Clinical trial results:
A Multicenter, Open-Label, Randomized, Phase 2 Study to Evaluate the Efficacy and Safety of NKTR-102 Versus Irinotecan in Patients with Second-Line, Irinotecan-Naïve, KRAS-Mutant, Metastatic Colorectal Cancer (mCRC)

Summary

EudraCT number	2008-004093-40
Trial protocol	ES BE DE GB SK LV
Global end of trial date	12 December 2014

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-03

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00856375
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	01 February 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 December 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To estimate the progression-free survival (PFS), overall survival (OS), objective response rate (ORR) and duration of response (DoR) with NKTR-102 versus irinotecan, to characterize the safety profile of NKTR-102 and to evaluate the pharmacokinetics (PK) of NKTR-102 or irinotecan and their respective metabolites in a subset of patients.

Protection of trial subjects:

This study was carried out in compliance with the International Conference on Harmonisation Harmonized Tripartite Guidelines for Good Clinical Practice 1996, the United States (US) 21 Code of Federal Regulations dealing with clinical studies (including Parts 50 and 56 concerning informed consent and IRB regulations) and the Declaration of Helsinki, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West, South Africa, 1996, Edinburgh 2000, Washington 2002, Tokyo 2004, and Seoul 2008). Before implementing this study, the protocol, the proposed Informed Consent Form, and other information to patients were reviewed by a properly constituted Institutional Review Board or Independent Ethics Committee.

Background therapy: -

Evidence for comparator:

Irinotecan is a topoisomerase I inhibitor approved worldwide. In the US, irinotecan is indicated as a component of first-line therapy in combination with 5-fluorouracil (5-FU) and leucovorin for patients with metastatic carcinoma of the colon or rectum. Irinotecan is also indicated for patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following initial fluorouracil-based therapy. In the European Union, irinotecan is indicated for the treatment of patients with advanced colorectal cancer in combination with 5-fluorouracil and folinic acid in patients without prior chemotherapy for advanced disease, or as a single agent in patients who have failed an established 5-fluorouracil containing treatment regimen. Irinotecan was chosen as the control for this study because irinotecan is indicated for patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following initial fluorouracil-based therapy.

Actual start date of recruitment	25 February 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	United Kingdom: 13
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	India: 13
Country: Number of subjects enrolled	United States: 50

Worldwide total number of subjects	83
EEA total number of subjects	20

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)	60
From 65 to 84 years	23
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Patients must have received 1 but no more than 1 prior fluoropyrimidine-containing regimen for metastatic disease and were to be naïve to irinotecan. The patient may have received a fluoropyrimidine in an adjuvant or neoadjuvant setting.

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

Arm description:

NKTR-102 was administered as an intravenous (IV) infusion over 90 ± 10 minutes, on Day 1 of each 21-day [± 2 days] cycle) at a dose level of 145 mg/m^2.

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:

NKTR-102 was administered as an IV infusion over 90 ± 10 minutes, using low sorbing tubing, on Day 1 of each 21-day [± 2 days] cycle at a dose level of 145 mg/m^2. Body surface area was determined based on baseline height and current weight before the start of each cycle. The NKTR-102 drug product 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 for injection was reconstituted with commercially available 5% dextrose injection. Specific NKTR-102 dose modifications could be made for drug-related neutropenia, thrombocytopenia, anaemia, diarrhoea, and other drug-related, non-haematological toxicities. Study drug was continued until disease progression, unacceptable toxicity, death, withdrawal by patient, Principal Investigator decision, lost to follow-up, protocol violation, or study termination by Sponsor.

Arm title	Irinotecan

Arm description:

Irinotecan was administered as an IV infusion over 90 ± 10 minutes on Day 1 of a 21-day (± 2 days) treatment cycle at a dose level of 350 mg/m^2. Patients aged 65 or older, or those with prior abdominal or pelvic irradiation, were given a lower dose of 300 mg/m^2.

Arm type	Active comparator
Investigational medicinal product name	Irinotecan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Irinotecan was administered as an IV infusion over 90 ± 10 minutes on Day 1 of a 21-day (± 2 days) treatment cycle at a dose level of 350 mg/m^2. Patients aged 65 or older, or those with prior abdominal or pelvic irradiation, were given a lower dose of 300 mg/m^2. Body surface area was determined based on baseline height and current weight before the start of each cycle. The storage, preparation, dosage, and administration of the irinotecan and the irinotecan infusion solution were conducted per the product

labelling for the commercial product. Specific irinotecan dose modifications could be made for drug-related neutropenia, thrombocytopenia, anaemia, diarrhoea, and other drug-related, non-haematological toxicities. Study drug was continued until disease progression, unacceptable toxicity, death, withdrawal by patient, Principal Investigator decision, lost to follow-up, protocol violation, or study termination by Sponsor.

Number of subjects in period 1	NKTR-102	Irinotecan
Started	42	41
Completed	0	0
Not completed	42	41
Consent withdrawn by subject	2	1
Death	32	30
Lost to follow-up	1	2
Sponsor terminated study	7	7
unspecified	-	1

Baseline characteristics

Reporting groups	
Reporting group title	NKTR-102
Reporting group description:	
NKTR-102 was administered as an intravenous (IV) infusion over 90 ± 10 minutes, on Day 1 of each 21-day [± 2 days] cycle) at a dose level of 145 mg/m^2.	
Reporting group title	Irinotecan
Reporting group description:	
Irinotecan was administered as an IV infusion over 90 ± 10 minutes on Day 1 of a 21-day (± 2 days) treatment cycle at a dose level of 350 mg/m^2. Patients aged 65 or older, or those with prior abdominal or pelvic irradiation, were given a lower dose of 300 mg/m^2.	

Reporting group values	NKTR-102	Irinotecan	Total
Number of subjects	42	41	83
Age categorical			
Units: Subjects			
Adults (18-64 years)	30	30	60
From 65-84 years	12	11	23
Age continuous			
Units: years			
arithmetic mean	58.5	57.8	
standard deviation	± 10.65	± 11.4	-
Gender categorical			
Units: Subjects			
Female	18	16	34
Male	24	25	49

End points

End points reporting groups

Reporting group title	NKTR-102
Reporting group description:	
NKTR-102 was administered as an intravenous (IV) infusion over 90 ± 10 minutes, on Day 1 of each 21-day [± 2 days] cycle) at a dose level of 145 mg/m^2.	
Reporting group title	Irinotecan
Reporting group description:	
Irinotecan was administered as an IV infusion over 90 ± 10 minutes on Day 1 of a 21-day (± 2 days) treatment cycle at a dose level of 350 mg/m^2. Patients aged 65 or older, or those with prior abdominal or pelvic irradiation, were given a lower dose of 300 mg/m^2.	

Primary: Kaplan-Meier Estimate of PFS by Central Radiological Review: ITT Population

End point title	Kaplan-Meier Estimate of PFS by Central Radiological Review: ITT Population
End point description:	
PFS was defined as the time from the date of randomisation to the date of disease progression (assessed by central radiological review according to Response Evaluation Criteria in Solid Tumors [RECIST] 1.1) or death due to any cause, whichever comes first. PFS was determined using the intention-to-treat (ITT) population which included all randomised patients who underwent baseline evaluation, with treatment assigned according to randomised arm. For patients whose disease did not progress or who did not die, the PFS time was censored at the time of the last tumor assessment that demonstrated lack of disease progression. For patients who received new anti-cancer therapy, the PFS time was censored at the time of last tumor assessment prior to the new anti-cancer therapy starts.	
End point type	Primary
End point timeframe:	
Every 6 weeks (± 5 days) from Cycle 1, Day 1 until documented disease progression, start of new therapy for cancer, death, or end of study.	

End point values	NKTR-102	Irinotecan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	41		
Units: Months				
median (confidence interval 95%)	4 (2.7 to 5.9)	2.8 (1.4 to 4.1)		

Statistical analyses

Statistical analysis title	Analysis of PFS
Comparison groups	NKTR-102 v Irinotecan

Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.07
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.645
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	1.041

Notes:

[1] - Hazard Ratio and 95% CI from univariate Cox regression model

Secondary: Kaplan-Meier Estimate of OS: ITT Population

End point title	Kaplan-Meier Estimate of OS: ITT Population

End point description:

Duration of OS was defined as the time from the date of randomisation to the date of death due to any cause. Patients were followed until their date of death, loss to follow-up, withdrawal of consent for further follow-up for survival, or final database closure. Patients who were lost-to-follow-up or were not known to have died were censored at last date they were shown to be alive. Patients who did not have any follow-up since the date of randomisation were censored at the date of randomization.

End point type	Secondary

End point timeframe:

From randomisation to death, loss to follow-up, withdrawal of consent for further follow-up for survival, or final database closure.

End point values	NKTR-102	Irinotecan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	41		
Units: Months				
median (confidence interval 95%)	9.6 (7.3 to 13.2)	8.4 (4.4 to 13.3)		

Statistical analyses

Statistical analysis title	Analysis of OS
Comparison groups	NKTR-102 v Irinotecan
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 0.706
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.91

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.557
upper limit	1.486

Notes:

[2] - Hazard ratio and 95% CI from univariate Cox regression model.

Secondary: ORR by Central Radiological Review: ITT Population

End point title	ORR by Central Radiological Review: ITT Population

End point description:

ORR was defined as the proportion of patients with a complete response (CR) or a partial response (PR) per RECIST 1.1 based upon the best response as assessed by central radiological review; confirmation of response was not required. The analyses were performed for patients in the ITT population who had measurable disease as determined by the central imaging facility at baseline.

End point type	Secondary

End point timeframe:

Every 6 weeks (± 5 days) from Cycle 1, Day 1 until documented disease progression, start of new therapy for cancer, death, or end of study.

End point values	NKTR-102	Irinotecan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	41		
Units: Percentage of Patients				
number (confidence interval 95%)	9.8 (2.7 to 23.1)	5 (0.6 to 16.9)		

Statistical analyses

Statistical analysis title	Analysis of ORR
Comparison groups	NKTR-102 v Irinotecan
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.676
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	2.054
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.355
upper limit	11.9

Secondary: DoR by Central Radiological Review: ITT Population

End point title	DoR by Central Radiological Review: ITT Population

End point description:

DoR was defined as the time from the first documented CR or PR, the date of PD (assessed by central radiological review according to RECIST 1.1), or death due to any cause, whichever came first. Patients who were alive without documented PD per RECIST were censored at the date of last tumor assessment without disease progression or start of new anti-cancer therapy for the study disease, whichever was earlier.

End point type	Secondary

End point timeframe:

From the time measurement criteria for CR/PR (whichever was first recorded) were first met until the first date that recurrent disease or PD or death was objectively documented.

End point values	NKTR-102	Irinotecan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	41		
Units: Months				
median (confidence interval 95%)	7.9 (1.5 to 11.6)	1.4 (1.4 to 1.4)		

Statistical analyses

Statistical analysis title	Analysis of DoR
Comparison groups	NKTR-102 v Irinotecan
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.018
Method	Logrank

Secondary: Incidence of Treatment-Emergent Adverse Events NCI-CTCAE Grade 3 or Higher With Incidence Rate ≥ 2% in Either Treatment Group

End point title	Incidence of Treatment-Emergent Adverse Events NCI-CTCAE Grade 3 or Higher With Incidence Rate ≥ 2% in Either Treatment Group

End point description:

An adverse event (AE) was any untoward medical occurrence in a patient administered a pharmaceutical product which did not necessarily have a causal relationship with the treatment. An AE could have been any unfavourable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Pre-existing events, which increased in frequency or severity or changed in nature during or as a consequence of use of the study medication were also considered as AEs. 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 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 (30 ± 3 days from last dose

of study drug).

End point values	NKTR-102	Irinotecan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	41		
Units: Percentage of Patients				
number (not applicable)				
Percentage of Patients with ≥1 TEAE	61.9	63.9		
Diarrhea	21.4	19.5		
Neutropenia	7.1	14.6		
Abdominal Pain	14.3	4.9		
Dehydration	9.5	9.8		
Vomiting	11.9	7.3		
Nausea	14.3	2.4		
Hypokalemia	7.1	7.3		
Fatigue	9.5	2.4		
Intestinal Obstruction	2.4	9.8		
Leukopenia	7.1	4.9		
Febrile Neutropenia	2.4	7.3		
Alopecia	2.4	4.9		
Disease Progression	4.8	2.4		
Hyponatremia	2.4	4.9		
Acute Prerenal Failure	2.4	2.4		
Asthenia	2.4	2.4		
Hyperbilirubinemia	2.4	2.4		
Performance Status Decreased	4.8	0		
Sepsis	0	4.9		

Statistical analyses

No statistical analyses for this end point

Secondary: PK Parameters of NKTR-102 or Irinotecan and Respective Metabolites

End point title	PK Parameters of NKTR-102 or Irinotecan and Respective Metabolites

End point description:

Blood samples for PK analysis were collected from 4 patients only, 3 from the irinotecan treatment arm and 1 from the NKTR-102 treatment arm. NKTR-102, irinotecan, SN38, SN38-G, 7-ethyl-10-[4-N-(5-aminopentanoic acid)-1-piperidino]carbonyloxycamptothecin, and 7-ethyl-10-(4-amino-1-piperidino) carbonyloxycamptothecin concentration levels were determined. However, due to the limited number of patients with PK samples, no further PK analysis was conducted.

End point type	Secondary

End point timeframe:

Days 1, 2, 3, 4, 8 and 15 of Cycles 1 and 3 and Day 1 of Cycles 2, 4 and all subsequent cycles.

End point values	NKTR-102	Irinotecan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[3]	0[4]		
Units: ng/mL				
number (not applicable)				

Notes:

[3] - Due to the limited number of patients with PK samples, no PK analysis was conducted.

[4] - Due to the limited number of patients with PK samples, no PK analysis was conducted.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events and serious adverse events were reported from the time the patient received the first dose of study drug through the End-of-Treatment Visit (i.e., 30 ± 3 days after the last dose of study drug).

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	12.0

Reporting groups

Reporting group title	NKTR-102
Reporting group description: -	
Reporting group title	Irinotecan
Reporting group description: -	

Serious adverse events	NKTR-102	Irinotecan	
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 42 (45.24%)	24 / 41 (58.54%)	
number of deaths (all causes)	32	30	
number of deaths resulting from adverse events	1	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour ulceration			
subjects affected / exposed	0 / 42 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Therapeutic agent toxicity			
subjects affected / exposed	0 / 42 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 42 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			

Dizziness			
subjects affected / exposed	0 / 42 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somnolence			
subjects affected / exposed	1 / 42 (2.38%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 42 (2.38%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	0 / 42 (0.00%)	3 / 41 (7.32%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	1 / 42 (2.38%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	0 / 42 (0.00%)	2 / 41 (4.88%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	0 / 42 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 42 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration			

site conditions			
Disease progression			
subjects affected / exposed	2 / 42 (4.76%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Asthenia			
subjects affected / exposed	1 / 42 (2.38%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	1 / 42 (2.38%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	1 / 42 (2.38%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Performance status decreased			
subjects affected / exposed	1 / 42 (2.38%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	4 / 42 (9.52%)	7 / 41 (17.07%)	
occurrences causally related to treatment / all	5 / 5	8 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 42 (2.38%)	4 / 41 (9.76%)	
occurrences causally related to treatment / all	0 / 1	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vomiting			
subjects affected / exposed	2 / 42 (4.76%)	2 / 41 (4.88%)	
occurrences causally related to treatment / all	2 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Abdominal pain			
subjects affected / exposed	2 / 42 (4.76%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	2 / 42 (4.76%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anorectal discomfort			
subjects affected / exposed	0 / 42 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	0 / 42 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 42 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 42 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma			
subjects affected / exposed	1 / 42 (2.38%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 42 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal obstruction			

subjects affected / exposed	1 / 42 (2.38%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	1 / 42 (2.38%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal haemorrhage			
subjects affected / exposed	0 / 42 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 42 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	1 / 42 (2.38%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	0 / 42 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 42 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 42 (2.38%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hypoxia			
subjects affected / exposed	1 / 42 (2.38%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 42 (2.38%)	0 / 41 (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			
Acute prerenal failure			
subjects affected / exposed	1 / 42 (2.38%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Renal failure acute			
subjects affected / exposed	1 / 42 (2.38%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Sepsis			
subjects affected / exposed	0 / 42 (0.00%)	3 / 41 (7.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Diarrhoea Infectious			
subjects affected / exposed	0 / 42 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia infection			
subjects affected / exposed	1 / 42 (2.38%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orchitis			
subjects affected / exposed	0 / 42 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	3 / 42 (7.14%)	3 / 41 (7.32%)	
occurrences causally related to treatment / all	2 / 3	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 42 (2.38%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 42 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
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	Irinotecan	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	42 / 42 (100.00%)	38 / 41 (92.68%)	
Investigations			
Haemoglobin decreased			
subjects affected / exposed	2 / 42 (4.76%)	6 / 41 (14.63%)	
occurrences (all)	7	8	
Weight decreased			
subjects affected / exposed	13 / 42 (30.95%)	6 / 41 (14.63%)	
occurrences (all)	14	6	
Neutrophil count decreased			
subjects affected / exposed	5 / 42 (11.90%)	2 / 41 (4.88%)	
occurrences (all)	8	3	
Nervous system disorders			
Lethargy			
subjects affected / exposed	3 / 42 (7.14%)	5 / 41 (12.20%)	
occurrences (all)	10	19	
Headache			
subjects affected / exposed	5 / 42 (11.90%)	1 / 41 (2.44%)	
occurrences (all)	5	1	

Dizziness			
subjects affected / exposed	7 / 42 (16.67%)	6 / 41 (14.63%)	
occurrences (all)	7	10	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 42 (14.29%)	6 / 41 (14.63%)	
occurrences (all)	7	7	
Leukopenia			
subjects affected / exposed	5 / 42 (11.90%)	1 / 41 (2.44%)	
occurrences (all)	7	1	
Neutropenia			
subjects affected / exposed	7 / 42 (16.67%)	5 / 41 (12.20%)	
occurrences (all)	14	8	
Thrombocytopenia			
subjects affected / exposed	4 / 42 (9.52%)	4 / 41 (9.76%)	
occurrences (all)	5	4	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	20 / 42 (47.62%)	18 / 41 (43.90%)	
occurrences (all)	25	34	
Pyrexia			
subjects affected / exposed	4 / 42 (9.52%)	7 / 41 (17.07%)	
occurrences (all)	8	7	
Asthenia			
subjects affected / exposed	6 / 42 (14.29%)	3 / 41 (7.32%)	
occurrences (all)	9	4	
Oedema peripheral			
subjects affected / exposed	1 / 42 (2.38%)	4 / 41 (9.76%)	
occurrences (all)	1	4	
Eye disorders			
Vision blurred			
subjects affected / exposed	5 / 42 (11.90%)	1 / 41 (2.44%)	
occurrences (all)	5	1	
Gastrointestinal disorders			
Diarrhoea			

subjects affected / exposed	26 / 42 (61.90%)	28 / 41 (68.29%)	
occurrences (all)	62	66	
Nausea			
subjects affected / exposed	23 / 42 (54.76%)	24 / 41 (58.54%)	
occurrences (all)	41	45	
Vomiting			
subjects affected / exposed	17 / 42 (40.48%)	20 / 41 (48.78%)	
occurrences (all)	27	33	
Abdominal pain			
subjects affected / exposed	17 / 42 (40.48%)	13 / 41 (31.71%)	
occurrences (all)	25	21	
Constipation			
subjects affected / exposed	12 / 42 (28.57%)	10 / 41 (24.39%)	
occurrences (all)	18	16	
Abdominal pain upper			
subjects affected / exposed	5 / 42 (11.90%)	4 / 41 (9.76%)	
occurrences (all)	5	5	
Dyspepsia			
subjects affected / exposed	3 / 42 (7.14%)	4 / 41 (9.76%)	
occurrences (all)	3	4	
Abdominal distension			
subjects affected / exposed	1 / 42 (2.38%)	5 / 41 (12.20%)	
occurrences (all)	1	5	
Proctalgia			
subjects affected / exposed	2 / 42 (4.76%)	3 / 41 (7.32%)	
occurrences (all)	2	3	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 42 (4.76%)	3 / 41 (7.32%)	
occurrences (all)	2	4	
Dyspnoea			
subjects affected / exposed	3 / 42 (7.14%)	2 / 41 (4.88%)	
occurrences (all)	3	2	
Skin and subcutaneous tissue disorders			

Alopecia			
subjects affected / exposed	7 / 42 (16.67%)	24 / 41 (58.54%)	
occurrences (all)	8	27	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	5 / 42 (11.90%)	0 / 41 (0.00%)	
occurrences (all)	7	0	
Insomnia			
subjects affected / exposed	3 / 42 (7.14%)	2 / 41 (4.88%)	
occurrences (all)	3	2	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	3 / 42 (7.14%)	3 / 41 (7.32%)	
occurrences (all)	3	4	
Pain in extremity			
subjects affected / exposed	3 / 42 (7.14%)	3 / 41 (7.32%)	
occurrences (all)	3	3	
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	13 / 42 (30.95%)	10 / 41 (24.39%)	
occurrences (all)	15	11	
Dehydration			
subjects affected / exposed	5 / 42 (11.90%)	5 / 41 (12.20%)	
occurrences (all)	5	5	
Hypokalaemia			
subjects affected / exposed	9 / 42 (21.43%)	3 / 41 (7.32%)	
occurrences (all)	17	9	
Hyponatraemia			
subjects affected / exposed	5 / 42 (11.90%)	2 / 41 (4.88%)	
occurrences (all)	5	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 March 2009	"Locally advanced" was removed throughout. Length of study period was increased. Treatment with NKTR-102 & irinotecan was concluded at 12 months from randomization. Exclusion of erythroid stimulating agents was removed. Patients discontinuing due to toxicity were followed in quarterly follow-up visits. Unnecessary duplication between the Investigator's Brochure & protocol was removed. Quarterly follow-up visits were added. Patient eligibility criteria were modified to reflect criteria used for NKTR-102 Phase 1 study. Patients & partners with child-bearing potential must use at least 2 forms of contraception for at least 8 months after last dose of NKTR-102. Exclusion of patients receiving concomitant anti-cancer biologic therapy was added. Exclusion of patients who previously treated with a camptothecin derivative or with past intolerance to excipients of irinotecan was added. Patients should not have had any cancer within the last 5 years Exclusion of patients with past history of bowel disorders considered at increased risk to toxicity related to irinotecan therapy was added. Clarified patient withdrawal from study. Screening window was increased from 14 to 28 days Patients were required to provide a sample for UGT1A1 status. Non-treatment study day visits were removed. Repeated urinalyses were removed. Dose modifications based upon non-hematologic & non-diarrhoea toxicities were added. For study treatment delays, Sponsor/Investigator consideration was allowed for continuing therapy for delays beyond two weeks. Storage & Accountability & Reconstitution & Handling of NKTR-102 text was updated. In the anti-diarrheal therapy for toxicity management, "initiate" was changed to "recommend" anti-microbial therapy. For patients with Grade 3 neutropenia, requirements that patients "must" have daily laboratories was changed to "recommended". Pharmacokinetic assessment & procedures were clarified. Other administrative changes were made.
26 March 2009	Lowered the starting dose of NKTR-102 to 145 mg/m^2 from 170 mg/m^2 based on safety data from the Phase 1 study with NKTR-102. Pregnancy test was added to end of study treatment visit as the risks of the study drug on the fetus are unknown. This assessment, which was in the original protocol, was removed in Amendment 1.0 in error.
18 December 2009	Nektar terminated the contract with PRA for services on the 08-PIR-03 study; as a result, the following changes are made to the administrative structure of study 08-PIR-03: 1. Nektar re-assigned all safety reporting responsibilities from PRA to Fulcrum Pharma Europe (Ltd). 2. Except as described in item 1, Nektar resumed primary responsibility for all remaining operational activities that had previously been delegated to PRA. To facilitate the change in scope, Nektar re-assigned medical monitoring and trial management activities. 3. The language identifying the analytical laboratory was corrected to better reflect the planned analysis of biological sample.

12 April 2010	Updated Study Drug Treatment Discontinuation Withdrawal from Study reasons. Clarified that patients who withdrew for a reason other than disease progression, withdrawal of consent or death were followed for progression by serial radiographic imaging. Clarified censoring rules for PFS and OS. Clarified that (with adoption of RECIST version 1.1 in the protocol) confirmation of response was not required. Radiographic imaging should have occurred at the end-of-treatment visit if these tests had not been performed within the prior 6 weeks. Clarified acceptable methods of determining KRAS mutation status. Slight modifications were made to inclusion/exclusion criteria. GGT was removed for assessments for liver function tests; AST and ALT continued to be required. The time frame in which patients had screening laboratory tests performed prior to study entry (up to 3 days) and the time frame from randomization to first study drug administration (up to 24 hours) were made more flexible. Clarified dose modification guidelines in a setting of nausea / vomiting. The time frame in which information regarding concomitant medications should be captured was clarified. Added language defining adequate forms of birth control to the protocol and informed consent document. Updated the pH of the formulation of NKTR-102 and the storage duration of reconstituted NKTR-102. Provided a window of ± 10 minutes for the 90-minute infusion time for NKTR-102 and irinotecan. Section 10 (Adverse Event Reporting) was made consistent with the language in other Phase 2 NKTR-102 protocols. Updated clinical and PK data (Sections 2.1.2.1, 2.1.2.2 and 2.1.2.3) were provided. Section 12.3.4.1 (Evaluation of Target Lesions) was updated to remove any reference to “New Lesions”, as assessment of new lesions are discussed in the overall assessment of response. Updated the Sponsor Medical Monitor information to reflect current team’s roles and responsibilities.
29 July 2011	Updated guidance on dose modifications & dose delays for dose-limiting toxicities, especially gastrointestinal & hematological toxicities, occuring following NKTR-102 or Irinotecan administration. Updated anti-diarrheal therapy text to indicate that prophylactic antidiarrheal medications should not be used to treat diarrhea AEs. Updated sponsor address and clinical contact. Updated address and fax numbers for the sponsor’s pharmacovigilance designee. Updated the date of the Camptosar® package insert to the most recent version. Specified that radiographic imaging should be performed every 6 weeks (±5 days) until progressive disease, start of new therapy for cancer, or end of study participation. Added to Inclusion Criteria that a patient was eligible if they had received prior fluoropyrimidine therapy in the neoadjuvant setting, clarifying the existing entry criterion. Updated estimated overall duration of the study to be about 42 months. Clarified that a local pathology laboratory may be used to determine KRAS mutation status, if approved by Nektar. Updated that 10 tumor tissue slides were needed by the Central Pathology Laboratory for KRAS mutation status instead of 5 to 6. Clarified that microscopic analysis of urine by the Central Laboratory was only needed if dipstick findings were abnormal. Removed the option that an alternate randomization system provided by the sponsor may be used, since only an IVRS was used in this study. Included a ± 2-day window for the duration of the 21-day treatment cycle. Removed a limit of 12 months from date of randomization for patients to receive study treatment. Corrected the acceptable methods of birth control for women to not include a male partner who has had a vasectomy. Updated text describing 2 patients who experienced kidney failure after treatment with NKTR-102 to include a third patient to be consistent with the most recent Investigator’s Brochure.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported