



Clinical trial results:

A Multicenter, Open-Label, Phase 2 Study to Evaluate the Safety and Efficacy of NKTR-102 (PEG-Irinotecan) When Given on a Q14 Day or a Q21 Day Schedule in Patients with Metastatic Breast Cancer Whose Disease has Failed Prior Taxane-Based Treatment

Summary

EudraCT number	2008-005577-36
Trial protocol	BE GB
Global end of trial date	04 October 2011

Results information

Result version number	v1 (current)
This version publication date	05 August 2017
First version publication date	05 August 2017

Trial information

Trial identification

Sponsor protocol code	08-PIR-05
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00802945
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Nektar Therapeutics
Sponsor organisation address	455 Mission Bay Boulevard South, San Francisco, United States, CA 94158
Public contact	Nektar Therapeutics, Nektar Therapeutics, +001 415.482.5300, StudyInquiry@nektar.com
Scientific contact	Nektar Therapeutics, Nektar Therapeutics, +001 415.482.5300, StudyInquiry@nektar.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	13 December 2013
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	04 October 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the objective response rate (ORR) with NKTR-102 given on one of two schedules: once every 14 days (q14d) and once every 21 days (q21d)

Protection of trial subjects:

This study was carried out in compliance with the protocol and in accordance with the International Conference on Harmonization guidelines concerning Good Clinical Practice, appropriate US Food and Drug Administration Code of Federal Regulations, appropriate local laws, and the Declaration of Helsinki concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Patients, Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West, South Africa, 1996). Before implementing this study, the protocol, the proposed Informed Consent Form, and other information to subjects were reviewed by a properly constituted Institutional Review Board or Independent Ethics Committee.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 February 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 27
Country: Number of subjects enrolled	Belgium: 26
Country: Number of subjects enrolled	United States: 17
Worldwide total number of subjects	70
EEA total number of subjects	53

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	13
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects must not have had more than 2 prior chemotherapy regimens given in a metastatic setting and prior treatment in the adjuvant or the metastatic setting must have included a taxane. The subject may also have received chemotherapy in an adjuvant setting. Subjects were to be camptothecin naïve.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	NKTR-102 q14d

Arm description:

NKTR-102 was administered via intravenous (IV) infusion over 90 minutes on a q14d schedule (i.e., on Day 1 of each 2-week cycle) at a dose level of 145 mg/m².

Arm type	Experimental
Investigational medicinal product name	NKTR-102
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The study drug was formulated as a sterile lyophilized powder of NKTR-102 in lactate buffer at pH 3.5 supplied in 25 mL type-I amber-coloured glass vials. Each vial contained lyophilized NKTR-102 equivalent to 100 mg of irinotecan. NKTR-102 was reconstituted with 5% dextrose injection and administered via IV infusion over 90 minutes on a q14d schedule (i.e., on Day 1 of each 2-week cycle) at a dose level of 145 mg/m². Body surface area was determined based on baseline height and current weight before the start of each cycle. Specific dose modifications for NKTR-102 were made for neutropenia, thrombocytopenia, anemia, diarrhea, and other drug-related non-hematological toxicities. Study drug was continued until progression of disease, unacceptable toxicity, completion of 12 months of therapy measured from the date of randomization, death, withdrawal from the study by subject or Principal Investigator (PI), lost to follow-up, protocol violation, or study termination by Sponsor.

Arm title	NKTR-102 q21d
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Arm description:

NKTR-102 was administered via IV infusion over 90 minutes on a q21d schedule (e.g., on Day 1 of each 3-week cycle) at a dose level of 145 mg/m².

Arm type	Experimental
Investigational medicinal product name	NKTR-102
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The study drug was formulated as a sterile lyophilized powder of NKTR-102 in lactate buffer at pH 3.5 supplied in 25 mL type-I amber-coloured glass vials. Each vial contained lyophilized NKTR-102 equivalent to 100 mg of irinotecan. NKTR-102 was reconstituted with 5% dextrose injection and administered via IV infusion over 90 minutes on a q21d schedule (e.g., on Day 1 of each 3-week cycle) at a dose level of 145 mg/m². Body surface area was determined based on baseline height and current weight before the start of each cycle. Specific dose modifications for NKTR-102 were made for

neutropenia, thrombocytopenia, anemia, diarrhea, and other drug-related non-hematological toxicities. Study drug was continued until progression of disease, unacceptable toxicity, completion of 12 months of therapy measured from the date of randomization, death, withdrawal from the study by subject or PI, lost to follow-up, protocol violation, or study termination by Sponsor.

Number of subjects in period 1	NKTR-102 q14d	NKTR-102 q21d
Started	35	35
Completed	0	0
Not completed	35	35
Death	27	23
Study terminated by sponsor	8	12

Baseline characteristics

Reporting groups

Reporting group title	NKTR-102 q14d
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Reporting group description:

NKTR-102 was administered via intravenous (IV) infusion over 90 minutes on a q14d schedule (i.e., on Day 1 of each 2-week cycle) at a dose level of 145 mg/m².

Reporting group title	NKTR-102 q21d
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Reporting group description:

NKTR-102 was administered via IV infusion over 90 minutes on a q21d schedule (e.g., on Day 1 of each 3-week cycle) at a dose level of 145 mg/m².

Reporting group values	NKTR-102 q14d	NKTR-102 q21d	Total
Number of subjects	35	35	70
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)	29	28	57
From 65-84 years	6	7	13
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	53.1	55.8	
standard deviation	± 12.3	± 10.5	-
Gender categorical			
Units: Subjects			
Female	34	35	69
Male	1	0	1

End points

End points reporting groups

Reporting group title	NKTR-102 q14d
Reporting group description: NKTR-102 was administered via intravenous (IV) infusion over 90 minutes on a q14d schedule (i.e., on Day 1 of each 2-week cycle) at a dose level of 145 mg/m ² .	
Reporting group title	NKTR-102 q21d
Reporting group description: NKTR-102 was administered via IV infusion over 90 minutes on a q21d schedule (e.g., on Day 1 of each 3-week cycle) at a dose level of 145 mg/m ² .	

Primary: ORR:

End point title	ORR: ^[1]
End point description: The ORR was defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 and calculated as the number of subjects with a confirmed complete response (CR) or partial response (PR) divided by the total number of subjects evaluable at baseline. Subjects who did not have a confirmed CR or PR were counted as non-responders. The analyses were performed in the Intent-to-Treat (ITT) population which included all subjects who were randomised into one of two treatment arms.	
End point type	Primary
End point timeframe: Every 6 weeks from Cycle 1 Day 1 until documented disease progression, start of new therapy for cancer, or end of study.	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per the protocol, the planned analysis was descriptive only.

End point values	NKTR-102 q14d	NKTR-102 q21d		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	35		
Units: Percentage of subjects				
number (confidence interval 95%)	28.6 (14.6 to 46.3)	28.6 (14.6 to 46.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan Meier estimate of Progression-Free Survival (PFS)

End point title	Kaplan Meier estimate of Progression-Free Survival (PFS)
End point description: PFS was defined as the time from the date of first study drug administration to the earliest date of documented progressive disease (PD) or death due to any cause. PFS was the assessment of tumor progression according to RECIST by the PI. For subjects whose disease did not progress or who did not die, the PFS time was censored at the time of last tumor assessment that demonstrated lack of disease progression or at time of start of new cancer therapy for subjects who took new cancer therapy prior to having a documented PD. Subjects who did not undergo repeated imaging on-study were censored on	

Day 1. PFS was analysed for the ITT population.

End point type	Secondary
End point timeframe:	
Every 6 weeks from Cycle 1 Day 1 until documented disease progression, start of new therapy for cancer, or end of study.	

End point values	NKTR-102 q14d	NKTR-102 q21d		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	35		
Units: Months				
median (confidence interval 95%)	3.3 (2.6 to 5.7)	5.6 (1.8 to 6.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan Meier estimate of Overall Survival (OS)

End point title	Kaplan Meier estimate of Overall Survival (OS)
End point description:	
OS was calculated as the time from the date of first study drug administration until death from any cause. Subjects alive at the time of analysis were censored at the time they were last known alive. OS was analysed for the ITT population.	
End point type	Secondary
End point timeframe:	
From Cycle 1 Day 1 to death, withdrawal from the study by subject or PI, lost to follow-up, or study terminated by Sponsor.	

End point values	NKTR-102 q14d	NKTR-102 q21d		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	35		
Units: Months				
median (confidence interval 95%)	8.8 (5.4 to 15)	13.1 (9.2 to 19.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan Meier estimate of 6-month survival

End point title	Kaplan Meier estimate of 6-month survival
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End point description:

Six-month survival (i.e., overall survival proportion at 6 months) was estimated using Kaplan Meier method. The analyses were performed in the ITT population.

End point type	Secondary
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End point timeframe:

From Cycle 1 Day 1 to the end of 6 months.

End point values	NKTR-102 q14d	NKTR-102 q21d		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	35		
Units: Percentage of subjects				
number (confidence interval 95%)	57.1 (39.3 to 71.5)	82.9 (65.8 to 91.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan Meier estimate of 1-year Survival

End point title	Kaplan Meier estimate of 1-year Survival
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End point description:

One year survival (i.e., overall survival proportion at 12 months) was estimated using Kaplan Meier method. The analyses were performed in the ITT population.

End point type	Secondary
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End point timeframe:

From Cycle 1 Day 1 to the end of 12 months.

End point values	NKTR-102 q14d	NKTR-102 q21d		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	35		
Units: Percentage of subjects				
number (confidence interval 95%)	42.9 (26.4 to 58.3)	51.4 (34 to 66.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of Treatment-Emergent Adverse Events (TEAE): NCI-CTCAE Grade 3 or Higher With Incidence Rate $\geq$ 2% in Either Treatment Group

End point title	Incidence of Treatment-Emergent Adverse Events (TEAE): NCI-
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End point description:

An adverse event (AE) was defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE could therefore have been any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not thought to be related to the investigational product. TEAE was any event not present before exposure to the study drug or any event already present that worsened in either intensity or frequency after exposure to the study drug. All AEs were assessed for severity using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 3.0. If a particular AE was not listed in the NCI CTCAE Version 3.0, the following criteria were used: Grade 1 = Mild; Grade 2 = Moderate; Grade 3 = Severe; Grade 4 = Life threatening or disabling; Grade 5 = Death.

End point type Secondary

End point timeframe:

From the first dose of study medication through the End-of-Treatment visit.

End point values	NKTR-102 q14d	NKTR-102 q21d		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	35		
Units: Percentage of subjects				
number (not applicable)				
Number of Subjects With at Least 1 TEAE	68.6	54.3		
Diarrhoea	20	22.9		
Nausea	5.7	2.9		
Fatigue	14.3	8.6		
Vomiting	8.6	5.7		
Decreased appetite	2.9	0		
Abdominal pain	2.9	0		
Dehydration	8.6	11.4		
Neutropenia	11.4	11.4		
Anaemia	2.9	2.9		
Dyspnoea	2.9	0		
Disease progression	14.3	8.6		
Lethargy	2.9	0		
Dizziness	2.9	2.9		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the time of informed consent to the last study visit (30 days after the last infusion of study drug)

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	12.1
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Reporting groups

Reporting group title	NKTR-102 q14d
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Reporting group description:

NKTR-102 was administered via IV infusion over 90 minutes on a q14d schedule (i.e., on Day 1 of each 2-week cycle) at a dose level of 145 mg/m².

Reporting group title	NKTR-102 q21d
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Reporting group description:

NKTR-102 was administered via IV infusion over 90 minutes on a q21d schedule (e.g., on Day 1 of each 3-week cycle) at a dose level of 145 mg/m².

Serious adverse events	NKTR-102 q14d	NKTR-102 q21d	
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 35 (51.43%)	15 / 35 (42.86%)	
number of deaths (all causes)	27	23	
number of deaths resulting from adverse events	2	0	
Vascular disorders			
Lymphoedema			
subjects affected / exposed	1 / 35 (2.86%)	0 / 35 (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			
Disease Progression			
subjects affected / exposed	4 / 35 (11.43%)	3 / 35 (8.57%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 4	0 / 2	
Fatigue			
subjects affected / exposed	2 / 35 (5.71%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			

subjects affected / exposed	1 / 35 (2.86%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 35 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Lung Consolidation			
subjects affected / exposed	1 / 35 (2.86%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 35 (2.86%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Investigations			
Blood Pressure Decreased			
subjects affected / exposed	0 / 35 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ECG Signs Of Myocardial Ischaemia			
subjects affected / exposed	1 / 35 (2.86%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 35 (5.71%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Monoplegia			

subjects affected / exposed	1 / 35 (2.86%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal Cord Compression			
subjects affected / exposed	0 / 35 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 35 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile Neutropenia			
subjects affected / exposed	0 / 35 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 35 (2.86%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Vision Blurred			
subjects affected / exposed	1 / 35 (2.86%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	1 / 35 (2.86%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal Pain Lower			
subjects affected / exposed	1 / 35 (2.86%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Constipation			
subjects affected / exposed	0 / 35 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	6 / 35 (17.14%)	4 / 35 (11.43%)	
occurrences causally related to treatment / all	8 / 8	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileitis			
subjects affected / exposed	0 / 35 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	2 / 35 (5.71%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small Intestinal Obstruction			
subjects affected / exposed	0 / 35 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 35 (5.71%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	0 / 35 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal Failure Acute			
subjects affected / exposed	1 / 35 (2.86%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	

Musculoskeletal and connective tissue disorders			
Groin Pain			
subjects affected / exposed	0 / 35 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Neutropenic Sepsis			
subjects affected / exposed	0 / 35 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 35 (5.71%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Septic Shock			
subjects affected / exposed	1 / 35 (2.86%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 35 (5.71%)	4 / 35 (11.43%)	
occurrences causally related to treatment / all	2 / 2	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	NKTR-102 q14d	NKTR-102 q21d	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	35 / 35 (100.00%)	35 / 35 (100.00%)	
Investigations			
Weight decreased			
subjects affected / exposed	3 / 35 (8.57%)	7 / 35 (20.00%)	
occurrences (all)	4	8	
Vascular disorders			

Hypotension subjects affected / exposed occurrences (all)	3 / 35 (8.57%) 3	1 / 35 (2.86%) 1	
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 3	2 / 35 (5.71%) 2	
Dysgeusia subjects affected / exposed occurrences (all)	3 / 35 (8.57%) 4	4 / 35 (11.43%) 5	
Headache subjects affected / exposed occurrences (all)	4 / 35 (11.43%) 4	4 / 35 (11.43%) 5	
Lethargy subjects affected / exposed occurrences (all)	3 / 35 (8.57%) 6	5 / 35 (14.29%) 6	
Paraesthesia subjects affected / exposed occurrences (all)	3 / 35 (8.57%) 3	1 / 35 (2.86%) 1	
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	6 / 35 (17.14%) 7	3 / 35 (8.57%) 3	
Neutropenia subjects affected / exposed occurrences (all)	5 / 35 (14.29%) 9	7 / 35 (20.00%) 19	
General disorders and administration site conditions			
Asthenia subjects affected / exposed occurrences (all)	4 / 35 (11.43%) 7	2 / 35 (5.71%) 2	
Fatigue subjects affected / exposed occurrences (all)	15 / 35 (42.86%) 55	18 / 35 (51.43%) 31	
Oedema peripheral subjects affected / exposed occurrences (all)	4 / 35 (11.43%) 4	2 / 35 (5.71%) 2	

Pain subjects affected / exposed occurrences (all)	3 / 35 (8.57%) 3	1 / 35 (2.86%) 1	
Pyrexia subjects affected / exposed occurrences (all)	4 / 35 (11.43%) 5	3 / 35 (8.57%) 3	
Eye disorders Vision blurred subjects affected / exposed occurrences (all)	8 / 35 (22.86%) 11	6 / 35 (17.14%) 11	
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	7 / 35 (20.00%) 9	8 / 35 (22.86%) 11	
Abdominal pain upper subjects affected / exposed occurrences (all)	3 / 35 (8.57%) 3	4 / 35 (11.43%) 5	
Constipation subjects affected / exposed occurrences (all)	14 / 35 (40.00%) 21	8 / 35 (22.86%) 8	
Diarrhoea subjects affected / exposed occurrences (all)	24 / 35 (68.57%) 58	27 / 35 (77.14%) 61	
Dry mouth subjects affected / exposed occurrences (all)	3 / 35 (8.57%) 3	4 / 35 (11.43%) 4	
Dyspepsia subjects affected / exposed occurrences (all)	4 / 35 (11.43%) 4	2 / 35 (5.71%) 2	
Nausea subjects affected / exposed occurrences (all)	24 / 35 (68.57%) 33	26 / 35 (74.29%) 36	
Vomiting subjects affected / exposed occurrences (all)	18 / 35 (51.43%) 33	14 / 35 (40.00%) 18	
Respiratory, thoracic and mediastinal disorders			

Cough subjects affected / exposed occurrences (all)	4 / 35 (11.43%) 4	2 / 35 (5.71%) 2	
Dyspnoea subjects affected / exposed occurrences (all)	6 / 35 (17.14%) 8	3 / 35 (8.57%) 3	
Epistaxis subjects affected / exposed occurrences (all)	3 / 35 (8.57%) 5	1 / 35 (2.86%) 1	
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all)	7 / 35 (20.00%) 8	4 / 35 (11.43%) 5	
Pruritus subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2	2 / 35 (5.71%) 2	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	4 / 35 (11.43%) 4	2 / 35 (5.71%) 2	
Back pain subjects affected / exposed occurrences (all)	4 / 35 (11.43%) 4	2 / 35 (5.71%) 3	
Musculoskeletal chest pain subjects affected / exposed occurrences (all)	3 / 35 (8.57%) 3	1 / 35 (2.86%) 1	
Pain in extremity subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2	2 / 35 (5.71%) 2	
Infections and infestations Upper respiratory tract infection subjects affected / exposed occurrences (all)	3 / 35 (8.57%) 3	1 / 35 (2.86%) 1	
Urinary tract infection subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 3	2 / 35 (5.71%) 3	

Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	14 / 35 (40.00%)	12 / 35 (34.29%)	
occurrences (all)	15	15	
Dehydration			
subjects affected / exposed	6 / 35 (17.14%)	3 / 35 (8.57%)	
occurrences (all)	6	4	
Hyperglycaemia			
subjects affected / exposed	2 / 35 (5.71%)	2 / 35 (5.71%)	
occurrences (all)	3	2	
Hypokalaemia			
subjects affected / exposed	4 / 35 (11.43%)	2 / 35 (5.71%)	
occurrences (all)	7	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 March 2009	1. Lowered the starting dose of NKTR-102 from 170 mg/m² to 145 mg/m² based on safety data from the Phase 1 study with NKTR-102 (06-IN-IR001) and ongoing Phase 2 studies in colorectal and ovarian cancer. 2. A secondary objective to collect pharmacokinetic samples was removed and all procedures related to pharmacokinetic sampling were omitted. No pharmacokinetic samples had been collected prior to this amendment. 3. An exploratory objective of the study (CA27.29) was removed. 4. Eligibility was changed to clarify that subjects were to have metastatic breast cancer (subjects with locally advanced disease were excluded). 5. Eligibility criteria regarding measurable disease was clarified (RECIST version 1.0 would be used; the sponsor was no longer required to review the baseline radiological assessment for acceptability). 6. Entry criteria for total bilirubin was changed to be ≤ 2.0 mg/dL instead of below the upper limit of normal range. 7. Entry criteria for albumin ≥ 3.0 g/dL was deleted. 8. Amended exclusion criteria. 9. The washout period for prior malignancy was expanded from 3 to 5 years. 10. Screening period was expanded from 14 to 28 days. 11. Non-treatment day study visits were removed. 12. Period of birth control was changed to at least 8 months after the last dose of study drug per request from Health Canada. 13. Added that the duration of treatment will conclude at 12 months measured from the date of randomization. 14. Added the dose modifications of 25 mg/m² for non-hematologic and nondiarrheal toxicities of Grade 2, 3, and 4 excluding alopecia, anorexia, and asthenia. 15. Included sponsor consideration for treatment delays beyond 2 weeks. 16. Allowed the use of erythroid stimulating agents as clinically indicated rather than as a rescue setting only. 17. Defined interval for follow-up contacts as quarterly following the End-of-Treatment Visit. 18. Study personnel names and contact information were updated.
02 November 2009	1. Changed the eligibility criteria such that subjects who receive taxanes in the adjuvant setting as well as the metastatic setting were allowed to enter the study if they had failed taxanes and required additional chemotherapy. 2. The adverse event reporting requirements and follow-up were revised to require the collection and reporting of new Suspected Unexpected Serious Adverse Reactions that were experienced by subjects in the follow-up period. In addition, it also provided clarification on data entry regarding outcome of unrelated AEs that were ongoing at the time of End-of-Treatment visit. 3. Clarified the language on the screening tests for hematology, chemistry, and coagulation such that screening laboratories should have been performed within 28 days of first dose of study treatment. 4. Increased the pretreatment interval for clinical laboratory tests from 1 day to 3 days. 5. Updated the language concerning anti-diarrheal therapy. 6. Updated the pH of the formulation of NKTR-102 and the storage duration of reconstituted NKTR-102. 7. The infusion time for NKTR-102 was updated to include a window of ± 10 minutes. 8. Added language defining adequate forms of birth control. 9. Deleted requirement for reporting AEs using synonyms in NCI-CTCAE. 10. Study personnel names and contact information were updated.

30 March 2010	1. Clarified that study drug continued until progression of disease, unacceptable toxicity, completion of 12 months of therapy measured from the date of randomization, death, withdrawal by subject, PI decision, lost to follow-up, protocol violations, or study termination by Sponsor. 2. Provided instruction for use of antiemetic therapy. 3. Clarified censoring rules for progression-free survival and overall survival. 4. Radiographic imaging should only have occurred at the End-of-Treatment visit if these tests had not been performed within the prior 6 weeks. 5. Clarified that documented tumor measurements were required using computed tomography scans or magnetic resonance imaging, as appropriate, and were to be performed during screening, approximately every 6 weeks from Cycle 1 Day 1 until documented disease progression, start of new therapy for cancer, or end of study. 6. Progression was to be only assessed during the follow-up period if the subject did not progress during the study drug treatment period. Quarterly follow-up continued until death, withdrawal by subject, PI decision, lost to follow-up, or study termination by Sponsor. Quarterly follow-up continued until the completion of the study. 7. Section 8.4 (Dose Modification and Delays) clarified that dose medication should have only been made for "drug-related" non-hematologic toxicities. Clarified dose modification guidelines in a setting of nausea/vomiting. 8. The time frame in which information regarding collection of concomitant medications was clarified. 9. Glutamyl transpeptidase was removed for assessments for liver function tests; aspartate aminotransferase and alanine aminotransferase continue to be required for liver function test assessment. 10. Section 10 (AE Reporting) was made consistent with similar language in other Phase 2 NKTR-102 protocols. 11. Clarified that duration of response applied to partial responses as well as complete responses.
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported