



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 |
|-----------------------|-----------|

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 |
|------------------|---------------|

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 |
|-----------------------|---------------|

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 |
|-----------------------|---------------|

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 |
|-----------------|---|

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 |
|----------------|-----------|

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 |
|-----------------|--|

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 |
|----------------|-----------|

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- |
|-----------------|---|

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 |
|-----------------|----------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 12.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------------|
| Reporting group title | NKTR-102 q14d |
|-----------------------|---------------|

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 |
|-----------------------|---------------|

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 | <ol style="list-style-type: none">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 | <ol style="list-style-type: none">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 | <ol style="list-style-type: none"> 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. |
|---------------|--|

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported