Clinical trial results:
NGR016: Randomized phase II study evaluating two doses of NGR-hTNF administered either as single agent or in combination with doxorubicin in patients with advanced soft-tissue sarcoma (STS).

Summary

EudraCT number	2010-018851-88
Trial protocol	IT GB
Global end of trial date	09 May 2016

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	NGR016

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	25 July 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 May 2016
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 two NGR-hTNF doses administered either as single agent or in combination with doxorubicin

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 with locally advanced or metastatic soft-tissue sarcoma untreated or previously treated with one or more systemic regimen. The most commonly used therapies by 3rd level ATC code were: alkylating agents, cytotoxic antibiotics and related substances.

Evidence for comparator:

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Actual start date of recruitment	23 October 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 21
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	Italy: 42
Worldwide total number of subjects	69
EEA total number of subjects	69

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)	57
From 65 to 84 years	12
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study period: First patient enrolled: 23 October 2010; Last patient completed: 08 March 2016; End of study: 09 May 2016.
7 investigational study sites: Italy (4 sites), France (2 sites) and United Kingdom (1 site).

Pre-assignment

Screening details:

Totally 69 consented and screened patients were randomised to the assigned treatment arm. In particular, patients were stratified according to the prior cumulative dose of doxorubicin received.

Period 1

Period 1 title	Overall period (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: NGR-hTNF low dose

Arm description:

Patients were randomised to receive low-dose NGR-hTNF as single agent. Specifically, patients were treated with: NGR-hTNF 0.8 µg/m2 intravenous infusion over 1 hour once a week until progressive disease.

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:

NGR-hTNF administered at 0.8 µg/m2 intravenous (iv) infusion over 1 hour once a week until progressive disease.

Arm title	Arm B: NGR-hTNF high dose

Arm description:

Patients were randomised to receive high-dose NGR-hTNF as single agent.
Specifically, patients were treated with: NGR-hTNF 45 µg/m2 intravenous infusion over 1 hour once a week until progressive disease.

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:

NGR-hTNF administered at 45 µg/m2 iv infusion over 1 hour once a week until progressive disease.

Arm title	Arm C: NGR-hTNF low dose + Doxorubicin

Arm description:

Patients were randomised to receive low-dose NGR-hTNF + doxorubicin. Specifically, patients were treated with NGR-hTNF 0.8 µg/m2 intravenous infusion over 1 hour once a week until progressive disease, plus Doxorubicin 60 mg/m2 intravenous infusion over 15 minutes (starting 1 hour after the end of NGRhTNF infusion) on day 1 every 3 weeks for a maximum of 6 cycles (or until a cumulative dose of 550 mg/m2).

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:

NGR-hTNF administered at 0.8 µg/m2 iv infusion over 1 hour once a week until progressive disease, plus Doxorubicin 60 mg/m2 iv infusion over 15 minutes (starting 1 hour after the end of NGR-hTNF infusion) on day 1 every 3 weeks for a maximum of 6 cycles (or until cumulative dose of 550 mg/m2)

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

Dosage and administration details:

NGR-hTNF administered at 0.8 µg/m2 iv infusion over 1 hour once a week until progressive disease, plus Doxorubicin 60 mg/m2 iv infusion over 15 minutes (starting 1 hour after the end of NGR-hTNF infusion) on day 1 every 3 weeks for a maximum of 6 cycles (or until cumulative dose of 550 mg/m2)

Arm title	Arm D: NGR-hTNF high dose + Doxorubicin

Arm description:

Patients were randomised to receive high-dose NGR-hTNF + doxorubicin. Specifically, patients were treated with NGR-hTNF 45 µg/m2 intravenous infusion over 1 hour once a week until progressive disease, plus Doxorubicin 60 mg/m2 intravenous infusion over 15 minutes (starting 1 hour after the end of NGR-hTNF infusion) on day 1 every 3 weeks for a maximum of 6 cycles (or until a cumulative dose of 550 mg/m2).

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:

NGR-hTNF administered at 45 µg/m2 iv infusion over 1 hour once a week until progressive disease, plus Doxorubicin 60 mg/m2 iv infusion over 15 minutes (starting 1 hour after the end of NGR-hTNF infusion) on day 1 every 3 weeks for a maximum of 6 cycles (or until cumulative dose of 550 mg/m2).

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

Dosage and administration details:

NGR-hTNF administered at 45 µg/m2 iv infusion over 1 hour once a week until progressive disease, plus Doxorubicin 60 mg/m2 iv infusion over 15 minutes (starting 1 hour after the end of NGR-hTNF infusion) on day 1 every 3 weeks for a maximum of 6 cycles (or until cumulative dose of 550 mg/m2).

Number of subjects in period 1	Arm A: NGR-hTNF low dose	Arm B: NGR-hTNF high dose	Arm C: NGR-hTNF low dose + Doxorubicin
Started	14	14	28
Completed	13	14	28
Not completed	1	0	0
Death	1	-	-

Number of subjects in period 1	Arm D: NGR-hTNF high dose + Doxorubicin
Started	13
Completed	13
Not completed	0
Death	-

Baseline characteristics

Reporting groups	
Reporting group title	Arm A: NGR-hTNF low dose
Reporting group description:	
Patients were randomised to receive low-dose NGR-hTNF as single agent. Specifically, patients were treated with: NGR-hTNF 0.8 µg/m2 intravenous infusion over 1 hour once a week until progressive disease.	
Reporting group title	Arm B: NGR-hTNF high dose
Reporting group description:	
Patients were randomised to receive high-dose NGR-hTNF as single agent. Specifically, patients were treated with: NGR-hTNF 45 µg/m2 intravenous infusion over 1 hour once a week until progressive disease.	
Reporting group title	Arm C: NGR-hTNF low dose + Doxorubicin
Reporting group description:	
Patients were randomised to receive low-dose NGR-hTNF + doxorubicin. Specifically, patients were treated with NGR-hTNF 0.8 µg/m2 intravenous infusion over 1 hour once a week until progressive disease, plus Doxorubicin 60 mg/m2 intravenous infusion over 15 minutes (starting 1 hour after the end of NGRhTNF infusion) on day 1 every 3 weeks for a maximum of 6 cycles (or until a cumulative dose of 550 mg/m2).	
Reporting group title	Arm D: NGR-hTNF high dose + Doxorubicin
Reporting group description:	
Patients were randomised to receive high-dose NGR-hTNF + doxorubicin. Specifically, patients were treated with NGR-hTNF 45 µg/m2 intravenous infusion over 1 hour once a week until progressive disease, plus Doxorubicin 60 mg/m2 intravenous infusion over 15 minutes (starting 1 hour after the end of NGR-hTNF infusion) on day 1 every 3 weeks for a maximum of 6 cycles (or until a cumulative dose of 550 mg/m2).	

Reporting group values	Arm A: NGR-hTNF low dose	Arm B: NGR-hTNF high dose	Arm C: NGR-hTNF low dose + Doxorubicin
Number of subjects	14	14	28
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)	12	11	24
From 65-84 years	2	3	4
85 years and over	0	0	0
Age continuous Units: years			
median	54.6	55.6	50.1
standard deviation	± 10.33	± 14.57	± 13.00
Gender categorical Units: Subjects			
Female	5	8	11
Male	9	6	17

Reporting group values	Arm D: NGR-hTNF high dose + Doxorubicin	Total	
Number of subjects	13	69	
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)	10	57	
From 65-84 years	3	12	
85 years and over	0	0	
Age continuous			
Units: years			
median	54.8		
standard deviation	± 13.38	-	
Gender categorical			
Units: Subjects			
Female	7	31	
Male	6	38	

End points

End points reporting groups

Reporting group title	Arm A: NGR-hTNF low dose
Reporting group description:	
Patients were randomised to receive low-dose NGR-hTNF as single agent. Specifically, patients were treated with: NGR-hTNF 0.8 µg/m2 intravenous infusion over 1 hour once a week until progressive disease.	
Reporting group title	Arm B: NGR-hTNF high dose
Reporting group description:	
Patients were randomised to receive high-dose NGR-hTNF as single agent. Specifically, patients were treated with: NGR-hTNF 45 µg/m2 intravenous infusion over 1 hour once a week until progressive disease.	
Reporting group title	Arm C: NGR-hTNF low dose + Doxorubicin
Reporting group description:	
Patients were randomised to receive low-dose NGR-hTNF + doxorubicin. Specifically, patients were treated with NGR-hTNF 0.8 µg/m2 intravenous infusion over 1 hour once a week until progressive disease, plus Doxorubicin 60 mg/m2 intravenous infusion over 15 minutes (starting 1 hour after the end of NGRhTNF infusion) on day 1 every 3 weeks for a maximum of 6 cycles (or until a cumulative dose of 550 mg/m2).	
Reporting group title	Arm D: NGR-hTNF high dose + Doxorubicin
Reporting group description:	
Patients were randomised to receive high-dose NGR-hTNF + doxorubicin. Specifically, patients were treated with NGR-hTNF 45 µg/m2 intravenous infusion over 1 hour once a week until progressive disease, plus Doxorubicin 60 mg/m2 intravenous infusion over 15 minutes (starting 1 hour after the end of NGR-hTNF infusion) on day 1 every 3 weeks for a maximum of 6 cycles (or until a cumulative dose of 550 mg/m2).	

Primary: Progression-free survival (PFS)

End point title	Progression-free survival (PFS)
End point description:	
Progression-free survival (PFS) is defined as the time from the date of randomization until disease progression, or death due to any cause.	
End point type	Primary
End point timeframe:	
Progression-free survival (PFS) was measured after documented progressive disease (PD), specifically every 12 weeks.	

End point values	Arm A: NGR-hTNF low dose	Arm B: NGR-hTNF high dose	Arm C: NGR-hTNF low dose + Doxorubicin	Arm D: NGR-hTNF high dose + Doxorubicin
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	14	28	13
Units: Days				
median (confidence interval 95%)	42 (36 to 46)	63 (33 to 107)	96 (46 to 121)	58 (41 to 485)

Statistical analyses

Statistical analysis title	Progression Free Survival

Statistical analysis description:

The median PFS was 42 days (95% CI: 36-46 days) in arm A, 63 days (95% CI: 33-107 days) in arm B, 96 days (95% CI: 46-121 days) in arm C and 58 days (95% CI: 41-485 days) in arm D. Two (14.3%) patients in arm A, 1 (7.1%) in arm B, 2 (7.1%) in arm C and 2 (15.4%) in arm D were censored, while events (i.e. failures) were reported in 12 (85.7%) patients in arm A, in 13 (92.9%) in arm B, in 26 (92.9%) in arm C and in 11 (84.6%) in arm D.

Comparison groups	Arm A: NGR-hTNF low dose v Arm B: NGR-hTNF high dose v Arm C: NGR-hTNF low dose + Doxorubicin v Arm D: NGR-hTNF high dose + Doxorubicin
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.02
Method	Logrank

Secondary: Response rate (RR)

End point title	Response rate (RR)

End point description:

Response rate (RR) is defined as the percentage of patients who had a best-response rating of complete or partial response, according to standard RECIST criteria

End point type	Secondary

End point timeframe:

Complete or Partial Response was measured after documented progressive disease (PD), specifically every 12 weeks.

End point values	Arm A: NGR-hTNF low dose	Arm B: NGR-hTNF high dose	Arm C: NGR-hTNF low dose + Doxorubicin	Arm D: NGR-hTNF high dose + Doxorubicin
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	14	28	13
Units: number of patients	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival

End point description:

Overall Survival (OS) is defined as the time from the date of randomization until death due to any cause or last contact.

End point type	Secondary

End point timeframe:

Overall survival was measured after documented progressive disease (PD), specifically every 12 weeks.

End point values	Arm A: NGR-hTNF low dose	Arm B: NGR-hTNF high dose	Arm C: NGR-hTNF low dose + Doxorubicin	Arm D: NGR-hTNF high dose + Doxorubicin
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	14	28	13
Units: Days				
median (confidence interval 95%)	79 (46 to 286)	151 (48 to 320)	300 (166 to 707)	217 (67 to 485)

Statistical analyses

Statistical analysis title	Overall survival

Statistical analysis description:

The median OS was 79 days (95% CI: 46-286 days) in arm A, 151 days (95% CI: 48-320 days) in arm B, 300 days (95% CI: 166-707 days) in arm C and 217 days (95% CI: 67-485 days) in arm D. Two (14.3%) patients in arm A, 2 (14.3%) in arm B, 9 (32.1%) in arm C and 3 (23.1%) in arm D were censored, while events (i.e. deaths) were reported in 12 (85.7%) patients in arm A, in 12 (85.7%) in arm B, in 19 (67.9%) in arm C and in 10 (76.9%) in arm D.

Comparison groups	Arm A: NGR-hTNF low dose v Arm B: NGR-hTNF high dose v Arm C: NGR-hTNF low dose + Doxorubicin v Arm D: NGR-hTNF high dose + Doxorubicin
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.011
Method	Logrank

Secondary: Disease control rate

End point title	Disease control rate

End point description:

Disease Control Rate is defined as the percentage of subjects who have a Best Response of Complete Response, Partial Response or Stable Disease during the whole study.

End point type	Secondary

End point timeframe:

Disease control rate was recovered during the whole study.

End point values	Arm A: NGR-hTNF low dose	Arm B: NGR-hTNF high dose	Arm C: NGR-hTNF low dose + Doxorubicin	Arm D: NGR-hTNF high dose + Doxorubicin
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	14	28	13
Units: number of patients	1	4	16	5

Statistical analyses

Statistical analysis title	Disease Control Rate

Statistical analysis description:

DCR was reported in 1 (7.1%) patient in arm A, in 4 (28.6%) in arm B, in 16 (57.1%) in arm C and in 5 (38.5%) in arm D.

Comparison groups	Arm A: NGR-hTNF low dose v Arm B: NGR-hTNF high dose v Arm C: NGR-hTNF low dose + Doxorubicin v Arm D: NGR-hTNF high dose + Doxorubicin
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0143
Method	Logrank
Parameter estimate	means of Chi-quare tests

Secondary: Metabolic response rate (MRR)

End point title	Metabolic response rate (MRR)

End point description:

A complete metabolic response (CMR) was defined as the complete resolution of 18F-fluorodeoxyglucose (FDG) uptake within the tumor volume so that it was indistinguishable from surrounding normal tissue. A partial metabolic response (PMR) was defined as a 25% or more reduction in tumor FDG uptake. An increase in tumor standardised uptake value (SUV) 25% or more within the ROI defined on the baseline scan, or the appearance of new FDG uptake in another region, was classified as progressive metabolic disease (PMD). Stable metabolic disease (SMD) was defined as an increase in tumor SUV of less than 25% or a decrease of less than 25%.

End point type	Secondary

End point timeframe:

Metabolic response rate (MRR) was measured after first cycle (day 1) and at the time of documented progression.

End point values	Arm A: NGR-hTNF low dose	Arm B: NGR-hTNF high dose	Arm C: NGR-hTNF low dose + Doxorubicin	Arm D: NGR-hTNF high dose + Doxorubicin
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	14	28	13
Units: number of patients				
Cycle 1: Complete metabolic response	0	0	0	0
Cycle 1: Partial metabolic response	1	0	4	1
Cycle 1: Stable metabolic disease	7	8	11	4
Cycle 1: Progressive metabolic disease	1	1	3	2
Cycle 1: Inevaluable	5	5	10	6
At Progression: Complete metabolic response	0	0	0	0

At Progression: Partial metabolic response	0	0	1	0
At Progression: Stable metabolic disease	0	0	1	0
At Progression: Progressive metabolic disease	0	3	1	0
At Progression: Inevaluable	14	11	25	13

Statistical analyses

Statistical analysis title	Metabolic response rate: cycle 1

Statistical analysis description:

At cycle 1, none (0.0%) of patients in any arm had CMR. PMR was reported in 1 (7.1%) patient in arm A, in none (0.0%) in arm B, in 4 (14.3%) in arm C and in 1 (7.7%) in arm D. SMD was reported in 7 (50.0%) patients in arm A, in 8 (57.1%) in arm B, in 11 (39.3%) in arm C and in 4 (30.8%) in arm D. PMD was reported in 1 (7.1%) patient in arm A, in 1 (7.1%) in arm B, in 3 (10.7%) in arm C and in 2 (15.4%) in arm D.

Comparison groups	Arm B: NGR-hTNF high dose v Arm C: NGR-hTNF low dose + Doxorubicin v Arm D: NGR-hTNF high dose + Doxorubicin v Arm A: NGR-hTNF low dose
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8735
Method	Logrank
Parameter estimate	means of Chi-quare tests

Statistical analysis title	Metabolic response rate: at Progression

Statistical analysis description:

At progression, none (0.0%) of patients in any arm had CMR. PMR and SMD were reported in none (0.0%) of patients in arms A, C and D, and in 1 (3.6%) patient in arm C. PMD was reported in none (0.0%) of patients in arms A and D, in 3 (21.4%) patients in arm B and in 1 (3.6%) in arm C.

Comparison groups	Arm A: NGR-hTNF low dose v Arm B: NGR-hTNF high dose v Arm C: NGR-hTNF low dose + Doxorubicin v Arm D: NGR-hTNF high dose + Doxorubicin
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2677
Method	Logrank
Parameter estimate	means of Chi-quare tests

Secondary: Duration of stable disease

End point title	Duration of stable disease

End point description:

Duration of stable disease was measured from the date of randomization until the criteria for disease progression was met.

End point type	Secondary

End point timeframe:

Duration of stable disease is measured until the criterion for disease progression is met, up to 24 months

End point values	Arm A: NGR-hTNF low dose	Arm B: NGR-hTNF high dose	Arm C: NGR-hTNF low dose + Doxorubicin	Arm D: NGR-hTNF high dose + Doxorubicin
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	14	28	13
Units: Days				
median (confidence interval 95%)	42 (36 to 46)	90 (37 to 168)	114 (85 to 138)	58 (41 to 502)

Statistical analyses

Statistical analysis title	Duration of stable disease

Statistical analysis description:

The median duration of stable disease was 42 days (95% CI: 36-46 days) in arm A, 90 days (95% CI: 37-NE days) in arm B, 114 days (95% CI: 85-138 days) in arm C and 58 days (95% CI: 41-502 days) in arm D. Two (14.3%) patients in arm A, 6 (42.9%) in arm B, 5 (17.9%) in arm C and 4 (30.8%) in arm D were censored, while events (i.e. disease progression) were reported in 12 (85.7%) patients in arm A, in 8 (57.1%) in arm B, in 23 (82.1%) in arm C and in 9 (69.2%) in arm D.

Comparison groups	Arm A: NGR-hTNF low dose v Arm B: NGR-hTNF high dose v Arm C: NGR-hTNF low dose + Doxorubicin v Arm D: NGR-hTNF high dose + Doxorubicin
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.009
Method	Logrank

Secondary: Duration of response

End point title	Duration of response

End point description:

Duration of response (DR) was measured from the time that measurement criteria were met for complete response or partial response (whichever status was recorded first) until the progressive disease was objectively documented.

End point type	Secondary

End point timeframe:

Duration of response was measured until the progressive disease was objectively documented.

End point values	Arm A: NGR-hTNF low dose	Arm B: NGR-hTNF high dose	Arm C: NGR-hTNF low dose + Doxorubicin	Arm D: NGR-hTNF high dose + Doxorubicin
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	14	28	13
Units: number of patients	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events occurring after initiation of trial treatment will be recorded for 28 days after completion of the last treatment administration.
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	Arm A: NGR-hTNF low dose
Reporting group description: -	
Reporting group title	Arm B: NGR-hTNF high dose
Reporting group description: -	
Reporting group title	Arm C: NGR-hTNF low dose + Doxorubicin
Reporting group description: -	
Reporting group title	Arm D: NGR-hTNF high dose + Doxorubicin

Reporting group description: -

Serious adverse events	Arm A: NGR-hTNF low dose	Arm B: NGR-hTNF high dose	Arm C: NGR-hTNF low dose + Doxorubicin
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 13 (0.00%)	1 / 14 (7.14%)	3 / 28 (10.71%)
number of deaths (all causes)	11	12	19
number of deaths resulting from adverse events			
Blood and lymphatic system disorders			
Pancytopenia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 14 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile Neutropenia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 14 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain upper			

subjects affected / exposed	0 / 13 (0.00%)	0 / 14 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 13 (0.00%)	0 / 14 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Urinary Retention			
subjects affected / exposed	0 / 13 (0.00%)	0 / 14 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	0 / 13 (0.00%)	0 / 14 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Localised Infection			
subjects affected / exposed	0 / 13 (0.00%)	1 / 14 (7.14%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 14 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Arm D: NGR-hTNF high dose + Doxorubicin		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 13 (15.38%)		
number of deaths (all causes)	10		
number of deaths resulting from adverse events			

Blood and lymphatic system disorders			
Pancytopenia			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Febrile Neutropenia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Urinary Retention			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Localised Infection			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			

subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Arm A: NGR-hTNF low dose	Arm B: NGR-hTNF high dose	Arm C: NGR-hTNF low dose + Doxorubicin
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 13 (76.92%)	14 / 14 (100.00%)	28 / 28 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour Pain			
subjects affected / exposed	0 / 13 (0.00%)	1 / 14 (7.14%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 13 (0.00%)	1 / 14 (7.14%)	1 / 28 (3.57%)
occurrences (all)	0	1	1
Flushing			
subjects affected / exposed	0 / 13 (0.00%)	0 / 14 (0.00%)	2 / 28 (7.14%)
occurrences (all)	0	0	2
General disorders and administration site conditions			
Chills			
subjects affected / exposed	5 / 13 (38.46%)	11 / 14 (78.57%)	7 / 28 (25.00%)
occurrences (all)	5	36	14
Pyrexia			
subjects affected / exposed	4 / 13 (30.77%)	4 / 14 (28.57%)	6 / 28 (21.43%)
occurrences (all)	5	4	8
Chest Pain			
subjects affected / exposed	3 / 13 (23.08%)	2 / 14 (14.29%)	1 / 28 (3.57%)
occurrences (all)	3	3	1
Asthenia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 14 (0.00%)	5 / 28 (17.86%)
occurrences (all)	1	0	5
Chest Discomfort			

subjects affected / exposed	1 / 13 (7.69%)	0 / 14 (0.00%)	0 / 28 (0.00%)
occurrences (all)	1	0	0
Fatigue			
subjects affected / exposed	1 / 13 (7.69%)	0 / 14 (0.00%)	11 / 28 (39.29%)
occurrences (all)	2	0	14
Oedema Peripheral			
subjects affected / exposed	1 / 13 (7.69%)	0 / 14 (0.00%)	4 / 28 (14.29%)
occurrences (all)	1	0	5
Influenza Like Illness			
subjects affected / exposed	0 / 13 (0.00%)	1 / 14 (7.14%)	3 / 28 (10.71%)
occurrences (all)	0	1	3
Peripheral Swelling			
subjects affected / exposed	0 / 13 (0.00%)	1 / 14 (7.14%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
Mucosal Inflammation			
subjects affected / exposed	0 / 13 (0.00%)	0 / 14 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	1
Pain			
subjects affected / exposed	0 / 13 (0.00%)	0 / 14 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	1
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 13 (7.69%)	0 / 14 (0.00%)	1 / 28 (3.57%)
occurrences (all)	1	0	1
Drug Hypersensitivity			
subjects affected / exposed	0 / 13 (0.00%)	0 / 14 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 13 (15.38%)	2 / 14 (14.29%)	3 / 28 (10.71%)
occurrences (all)	2	2	4
Bronchospasm			
subjects affected / exposed	1 / 13 (7.69%)	1 / 14 (7.14%)	0 / 28 (0.00%)
occurrences (all)	1	1	0
Cough			

subjects affected / exposed	1 / 13 (7.69%)	0 / 14 (0.00%)	6 / 28 (21.43%)
occurrences (all)	1	0	6
Oropharyngeal Pain			
subjects affected / exposed	1 / 13 (7.69%)	0 / 14 (0.00%)	4 / 28 (14.29%)
occurrences (all)	1	0	5
Productive Cough			
subjects affected / exposed	1 / 13 (7.69%)	0 / 14 (0.00%)	0 / 28 (0.00%)
occurrences (all)	1	0	0
Epistaxis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 14 (0.00%)	2 / 28 (7.14%)
occurrences (all)	0	0	3
Haemoptysis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 14 (0.00%)	2 / 28 (7.14%)
occurrences (all)	0	0	3
Nasal Congestion			
subjects affected / exposed	0 / 13 (0.00%)	0 / 14 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Sinus Pain			
subjects affected / exposed	0 / 13 (0.00%)	0 / 14 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 14 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Mood Altered			
subjects affected / exposed	0 / 13 (0.00%)	0 / 14 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Investigations			
Breath Sounds Abnormal			
subjects affected / exposed	1 / 13 (7.69%)	0 / 14 (0.00%)	0 / 28 (0.00%)
occurrences (all)	1	0	0
Weight Decreased			
subjects affected / exposed	1 / 13 (7.69%)	0 / 14 (0.00%)	4 / 28 (14.29%)
occurrences (all)	1	0	4
Ejection Fraction Decreased			

subjects affected / exposed	0 / 13 (0.00%)	1 / 14 (7.14%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
Gamma-Glutamyltransferase Increased			
subjects affected / exposed	0 / 13 (0.00%)	1 / 14 (7.14%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
Platelet Count Decreased			
subjects affected / exposed	0 / 13 (0.00%)	1 / 14 (7.14%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
Neutrophil Count Decreased			
subjects affected / exposed	0 / 13 (0.00%)	0 / 14 (0.00%)	2 / 28 (7.14%)
occurrences (all)	0	0	7
Activated Partial Thromboplastin Time Prolonged			
subjects affected / exposed	0 / 13 (0.00%)	0 / 14 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	1
Lymphocyte Count Decreased			
subjects affected / exposed	0 / 13 (0.00%)	0 / 14 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	7
Alanine Aminotransferase Increased			
subjects affected / exposed	0 / 13 (0.00%)	0 / 14 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Aspartate Aminotransferase Increased			
subjects affected / exposed	0 / 13 (0.00%)	0 / 14 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Blood Bilirubin Increased			
subjects affected / exposed	0 / 13 (0.00%)	0 / 14 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Oxygen Saturation Decreased			
subjects affected / exposed	0 / 13 (0.00%)	0 / 14 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
White Blood Cell Count Decreased			
subjects affected / exposed	0 / 13 (0.00%)	0 / 14 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			

Tooth Avulsion			
subjects affected / exposed	1 / 13 (7.69%)	0 / 14 (0.00%)	0 / 28 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Extrasystoles			
subjects affected / exposed	1 / 13 (7.69%)	0 / 14 (0.00%)	1 / 28 (3.57%)
occurrences (all)	1	0	1
Cyanosis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 14 (7.14%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
Palpitations			
subjects affected / exposed	0 / 13 (0.00%)	1 / 14 (7.14%)	1 / 28 (3.57%)
occurrences (all)	0	1	1
Tachycardia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 14 (0.00%)	3 / 28 (10.71%)
occurrences (all)	0	0	3
Pericardial Effusion			
subjects affected / exposed	0 / 13 (0.00%)	0 / 14 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 13 (7.69%)	1 / 14 (7.14%)	4 / 28 (14.29%)
occurrences (all)	1	11	5
Presyncope			
subjects affected / exposed	0 / 13 (0.00%)	1 / 14 (7.14%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
Seizure			
subjects affected / exposed	0 / 13 (0.00%)	1 / 14 (7.14%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
Syncope			
subjects affected / exposed	0 / 13 (0.00%)	1 / 14 (7.14%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
Dysgeusia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 14 (0.00%)	2 / 28 (7.14%)
occurrences (all)	0	0	2
Paraesthesia			

subjects affected / exposed	0 / 13 (0.00%)	0 / 14 (0.00%)	2 / 28 (7.14%)
occurrences (all)	0	0	2
Somnolence			
subjects affected / exposed	0 / 13 (0.00%)	0 / 14 (0.00%)	2 / 28 (7.14%)
occurrences (all)	0	0	2
Dizziness			
subjects affected / exposed	0 / 13 (0.00%)	0 / 14 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	1
Amputation Stump Pain			
subjects affected / exposed	0 / 13 (0.00%)	0 / 14 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Epilepsy			
subjects affected / exposed	0 / 13 (0.00%)	0 / 14 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 14 (0.00%)	11 / 28 (39.29%)
occurrences (all)	0	0	21
Anaemia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 14 (0.00%)	6 / 28 (21.43%)
occurrences (all)	0	0	10
Thrombocytopenia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 14 (0.00%)	2 / 28 (7.14%)
occurrences (all)	0	0	2
Leukopenia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 14 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	1
Febrile Neutropenia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 14 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 13 (0.00%)	0 / 14 (0.00%)	2 / 28 (7.14%)
occurrences (all)	0	0	2
Eye disorders			

Lacrimation Increased			
subjects affected / exposed	0 / 13 (0.00%)	0 / 14 (0.00%)	2 / 28 (7.14%)
occurrences (all)	0	0	2
Dry Eye			
subjects affected / exposed	0 / 13 (0.00%)	0 / 14 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	1
Eyelid Irritation			
subjects affected / exposed	0 / 13 (0.00%)	0 / 14 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	2 / 13 (15.38%)	0 / 14 (0.00%)	11 / 28 (39.29%)
occurrences (all)	2	0	19
Nausea			
subjects affected / exposed	1 / 13 (7.69%)	1 / 14 (7.14%)	18 / 28 (64.29%)
occurrences (all)	1	1	25
Abdominal Pain Upper			
subjects affected / exposed	0 / 13 (0.00%)	3 / 14 (21.43%)	2 / 28 (7.14%)
occurrences (all)	0	4	3
Constipation			
subjects affected / exposed	0 / 13 (0.00%)	1 / 14 (7.14%)	11 / 28 (39.29%)
occurrences (all)	0	1	15
Diarrhoea			
subjects affected / exposed	0 / 13 (0.00%)	1 / 14 (7.14%)	4 / 28 (14.29%)
occurrences (all)	0	1	5
Haemorrhoids			
subjects affected / exposed	0 / 13 (0.00%)	1 / 14 (7.14%)	1 / 28 (3.57%)
occurrences (all)	0	1	1
Dyspepsia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 14 (0.00%)	5 / 28 (17.86%)
occurrences (all)	0	0	5
Abdominal Pain			
subjects affected / exposed	0 / 13 (0.00%)	0 / 14 (0.00%)	4 / 28 (14.29%)
occurrences (all)	0	0	4
Stomatitis			

subjects affected / exposed	0 / 13 (0.00%)	0 / 14 (0.00%)	3 / 28 (10.71%)
occurrences (all)	0	0	3
Anorectal Discomfort			
subjects affected / exposed	0 / 13 (0.00%)	0 / 14 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal Pain			
subjects affected / exposed	0 / 13 (0.00%)	0 / 14 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Gingival Disorder			
subjects affected / exposed	0 / 13 (0.00%)	0 / 14 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Lip Oedema			
subjects affected / exposed	0 / 13 (0.00%)	0 / 14 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Hepatobiliary disorders			
Hepatomegaly			
subjects affected / exposed	0 / 13 (0.00%)	0 / 14 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 14 (0.00%)	13 / 28 (46.43%)
occurrences (all)	0	0	13
Hyperhidrosis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 14 (0.00%)	2 / 28 (7.14%)
occurrences (all)	0	0	2
Skin Reaction			
subjects affected / exposed	0 / 13 (0.00%)	0 / 14 (0.00%)	2 / 28 (7.14%)
occurrences (all)	0	0	3
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 13 (7.69%)	0 / 14 (0.00%)	0 / 28 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Musculoskeletal Pain			
subjects affected / exposed	1 / 13 (7.69%)	1 / 14 (7.14%)	1 / 28 (3.57%)
occurrences (all)	1	2	2

Back Pain			
subjects affected / exposed	0 / 13 (0.00%)	1 / 14 (7.14%)	1 / 28 (3.57%)
occurrences (all)	0	1	4
Musculoskeletal Chest Pain			
subjects affected / exposed	0 / 13 (0.00%)	1 / 14 (7.14%)	2 / 28 (7.14%)
occurrences (all)	0	1	4
Pain In Extremity			
subjects affected / exposed	0 / 13 (0.00%)	1 / 14 (7.14%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
Spinal Pain			
subjects affected / exposed	0 / 13 (0.00%)	1 / 14 (7.14%)	0 / 28 (0.00%)
occurrences (all)	0	3	0
Arthralgia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 14 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	2
Neck Pain			
subjects affected / exposed	0 / 13 (0.00%)	0 / 14 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	2
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	2 / 13 (15.38%)	0 / 14 (0.00%)	1 / 28 (3.57%)
occurrences (all)	2	0	1
Influenza			
subjects affected / exposed	1 / 13 (7.69%)	0 / 14 (0.00%)	7 / 28 (25.00%)
occurrences (all)	2	0	9
Fungal Infection			
subjects affected / exposed	0 / 13 (0.00%)	1 / 14 (7.14%)	1 / 28 (3.57%)
occurrences (all)	0	1	1
Localised Infection			
subjects affected / exposed	0 / 13 (0.00%)	1 / 14 (7.14%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
Gastroenteritis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 14 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Gingivitis			

subjects affected / exposed	0 / 13 (0.00%)	0 / 14 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Oral Candidiasis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 14 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Pneumonia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 14 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Rhinitis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 14 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	1 / 13 (7.69%)	0 / 14 (0.00%)	6 / 28 (21.43%)
occurrences (all)	1	0	8
Glucose Tolerance Impaired			
subjects affected / exposed	0 / 13 (0.00%)	1 / 14 (7.14%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
Dehydration			
subjects affected / exposed	0 / 13 (0.00%)	0 / 14 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Arm D: NGR-hTNF high dose + Doxorubicin		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 13 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour Pain			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Flushing			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		

General disorders and administration site conditions			
Chills			
subjects affected / exposed	10 / 13 (76.92%)		
occurrences (all)	32		
Pyrexia			
subjects affected / exposed	3 / 13 (23.08%)		
occurrences (all)	8		
Chest Pain			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Asthenia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Chest Discomfort			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Fatigue			
subjects affected / exposed	7 / 13 (53.85%)		
occurrences (all)	10		
Oedema Peripheral			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Influenza Like Illness			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	3		
Peripheral Swelling			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Mucosal Inflammation			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Pain			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Immune system disorders			

Hypersensitivity			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Drug Hypersensitivity			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	5 / 13 (38.46%)		
occurrences (all)	9		
Bronchospasm			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Cough			
subjects affected / exposed	3 / 13 (23.08%)		
occurrences (all)	9		
Oropharyngeal Pain			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Productive Cough			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Epistaxis			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Haemoptysis			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Nasal Congestion			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Sinus Pain			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	2		
Psychiatric disorders			

Insomnia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Mood Altered			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Investigations			
Breath Sounds Abnormal			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Weight Decreased			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Ejection Fraction Decreased			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Gamma-Glutamyltransferase Increased			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	2		
Platelet Count Decreased			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Neutrophil Count Decreased			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Activated Partial Thromboplastin Time Prolonged			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Lymphocyte Count Decreased			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Alanine Aminotransferase Increased			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	2		
Aspartate Aminotransferase Increased			

subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Blood Bilirubin Increased			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	2		
Oxygen Saturation Decreased			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
White Blood Cell Count Decreased			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	10		
Injury, poisoning and procedural complications			
Tooth Avulsion			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Extrasystoles			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Cyanosis			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Palpitations			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Tachycardia			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	4		
Pericardial Effusion			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	5		
Presyncope			

subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Seizure			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Syncope			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Dysgeusia			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	2		
Paraesthesia			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Somnolence			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Dizziness			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Amputation Stump Pain			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Epilepsy			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	5 / 13 (38.46%)		
occurrences (all)	11		
Anaemia			
subjects affected / exposed	3 / 13 (23.08%)		
occurrences (all)	5		
Thrombocytopenia			
subjects affected / exposed	3 / 13 (23.08%)		
occurrences (all)	3		

Leukopenia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Febrile Neutropenia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Eye disorders			
Lacrimation Increased			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Dry Eye			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Eyelid Irritation			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	3 / 13 (23.08%)		
occurrences (all)	6		
Nausea			
subjects affected / exposed	7 / 13 (53.85%)		
occurrences (all)	10		
Abdominal Pain Upper			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	2		
Diarrhoea			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Haemorrhoids			

subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Dyspepsia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Abdominal Pain			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Stomatitis			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Anorectal Discomfort			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Gastrointestinal Pain			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	2		
Gingival Disorder			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Lip Oedema			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Hepatobiliary disorders			
Hepatomegaly			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	4 / 13 (30.77%)		
occurrences (all)	4		
Hyperhidrosis			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Skin Reaction			

subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Musculoskeletal Pain			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Back Pain			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	5		
Musculoskeletal Chest Pain			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Pain In Extremity			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Spinal Pain			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Arthralgia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	3		
Neck Pain			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Influenza			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	2		
Fungal Infection			

subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0		
Localised Infection subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0		
Gastroenteritis subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 2		
Gingivitis subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Oral Candidiasis subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Pneumonia subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Rhinitis subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 2		
Metabolism and nutrition disorders Decreased Appetite subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Glucose Tolerance Impaired subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0		
Dehydration subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported