Clinical trial results:
NGR018: Randomized phase II study of NGR-hTNF plus pegylated liposomal doxorubicin (PLD) versus PLD in platinum-resistant ovarian cancer

Summary

EudraCT number	2010-023613-61
Trial protocol	IT GB
Global end of trial date	23 December 2016

Results information

Result version number	v1 (current)
This version publication date	01 January 2020
First version publication date	01 January 2020

Trial information

Trial identification

Sponsor protocol code	NGR018

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 Development , MolMed S.p.A. , 0039 0221277234, clinical.operations@molmed.com
Scientific contact	Clinical Development , MolMed S.p.A. , 0039 0221277234, clinical.operations@molmed.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	25 July 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 December 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare progression-free survival (PFS) in patients randomized to NGR-hTNF plus PLD versus patients randomized to PLD

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 previously treated with a maximum of two platinum-based regimen (cisplatin or carboplatin) plus paclitaxel and with documented progressive disease on treatment (refractory patient population) or within 6 months from last chemotherapy cycle (resistant patient population).

Evidence for comparator:

-

Actual start date of recruitment	18 July 2011
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 Kingdom: 13
Country: Number of subjects enrolled	Italy: 120
Worldwide total number of subjects	133
EEA total number of subjects	133

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)	82
From 65 to 84 years	51
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study period: First patient enrolled: 18 July 2011; Last patient completed: 27 January 2016; End of study: 23 December 2016; 8 investigational study sites (6 sites in Italy and 2 sites in United Kingdom)

Pre-assignment

Screening details:

Totally 133 consented and screened patients were randomly assigned to the treatment group through a centralized randomization system using the following stratification factors: primary platinum resistance or acquired platinum resistance, type of anthracycline.

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 plus an anthracycline

Arm description:

Arm A (experimental arm = NGR-hTNF + anthracycline)
-NGR-hTNF: 0.8 ug/m² as 60-minute intravenous infusion every week until confirmed evidence of disease progression, plus Pegylated liposomal doxorubicin: 50 mg/m2 iv every 4 weeks until confirmed evidence of disease progression OR
- NGR-hTNF: 0.8 ug/m² as 60-minute intravenous infusion every week until confirmed evidence of disease progression, plus Doxorubicin: 60 mg/m2 iv every 3 weeks for a maximum of 8 cycles

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

Dosage and administration details:

NGR-hTNF: 0.8 ug/m² as 60-minute intravenous (iv) infusion every week until confirmed evidence of disease progression, plus Pegylated liposomal doxorubicin: 50 mg/m2 iv every 4 weeks until confirmed evidence of disease progression OR
NGR-hTNF: 0.8 ug/m² as 60-minute iv infusion every week until confirmed evidence of disease progression, plus Doxorubicin: 60 mg/m2 iv every 3 weeks for a maximum of 8 cycles

Investigational medicinal product name	Pegylated liposomal doxorubicin
Investigational medicinal product code	
Other name	Anthracycline
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

NGR-hTNF: 0.8 ug/m² as 60-minute intravenous (iv) infusion every week until confirmed evidence of disease progression, plus Pegylated liposomal doxorubicin: 50 mg/m2 iv every 4 weeks until confirmed evidence of disease progression OR
NGR-hTNF: 0.8 ug/m² as 60-minute iv infusion every week until confirmed evidence of disease progression, plus Doxorubicin: 60 mg/m2 iv every 3 weeks for a maximum of 8 cycles

Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	Anthracycline
Pharmaceutical forms	Concentrate for solution for infusion

Routes of administration	Intravenous use

Dosage and administration details:

NGR-hTNF: 0.8 ug/m² as 60-minute intravenous (iv) infusion every week until confirmed evidence of disease progression, plus Pegylated liposomal doxorubicin: 50 mg/m2 iv every 4 weeks until confirmed evidence of disease progression OR
NGR-hTNF: 0.8 ug/m² as 60-minute iv infusion every week until confirmed evidence of disease progression, plus Doxorubicin: 60 mg/m2 iv every 3 weeks for a maximum of 8 cycles

Arm title	Arm B: anthracycline alone

Arm description:

Arm B (control arm = anthracycline)
- Pegylated liposomal doxorubicin: 50 mg/m2 iv every 4 weeks until confirmed evidence of disease progression OR
- Doxorubicin: 60 mg/m2 iv every 3 weeks for a maximum of 8 cycles

Arm type	Active comparator
Investigational medicinal product name	Pegylated liposomal doxorubicin
Investigational medicinal product code	
Other name	Anthracycline
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

- Pegylated liposomal doxorubicin: 50 mg/m2 iv every 4 weeks until confirmed evidence of disease progression OR
- Doxorubicin: 60 mg/m2 iv every 3 weeks for a maximum of 8 cycles

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

Dosage and administration details:

- Pegylated liposomal doxorubicin: 50 mg/m2 iv every 4 weeks until confirmed evidence of disease progression OR
- Doxorubicin: 60 mg/m2 iv every 3 weeks for a maximum of 8 cycles

Number of subjects in period 1	Arm A: NGR-hTNF plus an anthracycline	Arm B: anthracycline alone
Started	68	65
Completed	52	49
Not completed	16	16
Physician decision	11	10
Consent withdrawn by subject	-	3
Adverse event, non-fatal	3	1
Death	2	-
Lost to follow-up	-	2

Baseline characteristics

Reporting groups	
Reporting group title	Arm A: NGR-hTNF plus an anthracycline
Reporting group description:	
Arm A (experimental arm = NGR-hTNF + anthracycline) -NGR-hTNF: 0.8 ug/m² as 60-minute intravenous infusion every week until confirmed evidence of disease progression, plus Pegylated liposomal doxorubicin: 50 mg/m2 iv every 4 weeks until confirmed evidence of disease progression OR - NGR-hTNF: 0.8 ug/m² as 60-minute intravenous infusion every week until confirmed evidence of disease progression, plus Doxorubicin: 60 mg/m2 iv every 3 weeks for a maximum of 8 cycles	
Reporting group title	Arm B: anthracycline alone
Reporting group description:	
Arm B (control arm = anthracycline) - Pegylated liposomal doxorubicin: 50 mg/m2 iv every 4 weeks until confirmed evidence of disease progression OR - Doxorubicin: 60 mg/m2 iv every 3 weeks for a maximum of 8 cycles	

Reporting group values	Arm A: NGR-hTNF plus an anthracycline	Arm B: anthracycline alone	Total
Number of subjects	68	65	133
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	42	40	82
From 65-84 years	26	25	51
85 years and over	0	0	0
Age continuous Units: years			
median	60.28	60.22	
standard deviation	± 9.77	± 9.17	-
Gender categorical Units: Subjects			
Female	68	65	133
Male	0	0	0

End points

End points reporting groups

Reporting group title	Arm A: NGR-hTNF plus an anthracycline

Reporting group description:

Arm A (experimental arm = NGR-hTNF + anthracycline)
-NGR-hTNF: 0.8 ug/m² as 60-minute intravenous infusion every week until confirmed evidence of disease progression, plus Pegylated liposomal doxorubicin: 50 mg/m2 iv every 4 weeks until confirmed evidence of disease progression OR
- NGR-hTNF: 0.8 ug/m² as 60-minute intravenous infusion every week until confirmed evidence of disease progression, plus Doxorubicin: 60 mg/m2 iv every 3 weeks for a maximum of 8 cycles

Reporting group title	Arm B: anthracycline alone

Reporting group description:

Arm B (control arm = anthracycline)
- Pegylated liposomal doxorubicin: 50 mg/m2 iv every 4 weeks until confirmed evidence of disease progression OR
- Doxorubicin: 60 mg/m2 iv every 3 weeks for a maximum of 8 cycles

Primary: Progression-free survival (PFS)

End point title	Progression-free survival (PFS)

End point description:

Progression-free survival (PFS), 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 plus an anthracycline	Arm B: anthracycline alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68	65		
Units: Days				
median (confidence interval 95%)	87 (63 to 111)	116 (61 to 158)		

Statistical analyses

Statistical analysis title	Progression-free survival (PFS)

Statistical analysis description:

The median PFS was 87 days (95% CI: 63-111 days) in arm A and 116 days (95% CI: 61-158 days) in arm B. Four (5.9%) patients in arm A and 9 (13.8%) in arm B were censored, while events (i.e. failures) were reported in 64 (94.1%) patients in arm A and in 56 (86.2%) in arm B. The comparison between arms in the log rank test did not show statistically significant differences (p = 0.232).

Comparison groups	Arm A: NGR-hTNF plus an anthracycline v Arm B: anthracycline alone

Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.232
Method	Logrank

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Overall Survival (OS), defined as the time from the date of randomization until death due to any cause

End point type	Secondary

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 plus an anthracycline	Arm B: anthracycline alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68	65		
Units: Days				
median (confidence interval 95%)	322 (167 to 406)	280 (236 to 304)		

Statistical analyses

Statistical analysis title	Overall Survival (OS)

Statistical analysis description:

The median OS was 322 days (95% CI: 167-406 days) in arm A and 280 days (95% CI: 236-304 days) in arm B. Three (4.4%) patients in arm A and 10 (15.4%) in arm B were censored, while events (i.e. deaths) were reported in 65 (95.6%) patients in arm A and in 55 (84.6%) in arm B. The comparison between arms in the log rank test did not show statistically significant differences (p = 0.98).

Comparison groups	Arm A: NGR-hTNF plus an anthracycline v Arm B: anthracycline alone
Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.98
Method	Logrank

Secondary: Response rate (RR)

End point title	Response rate (RR)

End point description:

Response rate (RR), 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:

Response rate was measured during the whole study and at each cycle.

End point values	Arm A: NGR-hTNF plus an anthracycline	Arm B: anthracycline alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68	65		
Units: Percentage of patients				
number (confidence interval 95%)	4.4 (0.9 to 12.4)	6.2 (1.7 to 15.0)		

Statistical analyses

Statistical analysis title	Response rate (RR)

Statistical analysis description:

Overall, response to treatment (CR or PR) was reported in 3 (4.4%; 95% CI: 0.9-12.4 %) patients in arm A and in 4 (6.2%; 95% CI: 1.7-15.0 %) in arm B. The difference between arms was not statistically significant (p = 0.6529).

Comparison groups	Arm A: NGR-hTNF plus an anthracycline v Arm B: anthracycline alone
Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6529
Method	Logrank

Secondary: Disease control rate (DCR)

End point title	Disease control rate (DCR)

End point description:

Disease Control Rate (overall/at each cycle) is defined as the percentage of subjects who have a Complete Response, a Partial Response or a Stable Disease(during the whole study/at each cycle).

End point type	Secondary

End point timeframe:

Disease control rate (DCR) was measured during the whole study/at each cycle.

End point values	Arm A: NGR-hTNF plus an anthracycline	Arm B: anthracycline alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68	65		
Units: Percentage of patients				
number (confidence interval 95%)	55.9 (43.3 to 67.9)	53.8 (41.0 to 66.3)		

Statistical analyses

Statistical analysis title	Disease Control Rate

Statistical analysis description:

Disease control (CR, PR or stable disease) was reported in 38 (55.9%; 95% CI: 43.3-67.9 %) patients in arm A and in 35 (53.8%; 95% CI: 41.0-66.3 %) in arm B. The difference between arms was not statistically significant (p = 0.8135). There were no statistically significant differences between arms in disease control rate at any treatment cycle.

Comparison groups	Arm B: anthracycline alone v Arm A: NGR-hTNF plus an anthracycline
Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8135
Method	Logrank

Secondary: Duration of disease control (DDC)

End point title	Duration of disease control (DDC)

End point description:

Duration of disease control: 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.

End point type	Secondary

End point timeframe:

Duration of disease control was measured from the date of randomization until disease progression.

End point values	Arm A: NGR-hTNF plus an anthracycline	Arm B: anthracycline alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68	65		
Units: Days				
median (confidence interval 95%)	144 (96 to 190)	120 (94 to 191)		

Statistical analyses

Statistical analysis title	Disease control rate (DDR)

Statistical analysis description:

The median duration of disease control was 144 days (95% CI: 96-190 days) in arm A and 120 days (95% CI: 94-191 days) in arm B. One (2.6%) patient in arm A and 3 (8.6%) patients in arm B were censored, while events (i.e. failure of disease control) were reported in 37 (97.4%) patients in arm A and in 32 (91.4%) in arm B. The comparison between arms in the log rank test did not show statistically significant differences (p = 0.755).

Comparison groups	Arm A: NGR-hTNF plus an anthracycline v Arm B: anthracycline alone
Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.755
Method	Logrank

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Unrelated events to be followed for 28 days after completion of the last treatment administration; related serious adverse events to be followed indefinitely until resolution or stabilization.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Arm A: NGR-hTNF plus an anthracycline
Reporting group description: -	
Reporting group title	Arm B: anthracycline alone

Reporting group description: -

Serious adverse events	Arm A: NGR-hTNF plus an anthracycline	Arm B: anthracycline alone	
Total subjects affected by serious adverse events			
subjects affected / exposed	24 / 68 (35.29%)	19 / 65 (29.23%)	
number of deaths (all causes)	65	55	
number of deaths resulting from adverse events	0	0	
Investigations			
Body Temperature			
subjects affected / exposed	0 / 68 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Left Ventricular Failure			
subjects affected / exposed	1 / 68 (1.47%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	0 / 68 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile Neutropenia			

subjects affected / exposed	2 / 68 (2.94%)	2 / 65 (3.08%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	1 / 68 (1.47%)	2 / 65 (3.08%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 68 (1.47%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 68 (1.47%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pain			
subjects affected / exposed	2 / 68 (2.94%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired self-care			
subjects affected / exposed	0 / 68 (0.00%)	1 / 65 (1.54%)	
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	6 / 68 (8.82%)	4 / 65 (6.15%)	
occurrences causally related to treatment / all	7 / 7	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	3 / 68 (4.41%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Ascites			
subjects affected / exposed	2 / 68 (2.94%)	4 / 65 (6.15%)	
occurrences causally related to treatment / all	2 / 2	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 68 (1.47%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 68 (1.47%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Jaundice Cholestatic			
subjects affected / exposed	1 / 68 (1.47%)	0 / 65 (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	3 / 68 (4.41%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural Effusion			
subjects affected / exposed	2 / 68 (2.94%)	3 / 65 (4.62%)	
occurrences causally related to treatment / all	2 / 2	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obliterative Bronchiolitis			
subjects affected / exposed	1 / 68 (1.47%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Hydronephrosis			

subjects affected / exposed	0 / 68 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oliguria			
subjects affected / exposed	0 / 68 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Sepsis			
subjects affected / exposed	2 / 68 (2.94%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cranial nerve infection			
subjects affected / exposed	1 / 68 (1.47%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral Fungal Infection			
subjects affected / exposed	1 / 68 (1.47%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 68 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Tract Infection			
subjects affected / exposed	0 / 68 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 68 (1.47%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Arm A: NGR-hTNF plus an anthracycline	Arm B: anthracycline alone	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	67 / 68 (98.53%)	63 / 65 (96.92%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	6 / 68 (8.82%)	3 / 65 (4.62%)	
occurrences (all)	7	4	
General disorders and administration site conditions			
Pain			
subjects affected / exposed	31 / 68 (45.59%)	28 / 65 (43.08%)	
occurrences (all)	71	39	
Fatigue			
subjects affected / exposed	30 / 68 (44.12%)	33 / 65 (50.77%)	
occurrences (all)	50	43	
Pyrexia			
subjects affected / exposed	17 / 68 (25.00%)	12 / 65 (18.46%)	
occurrences (all)	25	14	
Chills			
subjects affected / exposed	10 / 68 (14.71%)	1 / 65 (1.54%)	
occurrences (all)	13	1	
Mucosal Inflammation			
subjects affected / exposed	9 / 68 (13.24%)	6 / 65 (9.23%)	
occurrences (all)	11	7	
Oedema			
subjects affected / exposed	5 / 68 (7.35%)	6 / 65 (9.23%)	
occurrences (all)	5	6	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	8 / 68 (11.76%)	9 / 65 (13.85%)	
occurrences (all)	9	10	
Cough			
subjects affected / exposed	6 / 68 (8.82%)	9 / 65 (13.85%)	
occurrences (all)	6	9	

Pulmonary Embolism			
subjects affected / exposed	5 / 68 (7.35%)	1 / 65 (1.54%)	
occurrences (all)	5	1	
Pleural Effusion			
subjects affected / exposed	3 / 68 (4.41%)	4 / 65 (6.15%)	
occurrences (all)	3	4	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	6 / 68 (8.82%)	3 / 65 (4.62%)	
occurrences (all)	7	3	
Investigations			
Weight Decreased			
subjects affected / exposed	6 / 68 (8.82%)	6 / 65 (9.23%)	
occurrences (all)	6	7	
Activated partial thromboplastin time prolonged			
subjects affected / exposed	5 / 68 (7.35%)	2 / 65 (3.08%)	
occurrences (all)	6	2	
Gamma-Glutamyltransferase Increased			
subjects affected / exposed	5 / 68 (7.35%)	1 / 65 (1.54%)	
occurrences (all)	5	1	
Troponin Increased			
subjects affected / exposed	3 / 68 (4.41%)	1 / 65 (1.54%)	
occurrences (all)	3	1	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	4 / 68 (5.88%)	2 / 65 (3.08%)	
occurrences (all)	4	5	
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 68 (11.76%)	3 / 65 (4.62%)	
occurrences (all)	14	3	
Neuropathy Peripheral			
subjects affected / exposed	6 / 68 (8.82%)	4 / 65 (6.15%)	
occurrences (all)	7	4	
Dysgeusia			

subjects affected / exposed	4 / 68 (5.88%)	2 / 65 (3.08%)	
occurrences (all)	5	2	
Dizziness			
subjects affected / exposed	3 / 68 (4.41%)	3 / 65 (4.62%)	
occurrences (all)	4	3	
Lethargy			
subjects affected / exposed	2 / 68 (2.94%)	4 / 65 (6.15%)	
occurrences (all)	4	5	
Neurotoxicity			
subjects affected / exposed	2 / 68 (2.94%)	4 / 65 (6.15%)	
occurrences (all)	2	4	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	51 / 68 (75.00%)	39 / 65 (60.00%)	
occurrences (all)	123	113	
Leukopenia			
subjects affected / exposed	48 / 68 (70.59%)	41 / 65 (63.08%)	
occurrences (all)	107	115	
Anaemia			
subjects affected / exposed	43 / 68 (63.24%)	44 / 65 (67.69%)	
occurrences (all)	60	77	
Thrombocytopenia			
subjects affected / exposed	15 / 68 (22.06%)	18 / 65 (27.69%)	
occurrences (all)	29	47	
Lymphopenia			
subjects affected / exposed	13 / 68 (19.12%)	8 / 65 (12.31%)	
occurrences (all)	16	12	
Febrile Neutropenia			
subjects affected / exposed	5 / 68 (7.35%)	3 / 65 (4.62%)	
occurrences (all)	5	4	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	32 / 68 (47.06%)	30 / 65 (46.15%)	
occurrences (all)	54	42	
Constipation			

subjects affected / exposed	23 / 68 (33.82%)	19 / 65 (29.23%)	
occurrences (all)	41	20	
Vomiting			
subjects affected / exposed	23 / 68 (33.82%)	22 / 65 (33.85%)	
occurrences (all)	41	32	
Diarrhoea			
subjects affected / exposed	13 / 68 (19.12%)	9 / 65 (13.85%)	
occurrences (all)	20	10	
Stomatitis			
subjects affected / exposed	11 / 68 (16.18%)	9 / 65 (13.85%)	
occurrences (all)	12	14	
Intestinal Obstruction			
subjects affected / exposed	9 / 68 (13.24%)	5 / 65 (7.69%)	
occurrences (all)	10	7	
Ascites			
subjects affected / exposed	4 / 68 (5.88%)	6 / 65 (9.23%)	
occurrences (all)	4	7	
Dyspepsia			
subjects affected / exposed	3 / 68 (4.41%)	1 / 65 (1.54%)	
occurrences (all)	3	1	
Abdominal Discomfort			
subjects affected / exposed	2 / 68 (2.94%)	3 / 65 (4.62%)	
occurrences (all)	2	3	
Hepatobiliary disorders			
Hypertransaminasaemia			
subjects affected / exposed	5 / 68 (7.35%)	0 / 65 (0.00%)	
occurrences (all)	10	0	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	9 / 68 (13.24%)	10 / 65 (15.38%)	
occurrences (all)	11	11	
Palmar-Plantar Erythrodysaesthesia Syndrome			
subjects affected / exposed	9 / 68 (13.24%)	8 / 65 (12.31%)	
occurrences (all)	16	11	
Erythema			

subjects affected / exposed	2 / 68 (2.94%)	4 / 65 (6.15%)	
occurrences (all)	3	5	
Renal and urinary disorders			
Hydronephrosis			
subjects affected / exposed	1 / 68 (1.47%)	4 / 65 (6.15%)	
occurrences (all)	1	4	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 68 (7.35%)	1 / 65 (1.54%)	
occurrences (all)	9	6	
Infections and infestations			
Influenza			
subjects affected / exposed	2 / 68 (2.94%)	3 / 65 (4.62%)	
occurrences (all)	2	3	
Urinary Tract Infection			
subjects affected / exposed	1 / 68 (1.47%)	3 / 65 (4.62%)	
occurrences (all)	1	3	
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	14 / 68 (20.59%)	9 / 65 (13.85%)	
occurrences (all)	19	10	
Hypokalaemia			
subjects affected / exposed	5 / 68 (7.35%)	7 / 65 (10.77%)	
occurrences (all)	6	12	
Dehydration			
subjects affected / exposed	4 / 68 (5.88%)	1 / 65 (1.54%)	
occurrences (all)	4	1	
Hypercreatininaemia			
subjects affected / exposed	4 / 68 (5.88%)	2 / 65 (3.08%)	
occurrences (all)	4	2	
Hypoalbuminaemia			
subjects affected / exposed	3 / 68 (4.41%)	1 / 65 (1.54%)	
occurrences (all)	4	1	
Hyponatraemia			
subjects affected / exposed	3 / 68 (4.41%)	4 / 65 (6.15%)	
occurrences (all)	3	4	

Hypocalcaemia			
subjects affected / exposed	2 / 68 (2.94%)	2 / 65 (3.08%)	
occurrences (all)	2	2	
Hypomagnesaemia			
subjects affected / exposed	1 / 68 (1.47%)	3 / 65 (4.62%)	
occurrences (all)	1	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 February 2011	Summary of changes: The primary objective of the study was modified from the documentation of the preliminary antitumor activity to the comparison of the PFS in the two treatment arms. The rapid reporting, monitoring and analysis of all SSEs occurring during the first two treatment cycles of the first 24 patients randomized in both arms and treated with PLD was added. The parameters of the statistical analysis as a result of the modification of the primary objective were modified. The criteria of evaluation of adverse events were modified to specify the relation to PLD.
15 March 2011	Summary of changes: The dose of PLD to be administered was modified from 40 mg/m2 to 50 mg/m2 and the rationale was modified accordingly.
18 November 2011	Summary of changes: the possibility to administer doxorubicin as an alternative to the PLD was included and the title of the protocol was modified accordingly. The rationale and the primary objective of the study were modified in agreement to the inclusion of doxorubicin as an alternative to PLD. The trial design as the doxorubicin was administered every 3 weeks while PLD every 4 weeks was modified. The exclusion criterion No. 2 was modified as patients who had already received previous treatment with anthracycline were not eligible. The treatment duration was updated as doxorubicin was administered for a maximum of 8 cycles. The reference to management of allergic hypersensitivity reaction related to NGR-hTNF was included. The type of anthracycline as stratification factor was added. It was specified that the SSEs to be reported were those occurred in PLD-treated patients. The criteria of evaluation for the adverse events to specify the relation to the anthracycline and not just to PLD were specified. The guidelines regarding dose modification of doxorubicin for hematologic and nonhematologic toxicity were included.
16 October 2012	Summary of changes: an additional cohort of 24 patients to be included in the study was added. The study design was modified as the additional cohort of patients received NGR-hTNF every week instead of once every 3 weeks, and the rationale of the study in agreement to the inclusion of an additional cohort of patients was modified accordingly. Please note that Protocol IPR/24.E has been re-labelled as protocol IPR/26.A for Italy only.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported