Clinical trial results:
NGR015: Randomized 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)

Summary

EudraCT number	2009-016879-29
Trial protocol	IT AT IE GB NL BE SE ES
Global end of trial date	18 December 2017

Results information

Result version number	v1 (current)
This version publication date	20 June 2019
First version publication date	20 June 2019

Trial information

Trial identification

Sponsor protocol code	NGR015

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01098266
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	29 April 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 April 2014
Global end of trial reached?	Yes
Global end of trial date	18 December 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare overall survival (OS) in patients randomized to NGR-hTNF plus BIC versus patients randomized to placebo plus BIC.

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 a pemetrexed-based chemotherapy regimen for advanced or metastatic disease.

Evidence for comparator:

Considering the toxicity profile of NGR-hTNF characterized by mild-to-moderate constitutional symptoms registered in the NGR010 phase II trial in previously treated MPM patients, as well as the disease control observed in about half of the patients and maintained for more than four months and more than nine months in the triweekly and weekly cohorts, respectively, seems justified to compare in a randomized phase III trial the time-related efficacy of NGR-hTNF 0.8 µg/m2 weekly against best investigator’s choice (or option) in advanced MPM patients progressing after a standard pemetrexed-based chemotherapy.
Currently, there are no regulatory-approved or widely-accepted treatment options for patients failing a standard pemetrexed-based chemotherapy regimen.
For this reason, the best supportive care (BSC) alone might be considered as a standard reference for a randomized phase III trial in this setting.

Actual start date of recruitment	12 April 2010
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	United States: 25
Country: Number of subjects enrolled	Canada: 9
Country: Number of subjects enrolled	Egypt: 36

Country: Number of subjects enrolled	Netherlands: 7
Country: Number of subjects enrolled	Poland: 31
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	Sweden: 2
Country: Number of subjects enrolled	United Kingdom: 95
Country: Number of subjects enrolled	Belgium: 13
Country: Number of subjects enrolled	France: 10
Country: Number of subjects enrolled	Ireland: 4
Country: Number of subjects enrolled	Italy: 163
Worldwide total number of subjects	400
EEA total number of subjects	330

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)	179
From 65 to 84 years	219
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

Study period: 12 April 2010 (first enrollment); 21 January 2013 (last enrollment). 15 clinical sites in Italy, 10 in United Kingdom, 7 in United States, 4 in Belgium, 2 in Canada, 2 in Netherland, 2 in Poland, 1 in Egypt, 1 in Ireland and 1 in Sweden.

Pre-assignment

Screening details:

14 enrolled patients (7 NGR-hTNF and 7 placebo) dropped out before receiving treatment for the following reason:
- early symptomatic deterioration (physician decision, n=8)
- death (n=5)
- withdrawal of informed consent (n=1)

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A - NGR-hTNF + BSC ± single-agent chemotherapy

Arm description:

Group A will receive NGR-hTNF plus the current treatment option (best supportive care BSC with or without single-agent chemotherapy):
- NGR-hTNF: 0.8 µg/m² as 60-minute iv infusion every week;
- BSC: where applicable and according to clinical practice, includes antibiotics, analgesics, antiemetics, thoracentesis, pleurodesis, blood transfusions, nutritional support, and focal external-beam radiation for control of pain, cough, dyspnea, or hemoptysis;
- Investigator's Choice: at Investigator discretion, one of the following single-agent chemotherapy might be administered in combination:
a) Doxorubicin: 60-75 mg/m2 every 3 weeks, for a maximum of 6 cycles, OR
b) Gemcitabine: 1,000-1,250 mg/m2 on days 1 and 8, every 3 weeks, for a maximum of 6 cycles, OR
c) Vinorelbine: 25 mg/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

Arm type	Experimental
Investigational medicinal product name	NGR-hTNF
Investigational medicinal product code	MM102
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Before infusion to patients, NGR-hTNF in citrate buffer (50mM sodium citrate, 35 mg/ml mannitol, 10 mg/ml sucrose, pH 6.2) will be diluted to the appropriate concentration with 0.9% NaCl containing 1 mg/ml human serum albumin (HSA).
The patients will receive NGR-hTNF every week by 60-minute intravenous infusion at 0.8 µg/m² until progressive disease.
Acetaminophen/paracetamol 1000 mg p.o. or i.v. is recommended as prophylaxis 30 to 60 minutes prior starting each infusion of NGR-hTNF. No concomitant hydration is allowed during the NGR-hTNF infusion period. No chronic or high dose corticosteroid therapy is allowed during the study treatment period. Where applicable and according to the Institutional clinical practice, patients should receive Best Supportive Care (BSC). BSC includes antibiotics, analgesics, antiemetics, thoracentesis, pleurodesis, blood transfusions, nutritional support, and focal external-beam radiation for control of pain, cough, dyspnea, or hemoptysis.

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

Dosage and administration details:

At Investigator discretion, Doxorubicin (60-75 mg/m2 iv infusion on day 1 every 3 weeks, for a maximum of 6 cycles) might be administered in combination with NGR-hTNF one hour after the end of NGRhTNF administration.

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

Dosage and administration details:

At Investigator discretion, Gemcitabine (1,000-1,250 mg/m2 iv infusion, on days 1 and 8, every 3 weeks, for a maximum of 6 cycles) might be administered in combination with NGR-hTNF one hour after the end of NGRhTNF administration.

Investigational medicinal product name	Vinorelbine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft, Concentrate for solution for infusion
Routes of administration	Oral use, Intravenous use

Dosage and administration details:

At Investigator discretion, Vinorelbine (25 mg/m2 iv or 60 mg/m2 per os if approved in the Country on days 1 and 8 every 3 weeks, for a maximum of 6 cycles (or weekly for 12 weeks)) might be administered in combination with NGR-hTNF one hour after the end of NGRhTNF administration.

Arm title	Arm B - Placebo + BSC ± single-agent chemotherapy

Arm description:

Group B will receive placebo plus the current treatment option (best supportive care BSC with or without single-agent chemotherapy):
- placebo: 0.8 µg/m² as 60-minute iv infusion every week;
- BSC: where applicable and according to clinical practice, includes antibiotics, analgesics, antiemetics, thoracentesis, pleurodesis, blood transfusions, nutritional support, and focal external-beam radiation for control of pain, cough, dyspnea, or hemoptysis;
- Investigator's Choice: at Investigator discretion, one of the following single-agent chemotherapy might be administered in combination:
a) Doxorubicin: 60-75 mg/m2 every 3 weeks, for a maximum of 6 cycles, OR
b) Gemcitabine: 1,000-1,250 mg/m2 on days 1 and 8, every 3 weeks, for a maximum of 6 cycles, OR
c) Vinorelbine: 25 mg/m2 iv on days 1 and 8 every 3 weeks, for a maximum of 6 cycles (orweekly 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)

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

Dosage and administration details:

NGR-hTNF placebo consisted of a vehicle for NGR-hTNF without the active ingredients. The quantitative composition of the placebo consisted of 50mM citrate buffer, 35 mg/ml mannitol and 10 mg/ml sucrose in 3 ml type I glass vials (1 ml/vial).
The patients will receive placebo every week by 60-minute intravenous infusion at 0.8 µg/m² until progressive disease.
Acetaminophen/paracetamol 1000 mg p.o. or i.v. is recommended as prophylaxis 30 to 60 minutes prior starting each infusion of placebo. No concomitant hydration is allowed during the placebo infusion period. No chronic or high dose corticosteroid therapy is allowed during the study treatment period. Where applicable and according to the Institutional clinical practice, patients should receive Best Supportive Care (BSC). BSC includes antibiotics, analgesics, antiemetics, thoracentesis, pleurodesis,

blood transfusions, nutritional support, and focal external-beam radiation for control of pain, cough, dyspnea, or hemoptysis.

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

Dosage and administration details:

At Investigator discretion, Doxorubicin (60-75 mg/m2 iv infusion on day 1 every 3 weeks, for a maximum of 6 cycles) might be administered in combination with placebo one hour after the end of placebo administration.

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

Dosage and administration details:

At Investigator discretion, Gemcitabine (1,000-1,250 mg/m2 iv infusion, on days 1 and 8, every 3 weeks, for a
maximum of 6 cycles) might be administered in combination with placebo one hour after the end of placebo administration.

Investigational medicinal product name	Vinorelbine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft, Concentrate for solution for infusion
Routes of administration	Oral use, Intravenous use

Dosage and administration details:

At Investigator discretion, Vinorelbine (25 mg/m2 iv or 60 mg/m2 per os if approved in the Country on days 1 and 8 every 3 weeks, for a maximum of 6 cycles (or weekly for 12 weeks)) might be administered in combination with placebo one hour after the end of placebo administration.

Number of subjects in period 1	Arm A - NGR-hTNF + BSC ± single-agent chemotherapy	Arm B - Placebo + BSC ± single-agent chemotherapy
Started	200	200
Completed	193	193
Not completed	7	7
Consent withdrawn by subject	1	-
Physician decision	3	5
Death	3	2

Baseline characteristics

Reporting groups

Reporting group title	Arm A - NGR-hTNF + BSC ± single-agent chemotherapy

Reporting group description:

Group A will receive NGR-hTNF plus the current treatment option (best supportive care BSC with or without single-agent chemotherapy):
- NGR-hTNF: 0.8 µg/m² as 60-minute iv infusion every week;
- BSC: where applicable and according to clinical practice, includes antibiotics, analgesics, antiemetics, thoracentesis, pleurodesis, blood transfusions, nutritional support, and focal external-beam radiation for control of pain, cough, dyspnea, or hemoptysis;
- Investigator's Choice: at Investigator discretion, one of the following single-agent chemotherapy might be administered in combination:
a) Doxorubicin: 60-75 mg/m2 every 3 weeks, for a maximum of 6 cycles, OR
b) Gemcitabine: 1,000-1,250 mg/m2 on days 1 and 8, every 3 weeks, for a maximum of 6 cycles, OR
c) Vinorelbine: 25 mg/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

Reporting group title	Arm B - Placebo + BSC ± single-agent chemotherapy

Reporting group description:

Group B will receive placebo plus the current treatment option (best supportive care BSC with or without single-agent chemotherapy):
- placebo: 0.8 µg/m² as 60-minute iv infusion every week;
- BSC: where applicable and according to clinical practice, includes antibiotics, analgesics, antiemetics, thoracentesis, pleurodesis, blood transfusions, nutritional support, and focal external-beam radiation for control of pain, cough, dyspnea, or hemoptysis;
- Investigator's Choice: at Investigator discretion, one of the following single-agent chemotherapy might be administered in combination:
a) Doxorubicin: 60-75 mg/m2 every 3 weeks, for a maximum of 6 cycles, OR
b) Gemcitabine: 1,000-1,250 mg/m2 on days 1 and 8, every 3 weeks, for a maximum of 6 cycles, OR
c) Vinorelbine: 25 mg/m2 iv on days 1 and 8 every 3 weeks, for a maximum of 6 cycles (orweekly 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)

Reporting group values	Arm A - NGR-hTNF + BSC ± single-agent chemotherapy	Arm B - Placebo + BSC ± single-agent chemotherapy	Total
Number of subjects	200	200	400
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)	92	87	179
From 65-84 years	106	113	219
85 years and over	2	0	2
Age continuous Units: years			
median	65	67	
full range (min-max)	25 to 89	31 to 81	-

Gender categorical Units: Subjects			
Female	44	55	99
Male	156	145	301

End points

End points reporting groups

Reporting group title	Arm A - NGR-hTNF + BSC ± single-agent chemotherapy

Reporting group description:

Group A will receive NGR-hTNF plus the current treatment option (best supportive care BSC with or without single-agent chemotherapy):
- NGR-hTNF: 0.8 µg/m² as 60-minute iv infusion every week;
- BSC: where applicable and according to clinical practice, includes antibiotics, analgesics, antiemetics, thoracentesis, pleurodesis, blood transfusions, nutritional support, and focal external-beam radiation for control of pain, cough, dyspnea, or hemoptysis;
- Investigator's Choice: at Investigator discretion, one of the following single-agent chemotherapy might be administered in combination:
a) Doxorubicin: 60-75 mg/m2 every 3 weeks, for a maximum of 6 cycles, OR
b) Gemcitabine: 1,000-1,250 mg/m2 on days 1 and 8, every 3 weeks, for a maximum of 6 cycles, OR
c) Vinorelbine: 25 mg/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

Reporting group title	Arm B - Placebo + BSC ± single-agent chemotherapy

Reporting group description:

Group B will receive placebo plus the current treatment option (best supportive care BSC with or without single-agent chemotherapy):
- placebo: 0.8 µg/m² as 60-minute iv infusion every week;
- BSC: where applicable and according to clinical practice, includes antibiotics, analgesics, antiemetics, thoracentesis, pleurodesis, blood transfusions, nutritional support, and focal external-beam radiation for control of pain, cough, dyspnea, or hemoptysis;
- Investigator's Choice: at Investigator discretion, one of the following single-agent chemotherapy might be administered in combination:
a) Doxorubicin: 60-75 mg/m2 every 3 weeks, for a maximum of 6 cycles, OR
b) Gemcitabine: 1,000-1,250 mg/m2 on days 1 and 8, every 3 weeks, for a maximum of 6 cycles, OR
c) Vinorelbine: 25 mg/m2 iv on days 1 and 8 every 3 weeks, for a maximum of 6 cycles (orweekly 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)

Primary: Overall survival (OS) in patients randomized to NGR-hTNF plus BIC versus patients randomized to placebo plus BIC

End point title	Overall survival (OS) in patients randomized to NGR-hTNF plus BIC versus patients randomized to placebo plus BIC

End point description:

The overall survival (OS) was defined as the time from the date of randomization until the date of death due to any cause or the last date the patient was known to be alive.
The log-rank test (unstratified) will be used to compare the two treatment arms. In addition, a stratified version of the log-rank test will be performed with the stratification factors used for randomization. Kaplan-Meier curves will be displayed, and median survival estimates and confidence limits of them will be given.

End point type	Primary

End point timeframe:

From the date of randomization until the date of death due to any cause or the last date the patient was known to be alive.

End point values	Arm A - NGR-hTNF + BSC ± single-agent chemotherapy	Arm B - Placebo + BSC ± single-agent chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	200	200		
Units: Months				
median (confidence interval 95%)	8.5 (7.2 to 9.9)	8.0 (6.6 to 8.9)		

Statistical analyses

Statistical analysis title	Unstratified log-rank test p-value
Comparison groups	Arm A - NGR-hTNF + BSC ± single-agent chemotherapy v Arm B - Placebo + BSC ± single-agent chemotherapy
Number of subjects included in analysis	400
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.58
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	1.18
Variability estimate	Standard deviation

Secondary: Progression-free survival (PFS) in patients randomized to NGR-hTNF plus BIC versus patients randomized to placebo plus BIC

End point title	Progression-free survival (PFS) in patients randomized to NGR-hTNF plus BIC versus patients randomized to placebo plus BIC

End point description:

Progression-free survival (PFS) was defined as the time from the date of randomization until disease progression, or death due to any cause. Patients with no tumor assessments after baseline but who are still alive at the time of the clinical cut-off will be censored at day of randomization.
The log-rank test (unstratified and stratified) was used at an alpha level of 5% to test for differences in PFS between the two treatment arms. Kaplan-Meier curves and estimates were provided. Cox regression analyses (unstratified and stratified) was performed to assess the influence of baseline covariates in an exploratory manner.

End point type	Secondary

End point timeframe:

From the date of randomization until disease progression, or death due to any cause.

End point values	Arm A - NGR-hTNF + BSC ± single-agent chemotherapy	Arm B - Placebo + BSC ± single-agent chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	200	200		
Units: Months				
median (confidence interval 95%)	3.4 (2.7 to 4.1)	3.0 (2.3 to 3.7)		

Statistical analyses

Statistical analysis title	Unstratified log-rank test p-value

Statistical analysis description:

The log-rank test (unstratified and stratified) was used at an alpha level of 5% to test for differences in PFS between the two treatment arms. Kaplan-Meier curves and estimates were provided.

Comparison groups	Arm A - NGR-hTNF + BSC ± single-agent chemotherapy v Arm B - Placebo + BSC ± single-agent chemotherapy
Number of subjects included in analysis	400
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.65
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	1.17

Notes:

[1] - Cox regression analyses (unstratified and stratified) was performed to assess the influence of baseline covariates in an exploratory manner.

Secondary: Disease control rate (DCR) in patients randomized to NGR-hTNF plus BIC versus patients randomized to placebo plus BIC

End point title	Disease control rate (DCR) in patients randomized to NGR-hTNF plus BIC versus patients randomized to placebo plus BIC

End point description:

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. The difference in DCR between the two treatment arms will be tested using a chi-squared test with 95% confidence intervals calculated in each treatment arm.

End point type	Secondary

End point timeframe:

At any time.

End point values	Arm A - NGR-hTNF + BSC ± single-agent chemotherapy	Arm B - Placebo + BSC ± single-agent chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	200	200		
Units: Subjects				
number (not applicable)	114	109		

Statistical analyses

Statistical analysis title	Fisher exact test p-value

Statistical analysis description:

The difference in DCR between the two treatment arms were tested using a chi-squared test with 95% confidence intervals calculated in each treatment arm.

Comparison groups	Arm A - NGR-hTNF + BSC ± single-agent chemotherapy v Arm B - Placebo + BSC ± single-agent chemotherapy
Number of subjects included in analysis	400
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.62
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	1.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	1.68

Notes:

[2] - Logistic regression analyses were performed to assess the influence of baseline covariates in an exploratory manner.

Secondary: Duration of disease control in patients randomized to NGR-hTNF plus BIC versus patients randomized to placebo plus BIC

End point title	Duration of disease control in patients randomized to NGR-hTNF plus BIC versus patients randomized to placebo plus BIC

End point description:

In the subset of patients who achieve disease control, the duration of disease control was measured from the date of randomization until disease progression, or death due to any cause. For the duration of disease control, the same methods were used as for PFS. Kaplan-Meier curves and estimates were provided and the log-rank test were used to assess differences between the two treatment groups, even though no formal hypothesis testing were performed, as this analysis was based on a non-randomized subset of patients.

End point type	Secondary

End point timeframe:

The duration of disease control was measured from the date of randomization until disease progression, or death due to any cause.

End point values	Arm A - NGR-hTNF + BSC ± single-agent chemotherapy	Arm B - Placebo + BSC ± single-agent chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	200	200		
Units: Subjects	84	76		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety and Toxicity profile related to NGR-hTNF according to NCI-CTCAE Criteria (Version 4.02)

End point title	Safety and Toxicity profile related to NGR-hTNF according to NCI-CTCAE Criteria (Version 4.02)

End point description:

Adverse events were recorded according to the CTC-AE v .4.02 (CTC reference: http://ctep.cancer.gov/reporting/ctc.html) on the case report forms (CRFs); the investigator decided if those events were drug related and his decision was recorded on the forms for all adverse event. Adverse events were displayed in standard frequency tables. For laboratory parameters, descriptive summary tables of change from baseline over time based on SI units were produced. Descriptive summary tables of change from baseline over time were provided for vital signs parameters.

End point type	Secondary

End point timeframe:

During the study (from day 1 to 28 days after last treatment).

End point values	Arm A - NGR-hTNF + BSC ± single-agent chemotherapy	Arm B - Placebo + BSC ± single-agent chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193[3]	193[4]		
Units: Subjects	191	185		

Notes:

[3] - The safety data referred to patients of both arms who received at least one treatment

[4] - The safety data referred to patients of both arms who received at least one treatment

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of Life (QoL) in patients randomized to NGR-hTNF plus BIC versus patients randomized to placebo plus BIC

End point title	Quality of Life (QoL) in patients randomized to NGR-hTNF plus BIC versus patients randomized to placebo plus BIC

End point description:

Quality of life assessment was performed by using a questionnaire according to Lung Cancer Symptom Scale (LCSS). The LCSS is designed as a disease and site-specific measure of quality of life (QoL) particularly for use in clinical trials. It evaluates six major symptoms (loss of appetite, fatigue, cough, dyspnea, hemoptysis, and pain) associated with lung malignancies and their effect on overall symptomatic distress, functional activities, and global QoL. Within this trial the questionnaire according

to LCSS was only recorded by the patient (patient's scale).
Symptomatic progression was defined as a worsening in the average symptom burden index by 25%.
Time to symptomatic progression was defined as time from randomization to the date of the LCSS assessment on which symptomatic progression was identified.

End point type	Secondary

End point timeframe:

Every 6 weeks.

End point values	Arm A - NGR-hTNF + BSC ± single-agent chemotherapy	Arm B - Placebo + BSC ± single-agent chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	200[5]	200[6]		
Units: Subjects	175	185		

Notes:

[5] - After one treatment cycle.

[6] - After one treatment cycle

Statistical analyses

Statistical analysis title	Stratified log-rank test p-value
Comparison groups	Arm A - NGR-hTNF + BSC ± single-agent chemotherapy v Arm B - Placebo + BSC ± single-agent chemotherapy
Number of subjects included in analysis	400
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.59
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	1.26

Secondary: Medical Care Utilization (MCU) in patients randomized to NGR-hTNF plus BIC versus patients randomized to placebo plus BIC

End point title	Medical Care Utilization (MCU) in patients randomized to NGR-hTNF plus BIC versus patients randomized to placebo plus BIC

End point description:

Medical resource use data collected will be used in health economic analyses where it may be combined with other data from other sources such as cost data or other clinical parameters.

End point type	Secondary

End point timeframe:

on ongoing-basis

End point values	Arm A - NGR-hTNF + BSC ± single-agent chemotherapy	Arm B - Placebo + BSC ± single-agent chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	200	200		
Units: Patient	187	186		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

FconsAll Serious Adverse Events (SAE), related or not to the protocol treatment, occurring during the trial and within 28 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	18.1

Reporting groups

Reporting group title	NGR-hTNF + BSC ± single-agent chemotherapy

Reporting group description:

safety analyses were done on 386 patients (safety population), since 14 patients (7 NGR-hTNF and 7 placebo)

Reporting group title	Placebo + BSC ± single-agent chemotherapy

Reporting group description:

safety analyses were done on 386 patients (safety population), since 14 patients (7 NGR-hTNF and 7 placebo)

Serious adverse events	NGR-hTNF + BSC ± single-agent chemotherapy	Placebo + BSC ± single-agent chemotherapy	
Total subjects affected by serious adverse events			
subjects affected / exposed	56 / 193 (29.02%)	54 / 193 (27.98%)	
number of deaths (all causes)	149	149	
number of deaths resulting from adverse events	12	13	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Paraneoplastic fever			
subjects affected / exposed	1 / 193 (0.52%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain mets			
subjects affected / exposed	0 / 193 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pleural mesothelioma			
subjects affected / exposed	1 / 193 (0.52%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

General disorders and administration site conditions			
Chills			
subjects affected / exposed	2 / 193 (1.04%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucositis			
subjects affected / exposed	0 / 193 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	2 / 193 (1.04%)	2 / 193 (1.04%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	3 / 193 (1.55%)	2 / 193 (1.04%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 3	0 / 2	
Hyperpyrexia			
subjects affected / exposed	1 / 193 (0.52%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic ulcer to left heel			
subjects affected / exposed	0 / 193 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	3 / 193 (1.55%)	3 / 193 (1.55%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deterioration of clinical status			
subjects affected / exposed	1 / 193 (0.52%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	

Admitted for pain control			
subjects affected / exposed	1 / 193 (0.52%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	0 / 193 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Condition aggravated			
subjects affected / exposed	4 / 193 (2.07%)	5 / 193 (2.59%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	4 / 4	5 / 5	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 193 (0.52%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	2 / 193 (1.04%)	2 / 193 (1.04%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	4 / 193 (2.07%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 7	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	2 / 193 (1.04%)	2 / 193 (1.04%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 1	
Bronchospasm			
subjects affected / exposed	1 / 193 (0.52%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumonitis			
subjects affected / exposed	0 / 193 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Infection (chest) with normal ANC			
subjects affected / exposed	0 / 193 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 193 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	2 / 193 (1.04%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleuritic pain			
subjects affected / exposed	0 / 193 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 193 (0.52%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	0 / 193 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Uncertain study medication dose delivered			
subjects affected / exposed	4 / 193 (2.07%)	9 / 193 (4.66%)	
occurrences causally related to treatment / all	4 / 4	9 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	

Drug infusion reaction			
subjects affected / exposed	2 / 193 (1.04%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	1 / 193 (0.52%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 193 (0.52%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 193 (0.52%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Occipital trauma			
subjects affected / exposed	1 / 193 (0.52%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Pericardial effusion			
subjects affected / exposed	1 / 193 (0.52%)	2 / 193 (1.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 193 (0.52%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorder			
subjects affected / exposed	1 / 193 (0.52%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			

subjects affected / exposed	1 / 193 (0.52%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 193 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	0 / 193 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden cardiac arrest			
subjects affected / exposed	0 / 193 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			
Transient ischaemic attack			
subjects affected / exposed	0 / 193 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superior sagittal sinus thrombosis			
subjects affected / exposed	0 / 193 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right hemispheric cerebrovascular accident			
subjects affected / exposed	1 / 193 (0.52%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	1 / 193 (0.52%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Jacksonian seizure			

subjects affected / exposed	1 / 193 (0.52%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	2 / 193 (1.04%)	4 / 193 (2.07%)	
occurrences causally related to treatment / all	3 / 3	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 193 (0.52%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	0 / 193 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic fever			
subjects affected / exposed	0 / 193 (0.00%)	2 / 193 (1.04%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	0 / 193 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Intestinal obstruction			
subjects affected / exposed	0 / 193 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	2 / 193 (1.04%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			

subjects affected / exposed	0 / 193 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	2 / 193 (1.04%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	0 / 193 (0.00%)	2 / 193 (1.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal ascites			
subjects affected / exposed	1 / 193 (0.52%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 193 (0.52%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 193 (1.04%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	0 / 193 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Acute hepatitis			
subjects affected / exposed	0 / 193 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Abnormal renal function			
subjects affected / exposed	1 / 193 (0.52%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Pain right chest wall + right shoulder			
subjects affected / exposed	0 / 193 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 193 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 193 (0.00%)	2 / 193 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	1 / 193 (0.52%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendiceal abscess			
subjects affected / exposed	0 / 193 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 193 (0.52%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Infection - source unknown			
subjects affected / exposed	1 / 193 (0.52%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Viral gastroenteritis			
subjects affected / exposed	1 / 193 (0.52%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	2 / 193 (1.04%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	0 / 193 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 193 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 193 (0.52%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cachexia			
subjects affected / exposed	1 / 193 (0.52%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	NGR-hTNF + BSC ± single-agent chemotherapy	Placebo + BSC ± single-agent chemotherapy	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	190 / 193 (98.45%)	185 / 193 (95.85%)	
Investigations			
Transaminases increased			

subjects affected / exposed	14 / 193 (7.25%)	7 / 193 (3.63%)	
occurrences (all)	37	20	
Vascular disorders			
Hypertension			
subjects affected / exposed	12 / 193 (6.22%)	12 / 193 (6.22%)	
occurrences (all)	16	15	
Hypotension			
subjects affected / exposed	10 / 193 (5.18%)	7 / 193 (3.63%)	
occurrences (all)	12	9	
Nervous system disorders			
Dizziness			
subjects affected / exposed	11 / 193 (5.70%)	12 / 193 (6.22%)	
occurrences (all)	12	14	
Dysgeusia			
subjects affected / exposed	10 / 193 (5.18%)	6 / 193 (3.11%)	
occurrences (all)	10	7	
Headache			
subjects affected / exposed	15 / 193 (7.77%)	13 / 193 (6.74%)	
occurrences (all)	16	14	
Pheripheral neuropathy			
subjects affected / exposed	12 / 193 (6.22%)	12 / 193 (6.22%)	
occurrences (all)	20	15	
General disorders and administration site conditions			
Chills			
subjects affected / exposed	104 / 193 (53.89%)	23 / 193 (11.92%)	
occurrences (all)	462	29	
Fatigue			
subjects affected / exposed	93 / 193 (48.19%)	94 / 193 (48.70%)	
occurrences (all)	166	180	
Pain			
subjects affected / exposed	91 / 193 (47.15%)	89 / 193 (46.11%)	
occurrences (all)	179	184	
Pyrexia			
subjects affected / exposed	48 / 193 (24.87%)	39 / 193 (20.21%)	
occurrences (all)	103	67	
Oedema			

subjects affected / exposed	26 / 193 (13.47%)	25 / 193 (12.95%)	
occurrences (all)	31	29	
Mucosal inflammation			
subjects affected / exposed	20 / 193 (10.36%)	17 / 193 (8.81%)	
occurrences (all)	29	23	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	57 / 193 (29.53%)	60 / 193 (31.09%)	
occurrences (all)	162	119	
Anaemia			
subjects affected / exposed	34 / 193 (17.62%)	42 / 193 (21.76%)	
occurrences (all)	58	79	
Thrombocytopenia			
subjects affected / exposed	26 / 193 (13.47%)	23 / 193 (11.92%)	
occurrences (all)	56	47	
Leukopenia			
subjects affected / exposed	24 / 193 (12.44%)	20 / 193 (10.36%)	
occurrences (all)	85	24	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	61 / 193 (31.61%)	62 / 193 (32.12%)	
occurrences (all)	122	130	
Constipation			
subjects affected / exposed	42 / 193 (21.76%)	45 / 193 (23.32%)	
occurrences (all)	65	65	
Vomiting			
subjects affected / exposed	33 / 193 (17.10%)	38 / 193 (19.69%)	
occurrences (all)	61	81	
Diarrhoea			
subjects affected / exposed	20 / 193 (10.36%)	36 / 193 (18.65%)	
occurrences (all)	39	58	
Dyspepsia			
subjects affected / exposed	10 / 193 (5.18%)	11 / 193 (5.70%)	
occurrences (all)	12	13	
Abdominal discomfort			

subjects affected / exposed	1 / 193 (0.52%)	11 / 193 (5.70%)	
occurrences (all)	1	12	
Respiratory, thoracic and mediastinal disorders			
Dysponoea			
subjects affected / exposed	63 / 193 (32.64%)	56 / 193 (29.02%)	
occurrences (all)	94	80	
Cough			
subjects affected / exposed	39 / 193 (20.21%)	47 / 193 (24.35%)	
occurrences (all)	59	71	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	12 / 193 (6.22%)	4 / 193 (2.07%)	
occurrences (all)	12	4	
Rush			
subjects affected / exposed	11 / 193 (5.70%)	8 / 193 (4.15%)	
occurrences (all)	15	8	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	11 / 193 (5.70%)	12 / 193 (6.22%)	
occurrences (all)	12	12	
Infections and infestations			
Respiratory tract infection			
subjects affected / exposed	13 / 193 (6.74%)	10 / 193 (5.18%)	
occurrences (all)	15	13	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	46 / 193 (23.83%)	51 / 193 (26.42%)	
occurrences (all)	68	76	
Hypocalcaemia			
subjects affected / exposed	12 / 193 (6.22%)	5 / 193 (2.59%)	
occurrences (all)	21	6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 January 2010	Version B:It has been included a sub-study for Vinorelbine administration, to evaluate the safety of the combination with NGR-hTNF (protocol section 6.5)
02 September 2010	Version C:This was a local amendment for UK clinical sites only, in which has been added the paragraph for Special Warnings during and after treatment on contraceptive measures to be used (protocol section 6.7)
15 September 2011	Version D*:It has been included the type of chemotherapy, as a stratification factor for patients candidate for chemotherapy (protocol sections 3 and 6.1) It has been defined the use of oral Vinorelbine only if approved in the Country. (protocol sections 3, 5.4 and 6.5) It has been included in the inclusion criteria No. 3, that patients previously treated with anthracyclines should not receive Doxorubicin, as Investigator's choice (protocol section 4.2) It has been increased from 14 to 28 days the wash-out period from radiotherapy, in the inclusion criteria No. 8 (protocol section 4.2) It has been added the 12-lead EKG for evaluation of QTc interval at baseline, week 6, 12, 18, 24 and at the end of treatment (protocol sections 6.1, 6.2, 6.3 and 7) It has been included in the collection of adverse events and serious adverse events, also those related to disease under study, such as progression, hospitalization, signs and symptoms (protocol section 10.3.2) *This amendment has been suggested by FDA
29 March 2012	Version E:It has been concluded the sub-study for Vinorelbine administration and defined the lowest dose level of Vinorelbine to be used in combination with NGRhTNF/ placebo. (protocol section 6.3)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported