	6
Other	1	1
Need for surgery	-	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: The analyses were performed only on treated patients.

Baseline characteristics

Reporting groups

Reporting group title	Arm A (experimental arm = NGR-hTNF + standard chemotherapy)
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Reporting group description:

In patients with squamous histology (including also generic diagnosis of NSCLC without further subtype classification) the following regimen was recommended:

- NGR-hTNF administered at 0.8 µg/m² intravenous (iv) infusion over 1 hour every 3 weeks until progression of disease, followed (1 hour after the end of NGR-hTNF infusion) by:
- Cisplatin 80 mg/m² iv infusion on day 1 every 3 weeks for a maximum of 6 cycles;
- Gemcitabine 1,250 mg/m² iv infusion on days 1 and 8 every 3 weeks for a maximum of 6 cycles.

In patients with nonsquamous histology (including adenocarcinoma and large-cell carcinoma) the following regimen was recommended:

- NGR-hTNF administered at 0.8 µg/m² iv infusion over 1 hour every 3 weeks until progression of disease, followed (1 hour after the end of NGR-hTNF infusion) by:
- Cisplatin 80 mg/m² iv infusion on day 1 every 3 weeks for a maximum of 6 cycles;
- Pemetrexed 500 mg/m² iv infusion on day 1 every 3 weeks for a maximum of 6 cycles.

Reporting group title	Arm B (control arm = standard chemotherapy)
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Reporting group description:

Patients with squamous histology (including also generic diagnosis of NSCLC without further subtype classification):

- Cisplatin 80 mg/m² iv infusion on day 1 every 3 weeks for a maximum of 6 cycles;
- Gemcitabine 1,250 mg/m² iv infusion on days 1 and 8 every 3 weeks for a maximum of 6 cycles.

Patients with nonsquamous histology (including adenocarcinoma and large-cell carcinoma):

- Cisplatin 80 mg/m² iv infusion on day 1 every 3 weeks for a maximum of 6 cycles;
- Pemetrexed 500 mg/m² iv infusion on day 1 every 3 weeks for a maximum of 6 cycles.

Reporting group values	Arm A (experimental arm = NGR-hTNF + standard chemotherapy)	Arm B (control arm = standard chemotherapy)	Total
Number of subjects	60	55	115
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	42	32	74
From 65-84 years	18	23	41
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	60.15	61.75	
standard deviation	± 8.52	± 8.64	-
Gender categorical Units: Subjects			
Female	24	19	43
Male	36	36	72

Histology			
Units: Subjects			
Squamous	17	15	32
Non-squamous	43	40	83

End points

End points reporting groups

Reporting group title	Arm A (experimental arm = NGR-hTNF + standard chemotherapy)
Reporting group description: In patients with squamous histology (including also generic diagnosis of NSCLC without further subtype classification) the following regimen was recommended: - NGR-hTNF administered at 0.8 µg/m2 intravenous (iv) infusion over 1 hour every 3 weeks until progression of disease, followed (1 hour after the end of NGR-hTNF infusion) by: - Cisplatin 80 mg/m2 iv infusion on day 1 every 3 weeks for a maximum of 6 cycles; - Gemcitabine 1,250 mg/m2 iv infusion on days 1 and 8 every 3 weeks for a maximum of 6 cycles. In patients with nonsquamous histology (including adenocarcinoma and large-cell carcinoma) the following regimen was recommended: - NGR-hTNF administered at 0.8 µg/m2 iv infusion over 1 hour every 3 weeks until progression of disease, followed (1 hour after the end of NGR-hTNF infusion) by: - Cisplatin 80 mg/m2 iv infusion on day 1 every 3 weeks for a maximum of 6 cycles; - Pemetrexed 500 mg/m2 iv infusion on day 1 every 3 weeks for a maximum of 6 cycles.	
Reporting group title	Arm B (control arm = standard chemotherapy)
Reporting group description: Patients with squamous histology (including also generic diagnosis of NSCLC without further subtype classification): - Cisplatin 80 mg/m2 iv infusion on day 1 every 3 weeks for a maximum of 6 cycles; - Gemcitabine 1,250 mg/m2 iv infusion on days 1 and 8 every 3 weeks for a maximum of 6 cycles. Patients with nonsquamous histology (including adenocarcinoma and large-cell carcinoma): - Cisplatin 80 mg/m2 iv infusion on day 1 every 3 weeks for a maximum of 6 cycles; - Pemetrexed 500 mg/m2 iv infusion on day 1 every 3 weeks for a maximum of 6 cycles.	

Primary: Progression-free survival (PFS), defined as the time from the date of randomization until disease progression, or death due to any cause.

End point title	Progression-free survival (PFS), defined as the time from the date of randomization until disease progression, or death due to any cause.
End point description: Defined as the time from the date of randomization until disease progression, or death due to any cause or the last patient was known to be alive. Progression is defined using Response Evaluation Criteria In Solid Tumors Criteria (Recist v1.0), as a 20% increase in the sum of the 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 relative increase of 20% the sum must also demonstrate an absolute increase of at least 5 mm. In addition the appearance of one or more new lesions was also considered progression. The results of PFS in the PP set, computed with the Kaplan-Meier method, are presented as Median (95% CI)	
End point type	Primary
End point timeframe: every 6 weeks, up to the last treatment cycle.	

End point values	Arm A (experimental arm = NGR- hTNF + standard chemotherapy)	Arm B (control arm = standard chemotherapy)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	55		
Units: days	163	181		

Statistical analyses

Statistical analysis title	Progression-free survival (PFS)
Statistical analysis description:	
The median PFS was 163 days (95% CI: 107-198 days) in arm A and 181 days (95% CI: 133-207 days) in arm B. One (1.7%) patient in arm A and 2 (3.6%) in arm B were censored, while events (i.e. failures) were reported in 59 (98.3%) patients in arm A and in 53 (96.4%) in arm B. The comparison between arms in the log rank model did not show statistically significant differences (p = 0.38).	
Comparison groups	Arm A (experimental arm = NGR-hTNF + standard chemotherapy) v Arm B (control arm = standard chemotherapy)
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.38
Method	Logrank

Secondary: Objective response rate (ORR), according to RECIST 1.0 criteria.

End point title	Objective response rate (ORR), according to RECIST 1.0 criteria.
End point description:	
Objective response rate (ORR), according to RECIST 1.0 criteria. Tumor response rate was defined as the best overall response (Complete Response, Partial Response, Stable Disease or Progressive Disease) achieved. The best overall response was calculated as the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started) or until the start of another treatment.	
End point type	Secondary
End point timeframe:	
every 6 weeks, up to the last treatment cycle.	

End point values	Arm A (experimental arm = NGR- hTNF + standard chemotherapy)	Arm B (control arm = standard chemotherapy)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	55		
Units: subjects				
Complete response	0	1		
Partial response	14	13		
Stable disease	32	30		
Progressive disease	13	5		

Not evaluable	1	6		
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Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DR)

End point title	Duration of Response (DR)
End point description: From the time measurement criteria were met for Complete Response/Partial Response (whichever was first recorded) until the first date that recurrent or progressive disease was objectively documented or death for any cause.	
End point type	Secondary
End point timeframe: every 6 weeks, up to the last treatment cycle.	

End point values	Arm A (experimental arm = NGR- hTNF + standard chemotherapy)	Arm B (control arm = standard chemotherapy)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	55		
Units: days	114	188		

Statistical analyses

Statistical analysis title	Duration of Response (DR).
Statistical analysis description: The median duration of response was 114 days (95% CI: 67-142 days) in arm A and 188 days (95% CI: 97-210 days) in arm B. None (0.0%) of patients in arm A and 1 (5.9%) patient in arm B were censored, while events (i.e. failures) were reported in all 22 (100.0%) patients in arm A and in 16 (94.1%) in arm B. The comparison between arms in the log rank model showed a statistically significant difference (p = 0.044).	
Comparison groups	Arm A (experimental arm = NGR-hTNF + standard chemotherapy) v Arm B (control arm = standard chemotherapy)

Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.044
Method	Logrank

Secondary: Overall survival (OS)

End point title	Overall survival (OS)
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End point description:

Overall Survival (OS), defined as the time from the date of randomization until death due to any cause. End point related data are reported as median (95% CI)

End point type	Secondary
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End point timeframe:

Assessed every 6 weeks, up to the completion of the last treatment cycle or in case of discontinuation of the treatment before disease progression. OS was assessed every 12 weeks after the last treatment cycle up to study completion (an average 8 years).

End point values	Arm A (experimental arm = NGR- hTNF + standard chemotherapy)	Arm B (control arm = standard chemotherapy)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	55		
Units: days	360	380		

Statistical analyses

Statistical analysis title	Overall survival
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Statistical analysis description:

The median OS was 360 days (95% CI: 245-476 days) in arm A and 380 days (95% CI: 294-596 days) in arm B. Four (6.7%) patients in arm A and 7 (12.7%) in arm B were censored, while events (i.e. deaths) were reported in 56 (93.3%) patients in arm A and in 48 (87.3%) in arm B. The comparison between arms in the log rank model did not show statistically significant differences ($p = 0.217$).

Comparison groups	Arm B (control arm = standard chemotherapy) v Arm A (experimental arm = NGR-hTNF + standard chemotherapy)
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.217
Method	Logrank

Secondary: Number of Adverse Events

End point title	Number of Adverse Events
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End point description:

An Adverse Event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Treatment emergent adverse events (TEAEs) were defined as AEs that started or worsened in severity on or after the first dose of study medication, regardless of relationship with study treatment. All adverse events will be recorded according to CTC version 3.0 (CTC reference: <http://ctep.info.nih.gov/CTC3/default.htm>) on the case report forms (CRFs); the investigator will decide if those events are drug related and his decision will be recorded on the forms for all adverse events.

End point type	Secondary
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End point timeframe:

Assessed every 3 weeks, up to the completion of the last treatment cycle. After the last treatment cycle adverse events were registered for the following 28 days.

End point values	Arm A (experimental arm = NGR- hTNF + standard chemotherapy)	Arm B (control arm = standard chemotherapy)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	55		
Units: Number of patients				
with fatal TEAEs	2	2		
with at least one TESA	11	11		
with at least one TEAE	59	53		
with at least one TEAE related to NGR- hTNF	34	0		
with at least one TEAE related to chemotherapy	58	51		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Assessed every 3 weeks, up to the completion of the last treatment cycle. After the last treatment cycle adverse events were registered for the following 28 days.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Arm A (experimental arm = NGR-hTNF + standard chemotherapy)
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Reporting group description: -

Reporting group title	Arm B (control arm = standard chemotherapy)
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Reporting group description: -

Serious adverse events	Arm A (experimental arm = NGR-hTNF + standard chemotherapy)	Arm B (control arm = standard chemotherapy)	
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 60 (18.33%)	11 / 55 (20.00%)	
number of deaths (all causes)	56	48	
number of deaths resulting from adverse events	2	2	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour Thrombosis			
subjects affected / exposed	1 / 60 (1.67%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Embolism			
subjects affected / exposed	1 / 60 (1.67%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral Ischaemia			
subjects affected / exposed	0 / 60 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			

Fatigue			
subjects affected / exposed	0 / 60 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 60 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	1 / 60 (1.67%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 60 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Eastern Cooperative Oncology Group Performance Status Worsened			
subjects affected / exposed	1 / 60 (1.67%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Tendon Rupture			
subjects affected / exposed	1 / 60 (1.67%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial Fibrillation			
subjects affected / exposed	2 / 60 (3.33%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Failure			

subjects affected / exposed	1 / 60 (1.67%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Failure Acute			
subjects affected / exposed	1 / 60 (1.67%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Cerebrovascular Accident			
subjects affected / exposed	1 / 60 (1.67%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	1 / 60 (1.67%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischaemia			
subjects affected / exposed	0 / 60 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukoencephalopathy			
subjects affected / exposed	0 / 60 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 60 (1.67%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 60 (1.67%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile Neutropenia			

subjects affected / exposed	0 / 60 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 60 (0.00%)	2 / 55 (3.64%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis Haemorrhagic			
subjects affected / exposed	0 / 60 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute Kidney Injury			
subjects affected / exposed	1 / 60 (1.67%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Failure			
subjects affected / exposed	0 / 60 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 60 (1.67%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 60 (1.67%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Metabolism and nutrition disorders			
Hypocalcaemia			

subjects affected / exposed	2 / 60 (3.33%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Arm A (experimental arm = NGR-hTNF + standard chemotherapy)	Arm B (control arm = standard chemotherapy)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	59 / 60 (98.33%)	53 / 55 (96.36%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	8 / 60 (13.33%)	6 / 55 (10.91%)	
occurrences (all)	13	8	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	37 / 60 (61.67%)	32 / 55 (58.18%)	
occurrences (all)	80	58	
Chills			
subjects affected / exposed	31 / 60 (51.67%)	0 / 55 (0.00%)	
occurrences (all)	49	0	
Pain			
subjects affected / exposed	17 / 60 (28.33%)	15 / 55 (27.27%)	
occurrences (all)	29	25	
Mucosal Inflammation			
subjects affected / exposed	12 / 60 (20.00%)	11 / 55 (20.00%)	
occurrences (all)	16	19	
Pyrexia			
subjects affected / exposed	12 / 60 (20.00%)	9 / 55 (16.36%)	
occurrences (all)	14	12	
Oedema			
subjects affected / exposed	11 / 60 (18.33%)	10 / 55 (18.18%)	
occurrences (all)	12	10	
Injection Site Reaction			

subjects affected / exposed occurrences (all)	2 / 60 (3.33%) 3	4 / 55 (7.27%) 7	
Immune system disorders Drug Hypersensitivity subjects affected / exposed occurrences (all)	3 / 60 (5.00%) 3	2 / 55 (3.64%) 2	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Pulmonary Embolism subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all) Haemoptysis subjects affected / exposed occurrences (all) Hiccups subjects affected / exposed occurrences (all)	7 / 60 (11.67%) 8 4 / 60 (6.67%) 4 3 / 60 (5.00%) 3 3 / 60 (5.00%) 3 1 / 60 (1.67%) 1 1 / 60 (1.67%) 2	4 / 55 (7.27%) 5 3 / 55 (5.45%) 3 2 / 55 (3.64%) 3 4 / 55 (7.27%) 6 2 / 55 (3.64%) 2 2 / 55 (3.64%) 4	
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) Agitation subjects affected / exposed occurrences (all)	2 / 60 (3.33%) 2 1 / 60 (1.67%) 1	2 / 55 (3.64%) 2 2 / 55 (3.64%) 2	
Investigations Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all)	10 / 60 (16.67%) 12	8 / 55 (14.55%) 10	

Blood Alkaline Phosphatase Increased subjects affected / exposed occurrences (all)	6 / 60 (10.00%) 6	4 / 55 (7.27%) 5	
Weight decreased subjects affected / exposed occurrences (all)	2 / 60 (3.33%) 2	2 / 55 (3.64%) 3	
C-reactive protein increased subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	3 / 55 (5.45%) 3	
Cardiac disorders Atrial Fibrillation subjects affected / exposed occurrences (all)	4 / 60 (6.67%) 4	0 / 55 (0.00%) 0	
Nervous system disorders Neuropathy peripheral subjects affected / exposed occurrences (all)	14 / 60 (23.33%) 21	9 / 55 (16.36%) 14	
Dizziness subjects affected / exposed occurrences (all)	8 / 60 (13.33%) 11	1 / 55 (1.82%) 1	
Dysgeusia subjects affected / exposed occurrences (all)	5 / 60 (8.33%) 6	4 / 55 (7.27%) 4	
Headache subjects affected / exposed occurrences (all)	5 / 60 (8.33%) 6	4 / 55 (7.27%) 4	
Syncope subjects affected / exposed occurrences (all)	2 / 60 (3.33%) 2	1 / 55 (1.82%) 1	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	36 / 60 (60.00%) 66	32 / 55 (58.18%) 54	
Leukopenia subjects affected / exposed occurrences (all)	29 / 60 (48.33%) 90	29 / 55 (52.73%) 96	

Neutropenia subjects affected / exposed occurrences (all)	26 / 60 (43.33%) 74	25 / 55 (45.45%) 66	
Thrombocytopenia subjects affected / exposed occurrences (all)	21 / 60 (35.00%) 52	19 / 55 (34.55%) 45	
Lymphopenia subjects affected / exposed occurrences (all)	8 / 60 (13.33%) 22	13 / 55 (23.64%) 35	
Thrombocytosis subjects affected / exposed occurrences (all)	2 / 60 (3.33%) 2	4 / 55 (7.27%) 5	
Ear and labyrinth disorders Tinnitus subjects affected / exposed occurrences (all)	8 / 60 (13.33%) 14	5 / 55 (9.09%) 7	
Deafness subjects affected / exposed occurrences (all)	4 / 60 (6.67%) 5	4 / 55 (7.27%) 6	
Hypoacusis subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1	2 / 55 (3.64%) 2	
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	37 / 60 (61.67%) 92	33 / 55 (60.00%) 70	
Constipation subjects affected / exposed occurrences (all)	25 / 60 (41.67%) 48	13 / 55 (23.64%) 17	
Vomiting subjects affected / exposed occurrences (all)	21 / 60 (35.00%) 53	19 / 55 (34.55%) 37	
Diarrhoea subjects affected / exposed occurrences (all)	9 / 60 (15.00%) 17	9 / 55 (16.36%) 9	
Dyspepsia			

subjects affected / exposed	4 / 60 (6.67%)	4 / 55 (7.27%)	
occurrences (all)	4	5	
Salivary hypersecretion			
subjects affected / exposed	3 / 60 (5.00%)	0 / 55 (0.00%)	
occurrences (all)	5	0	
Stomatitis			
subjects affected / exposed	3 / 60 (5.00%)	4 / 55 (7.27%)	
occurrences (all)	3	4	
Rectal haemorrhage			
subjects affected / exposed	2 / 60 (3.33%)	1 / 55 (1.82%)	
occurrences (all)	2	1	
Dysphagia			
subjects affected / exposed	1 / 60 (1.67%)	2 / 55 (3.64%)	
occurrences (all)	1	2	
Hepatobiliary disorders			
Hypertransaminasaemia			
subjects affected / exposed	12 / 60 (20.00%)	4 / 55 (7.27%)	
occurrences (all)	26	10	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	8 / 60 (13.33%)	4 / 55 (7.27%)	
occurrences (all)	9	4	
Dry skin			
subjects affected / exposed	8 / 60 (13.33%)	5 / 55 (9.09%)	
occurrences (all)	14	8	
Pruritus			
subjects affected / exposed	7 / 60 (11.67%)	6 / 55 (10.91%)	
occurrences (all)	9	6	
Skin exfoliation			
subjects affected / exposed	5 / 60 (8.33%)	7 / 55 (12.73%)	
occurrences (all)	10	10	
Rash			
subjects affected / exposed	4 / 60 (6.67%)	3 / 55 (5.45%)	
occurrences (all)	7	3	
Renal and urinary disorders			

Dysuria subjects affected / exposed occurrences (all)	4 / 60 (6.67%) 5	1 / 55 (1.82%) 1	
Oliguria subjects affected / exposed occurrences (all)	4 / 60 (6.67%) 6	2 / 55 (3.64%) 3	
Musculoskeletal and connective tissue disorders Muscle spasms subjects affected / exposed occurrences (all)	2 / 60 (3.33%) 2	4 / 55 (7.27%) 4	
Infections and infestations Conjunctivitis allergic subjects affected / exposed occurrences (all)	13 / 60 (21.67%) 27	11 / 55 (20.00%) 17	
Bronchitis subjects affected / exposed occurrences (all)	3 / 60 (5.00%) 3	0 / 55 (0.00%) 0	
Candida infection subjects affected / exposed occurrences (all)	3 / 60 (5.00%) 3	1 / 55 (1.82%) 1	
Lung infection subjects affected / exposed occurrences (all)	2 / 60 (3.33%) 2	4 / 55 (7.27%) 4	
Respiratory tract infection subjects affected / exposed occurrences (all)	2 / 60 (3.33%) 2	1 / 55 (1.82%) 1	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	20 / 60 (33.33%) 43	14 / 55 (25.45%) 23	
Hypercreatininaemia subjects affected / exposed occurrences (all)	19 / 60 (31.67%) 27	9 / 55 (16.36%) 12	
Hyperuricaemia subjects affected / exposed occurrences (all)	13 / 60 (21.67%) 24	3 / 55 (5.45%) 3	

Hypocalcaemia			
subjects affected / exposed	11 / 60 (18.33%)	4 / 55 (7.27%)	
occurrences (all)	16	5	
Hyperkalaemia			
subjects affected / exposed	10 / 60 (16.67%)	10 / 55 (18.18%)	
occurrences (all)	11	17	
Hyponatraemia			
subjects affected / exposed	10 / 60 (16.67%)	8 / 55 (14.55%)	
occurrences (all)	15	10	
Hypomagnesaemia			
subjects affected / exposed	9 / 60 (15.00%)	4 / 55 (7.27%)	
occurrences (all)	11	5	
Hypokalaemia			
subjects affected / exposed	7 / 60 (11.67%)	3 / 55 (5.45%)	
occurrences (all)	15	4	
Hypoalbuminaemia			
subjects affected / exposed	2 / 60 (3.33%)	2 / 55 (3.64%)	
occurrences (all)	2	2	
Hyperglycaemia			
subjects affected / exposed	2 / 60 (3.33%)	6 / 55 (10.91%)	
occurrences (all)	2	7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 April 2010	One protocol amendmen was implemented (protocol NGR014-IPR/20B), by which the following changes of the original protocol NGR014-IPR/20A were made effective: - The order of administration of chemotherapies (cisplatin, gemcitabine, pemetrexed) was left at the Investigator's discretion, according to the institutional clinical practice; - A blood sample performed at Day 8 for the assessment of haematology was added for patients on treatment with gemcitabine; - The possibility of administration of paracetamol by systemic route was added (in addition to oral route).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported