



Clinical trial results:

A Phase 2, Single-arm Study of Bempegaldesleukin (NKTR-214) in Combination with Nivolumab in Cisplatin Ineligible, Locally Advanced or Metastatic Urothelial Cancer Patients

Summary

EudraCT number	2018-003636-79
Trial protocol	PT NL DK FI DE PL GR BE AT ES FR GB IT
Global end of trial date	30 June 2022

Results information

Result version number	v1 (current)
This version publication date	01 January 2023
First version publication date	01 January 2023

Trial information

Trial identification

Sponsor protocol code	18-214-10 (PIVOT-10)
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03785925
WHO universal trial number (UTN)	-
Other trial identifiers	US IND No.: 141226

Notes:

Sponsors

Sponsor organisation name	Nektar Therapeutics
Sponsor organisation address	455 Mission Bay Boulevard South, San Francisco, United States, CA 94158
Public contact	Serious AE Reporting, Nektar Drug Safety, 1-855 4827233(SAFE), pharmacovigilance@nektar.com
Scientific contact	Serious AE Reporting, Nektar Drug Safety, 1-855 4827233(SAFE), pharmacovigilance@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	06 October 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 June 2022
Global end of trial reached?	Yes
Global end of trial date	30 June 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the anti-tumor activity of NKTR-214 in combination with nivolumab by assessing the ORRa by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) per blinded independent central review (BICR) in patients whose tumors have low programmed cell death ligand 1 (PD-L1) expression

To evaluate the safety and tolerability of NKTR-214 in combination with nivolumab

Protection of trial subjects:

Written documentation of informed consent was obtained from each patient or legal representative before any protocol-specified procedures were performed. The patients or legal representatives were informed of the nature of the study, and the informed consent form was presented to each patient or legal representative in the language in which the patient or legal representative was fluent. Signed informed consent forms were retained by the Investigator with the study records. A copy of the signed and dated informed consent form was provided to each patient or legal representative. Additionally, before collecting pregnancy surveillance information for any pregnancy in a study patient or a female partner of a male study patient, an informed consent form for disclosure information was signed by the pregnant patient or partner.

The conduct of the study was consistent with the principles that have their origin in the Declaration of Helsinki and in accordance with FDA regulations, with the current ICH GCP guidelines (ICH E6), as well as with any applicable regulatory authority, federal, state, and/or local laws and regulations.

Background therapy:

Noncomparative, reference chemotherapy arm of gemcitabine and carboplatin (GemCarbo) to inform and confirm the treatment effect and safety. Under Amendment 2.0 patients were randomized in a 2:1 ratio to receive either NKTR-214 and nivolumab or GemCarbo. Protocol Amendment 3.0 eliminated the GemCarbo arm following consistent negative feedback from global health authorities regarding the utility of the noncomparative GemCarbo arm.

Evidence for comparator:

There is no comparator.

Actual start date of recruitment	29 April 2019
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Scientific research
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 6
Country: Number of subjects enrolled	Portugal: 2
Country: Number of subjects enrolled	Spain: 27
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	Belgium: 5

Country: Number of subjects enrolled	Finland: 2
Country: Number of subjects enrolled	France: 9
Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	Greece: 10
Country: Number of subjects enrolled	Italy: 8
Country: Number of subjects enrolled	Argentina: 14
Country: Number of subjects enrolled	Australia: 14
Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	Israel: 11
Country: Number of subjects enrolled	Mexico: 1
Country: Number of subjects enrolled	Russian Federation: 21
Country: Number of subjects enrolled	Turkey: 8
Country: Number of subjects enrolled	United States: 36
Worldwide total number of subjects	188
EEA total number of subjects	74

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)	37
From 65 to 84 years	141
85 years and over	10

Subject disposition

Recruitment

Recruitment details:

188 patients received NKTR-214 and nivolumab; of these, 89.4% discontinued from all study drugs (ie, both NKTR-214 and nivolumab) mainly due to disease progression. 2 additional patients received received Gemcitabine + Carboplatin and subsequently received NKTR-214 and nivolumab treatment on study. 2 patients enrolled and did not receive therapy.

Pre-assignment

Screening details:

The sample size was determined by the PD-L1 low population, which was to be at least 110 patients who received at least 1 dose of NKTR-214 and nivolumab. Overall, a maximum of approximately 190 patients were planned to be enrolled. Additionally, under Amendment 2, approximately 55 patients were to be randomized to receive GemCarbo.

Period 1

Period 1 title	Treatment period (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Combination of bempegaldesleukin (NKTR-214) + nivolumab
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Arm description:

Participants will receive bempegaldesleukin (NKTR-214) in combination with nivolumab. From the 188 patients, 123 had tumors with low PD-L1 expression, 59 had tumors with high PD-L1 expression, and 6 had unknown PD-L1 expression.

Arm type	Experimental
Investigational medicinal product name	NKTR-214
Investigational medicinal product code	
Other name	Bempegaldesleukin
Pharmaceutical forms	Powder for suspension for injection
Routes of administration	Intravenous use

Dosage and administration details:

The Treated Population included 188 patients who were enrolled and received at least one full (or partial dose) of NKTR-214 0.006 mg/kg intravenous (IV) q3w

Investigational medicinal product name	Nivolumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for suspension for injection
Routes of administration	Intravenous use

Dosage and administration details:

The Treated Population included 188 patients who were enrolled and received at least one full (or partial dose) of Nivolumab 360 mg intravenous (IV) q3w

Number of subjects in period 1	Combination of bempegaldesleukin (NKTR-214) + nivolumab
Started	188
Completed	0
Not completed	188
Consent withdrawn by subject	15
Death	121
Lost to follow-up	1
Sponsor decision	51

Baseline characteristics

Reporting groups

Reporting group title	Combination of bempegaldesleukin (NKTR-214) + nivolumab
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Reporting group description:

Participants will receive bempegaldesleukin (NKTR-214) in combination with nivolumab. From the 188 patients, 123 had tumors with low PD-L1 expression, 59 had tumors with high PD-L1 expression, and 6 had unknown PD-L1 expression.

Reporting group values	Combination of bempegaldesleukin (NKTR-214) + nivolumab	Total	
Number of subjects	188	188	
Age categorical			
Units: Subjects			
Adults (18-64 years)	37	37	
From 65-84 years	141	141	
85 years and over	10	10	
Age continuous			
Units: years			
arithmetic mean	72		
standard deviation	± 8.21	-	
Gender categorical			
Units: Subjects			
Female	42	42	
Male	146	146	

Subject analysis sets

Subject analysis set title	Treated Population
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Subject analysis set type	Full analysis
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Subject analysis set description:

The Treated Population included 188 patients who were enrolled and received at least one full (or partial dose) of NKTR-214 or nivolumab

Reporting group values	Treated Population		
Number of subjects	188		
Age categorical			
Units: Subjects			
Adults (18-64 years)	37		
From 65-84 years	141		
85 years and over	10		
Age continuous			
Units: years			
arithmetic mean	72		
standard deviation	± 8.21		
Gender categorical			
Units: Subjects			
Female	42		
Male	146		

End points

End points reporting groups

Reporting group title	Combination of bempegaldesleukin (NKTR-214) + nivolumab
Reporting group description:	
Participants will receive bempegaldesleukin (NKTR-214) in combination with nivolumab. From the 188 patients, 123 had tumors with low PD-L1 expression, 59 had tumors with high PD-L1 expression, and 6 had unknown PD-L1 expression.	
Subject analysis set title	Treated Population
Subject analysis set type	Full analysis
Subject analysis set description:	
The Treated Population included 188 patients who were enrolled and received at least one full (or partial dose) of NKTR-214 or nivolumab	

Primary: Objective Response Rate (ORR) per RECIST 1.1 by BICR in the Treated PD-L1 Low Population

End point title	Objective Response Rate (ORR) per RECIST 1.1 by BICR in the Treated PD-L1 Low Population ^[1]
End point description:	
ORR was defined as the percentage of patients with confirmed objective response of CR or PR on or before the first progressive disease and any subsequent anticancer therapy. The ORR was 17.9% (22 of 123 patients) (95% CI = 11.6, 25.8). Of the 22 patients who responded, 5.7% of patients achieved a complete response (7 of 123 patients). The null hypothesis that ORR was $\leq 21\%$ was based on the observed ORR of 20% in patients with PD-L1 combined positive score (CPS) <10 in the study of first-line pembrolizumab monotherapy in cisplatin-ineligible patients with locally advanced or metastatic urothelial cancer (KEYNOTE-052; NCT02335424; Vuky2018). Assuming an ORR of 34%, with 110 patients, the study had 82% power to demonstrate that the lower limit of the 95% two-sided confidence interval (CI) for ORR exceeded 21%, where the CI was calculated by the exact computation method.	
End point type	Primary
End point timeframe:	
Tumor assessments were performed at baseline and every 9 weeks from Cycle 1 Day 1 for the first 12 months, and then every 12 weeks as indicated in the Schedule of Events.	
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: Descriptive statistics have been used for this primary endpoint.	

End point values	Combination of bempegaldesleukin (NKTR-214) + nivolumab			
Subject group type	Reporting group			
Number of subjects analysed	123			
Units: percent				
number (confidence interval 95%)				
Confirmed ORR	17.9 (11.6 to 25.8)			
Complete response	5.7 (2.3 to 11.4)			
Partial response	12.2 (7.0 to 19.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of AEs, clinically significant laboratory abnormalities, and vital signs, and physical examinations in the Treated Population

End point title	Incidence of AEs, clinically significant laboratory abnormalities, and vital signs, and physical examinations in the Treated Population
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End point description:

Most patients reported at least 1 TEAE (99.5%) and Grade $\geq$ 3 TEAE (66.0%). TEAEs leading to death were reported by 7.4% of patients.

End point type	Secondary
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End point timeframe:

the median overall duration of NKTR-214 and nivolumab was 106.0 and 111.5 days, respectively; approximately 33% of patients received $\geq$ 6 months of NKTR-214 and nivolumab (33.5% and 35.6%, respectively).

End point values	Combination of bempegaldesleukin (NKTR-214) + nivolumab			
Subject group type	Reporting group			
Number of subjects analysed	188			
Units: percent				
number (not applicable)				
TEAE - leading to death	7.4			
Treatment-related	1.1			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

As of the data cutoff date (20 July 2022), the median overall duration of NKTR-214 and nivolumab was 106.0 and 111.5 days, respectively.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	Combination of bempegaldesleukin (NKTR-214) + nivolumab
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Reporting group description:

Participants will receive bempegaldesleukin (NKTR-214) in combination with nivolumab.

Serious adverse events	Combination of bempegaldesleukin (NKTR-214) + nivolumab		
Total subjects affected by serious adverse events			
subjects affected / exposed	98 / 188 (52.13%)		
number of deaths (all causes)	127		
number of deaths resulting from adverse events	14		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 188 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Malignant melanoma in situ			
subjects affected / exposed	1 / 188 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatic carcinoma metastatic			
subjects affected / exposed	1 / 188 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Deep vein thrombosis			

subjects affected / exposed	2 / 188 (1.06%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Hypotension			
subjects affected / exposed	2 / 188 (1.06%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Peripheral ischaemia			
subjects affected / exposed	2 / 188 (1.06%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 188 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peripheral artery thrombosis			
subjects affected / exposed	1 / 188 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombophlebitis superficial			
subjects affected / exposed	1 / 188 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	5 / 188 (2.66%)		
occurrences causally related to treatment / all	3 / 5		
deaths causally related to treatment / all	0 / 0		
Fatigue			
subjects affected / exposed	3 / 188 (1.60%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
General physical health deterioration			

subjects affected / exposed	2 / 188 (1.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Asthenia			
subjects affected / exposed	1 / 188 (0.53%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Sudden death			
subjects affected / exposed	1 / 188 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 188 (0.53%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Female genital tract fistula			
subjects affected / exposed	1 / 188 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Perineal pain			
subjects affected / exposed	1 / 188 (0.53%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Scrotal pain			
subjects affected / exposed	1 / 188 (0.53%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			

subjects affected / exposed	3 / 188 (1.60%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 2		
Lung disorder			
subjects affected / exposed	1 / 188 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 188 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Delirium			
subjects affected / exposed	1 / 188 (0.53%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Product issues			
Device occlusion			
subjects affected / exposed	1 / 188 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Cervical vertebral fracture			
subjects affected / exposed	1 / 188 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lumbar vertebral fracture			
subjects affected / exposed	1 / 188 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Procedural pain			
subjects affected / exposed	1 / 188 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	2 / 188 (1.06%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			
subjects affected / exposed	2 / 188 (1.06%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 1		
Myocarditis			
subjects affected / exposed	2 / 188 (1.06%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	1 / 1		
Acute myocardial infarction			
subjects affected / exposed	1 / 188 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardio-respiratory arrest			
subjects affected / exposed	1 / 188 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	2 / 188 (1.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cerebral infarction			
subjects affected / exposed	1 / 188 (0.53%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebral microembolism			
subjects affected / exposed	1 / 188 (0.53%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		

Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 188 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eosinophilia			
subjects affected / exposed	1 / 188 (0.53%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	1 / 188 (0.53%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Haemorrhagic anaemia			
subjects affected / exposed	1 / 188 (0.53%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	6 / 188 (3.19%)		
occurrences causally related to treatment / all	2 / 6		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	2 / 188 (1.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	1 / 188 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diverticulum intestinal			
subjects affected / exposed	1 / 188 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Ileus				
subjects affected / exposed	1 / 188 (0.53%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Inguinal hernia				
subjects affected / exposed	1 / 188 (0.53%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intestinal obstruction				
subjects affected / exposed	1 / 188 (0.53%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intestinal perforation				
subjects affected / exposed	1 / 188 (0.53%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Large intestinal obstruction				
subjects affected / exposed	1 / 188 (0.53%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Obstruction gastric				
subjects affected / exposed	1 / 188 (0.53%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pancreatitis				
subjects affected / exposed	1 / 188 (0.53%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rectal haemorrhage				
subjects affected / exposed	1 / 188 (0.53%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Retroperitoneal haemorrhage				

subjects affected / exposed	1 / 188 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 188 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatic failure			
subjects affected / exposed	1 / 188 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Cutaneous vasculitis			
subjects affected / exposed	1 / 188 (0.53%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Stevens-Johnson syndrome			
subjects affected / exposed	1 / 188 (0.53%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	9 / 188 (4.79%)		
occurrences causally related to treatment / all	1 / 9		
deaths causally related to treatment / all	0 / 0		
Haematuria			
subjects affected / exposed	7 / 188 (3.72%)		
occurrences causally related to treatment / all	0 / 10		
deaths causally related to treatment / all	0 / 0		
Hydronephrosis			
subjects affected / exposed	2 / 188 (1.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Nephritis			
subjects affected / exposed	2 / 188 (1.06%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Bladder neck obstruction			
subjects affected / exposed	1 / 188 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chronic kidney disease			
subjects affected / exposed	1 / 188 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Kidney congestion			
subjects affected / exposed	1 / 188 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal failure			
subjects affected / exposed	1 / 188 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary retention			
subjects affected / exposed	1 / 188 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract discomfort			
subjects affected / exposed	1 / 188 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract obstruction			
subjects affected / exposed	1 / 188 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			

Hypophysitis			
subjects affected / exposed	1 / 188 (0.53%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	3 / 188 (1.60%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Arthralgia			
subjects affected / exposed	2 / 188 (1.06%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Back pain			
subjects affected / exposed	1 / 188 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bone pain			
subjects affected / exposed	1 / 188 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal chest pain			
subjects affected / exposed	1 / 188 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pathological fracture			
subjects affected / exposed	1 / 188 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Polymyalgia rheumatica			
subjects affected / exposed	1 / 188 (0.53%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Infections and infestations Urinary tract infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	12 / 188 (6.38%) 0 / 15 0 / 1		
Pneumonia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	4 / 188 (2.13%) 1 / 4 0 / 1		
Urosepsis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	4 / 188 (2.13%) 0 / 4 0 / 1		
Corona virus infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	3 / 188 (1.60%) 0 / 3 0 / 1		
Urinary tract infection enterococcal subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	2 / 188 (1.06%) 0 / 2 0 / 0		
Bacterial sepsis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 188 (0.53%) 0 / 1 0 / 0		
Escherichia urinary tract infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 188 (0.53%) 0 / 1 0 / 0		
Gastroenteritis viral subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 188 (0.53%) 0 / 1 0 / 0		
Herpes zoster			

subjects affected / exposed	1 / 188 (0.53%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lung infection				
subjects affected / exposed	1 / 188 (0.53%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Peritonitis				
subjects affected / exposed	1 / 188 (0.53%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Pharyngitis				
subjects affected / exposed	1 / 188 (0.53%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis				
subjects affected / exposed	1 / 188 (0.53%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis acute				
subjects affected / exposed	1 / 188 (0.53%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis chronic				
subjects affected / exposed	1 / 188 (0.53%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Renal abscess				
subjects affected / exposed	1 / 188 (0.53%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				

subjects affected / exposed	1 / 188 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Spinal cord infection			
subjects affected / exposed	1 / 188 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Upper respiratory tract infection			
subjects affected / exposed	1 / 188 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular device infection			
subjects affected / exposed	1 / 188 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 188 (1.06%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Decreased appetite			
subjects affected / exposed	1 / 188 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperglycaemia			
subjects affected / exposed	1 / 188 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypervolaemia			
subjects affected / exposed	1 / 188 (0.53%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Type 2 diabetes mellitus			

subjects affected / exposed	1 / 188 (0.53%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Combination of bempegaldesleukin (NKTR-214) + nivolumab		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	185 / 188 (98.40%)		
Vascular disorders			
Hypotension			
subjects affected / exposed	22 / 188 (11.70%)		
occurrences (all)	34		
Hypertension			
subjects affected / exposed	11 / 188 (5.85%)		
occurrences (all)	15		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	82 / 188 (43.62%)		
occurrences (all)	196		
Fatigue			
subjects affected / exposed	58 / 188 (30.85%)		
occurrences (all)	96		
Asthenia			
subjects affected / exposed	36 / 188 (19.15%)		
occurrences (all)	65		
Oedema peripheral			
subjects affected / exposed	32 / 188 (17.02%)		
occurrences (all)	42		
Chills			
subjects affected / exposed	27 / 188 (14.36%)		
occurrences (all)	31		
Influenza like illness			

subjects affected / exposed occurrences (all) Face oedema subjects affected / exposed occurrences (all)	24 / 188 (12.77%) 61 10 / 188 (5.32%) 10		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all)	21 / 188 (11.17%) 30 19 / 188 (10.11%) 23		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	15 / 188 (7.98%) 15		
Investigations Blood creatinine increased subjects affected / exposed occurrences (all) Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all) Weight decreased subjects affected / exposed occurrences (all) Blood alkaline phosphatase increased subjects affected / exposed occurrences (all) Amylase increased subjects affected / exposed occurrences (all) Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	25 / 188 (13.30%) 30 15 / 188 (7.98%) 16 14 / 188 (7.45%) 16 12 / 188 (6.38%) 13 11 / 188 (5.85%) 20 11 / 188 (5.85%) 11		

Alanine aminotransferase increased subjects affected / exposed occurrences (all)	10 / 188 (5.32%) 10		
Injury, poisoning and procedural complications Injury, poisoning and procedural complications subjects affected / exposed occurrences (all)	12 / 188 (6.38%) 16		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all)	22 / 188 (11.70%) 27 19 / 188 (10.11%) 38		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Eosinophilia subjects affected / exposed occurrences (all)	57 / 188 (30.32%) 72 26 / 188 (13.83%) 37		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Abdominal pain	56 / 188 (29.79%) 92 54 / 188 (28.72%) 89 44 / 188 (23.40%) 49 35 / 188 (18.62%) 54		

subjects affected / exposed occurrences (all)	15 / 188 (7.98%) 15		
Dry mouth subjects affected / exposed occurrences (all)	11 / 188 (5.85%) 11		
Skin and subcutaneous tissue disorders			
Pruritus subjects affected / exposed occurrences (all)	43 / 188 (22.87%) 57		
Pruritus generalised subjects affected / exposed occurrences (all)	40 / 188 (21.28%) 52		
Rash subjects affected / exposed occurrences (all)	20 / 188 (10.64%) 23		
Rash maculo-papular subjects affected / exposed occurrences (all)	17 / 188 (9.04%) 24		
Rash generalised subjects affected / exposed occurrences (all)	15 / 188 (7.98%) 22		
Dry skin subjects affected / exposed occurrences (all)	13 / 188 (6.91%) 13		
Renal and urinary disorders			
Haematuria subjects affected / exposed occurrences (all)	31 / 188 (16.49%) 44		
Endocrine disorders			
Hypothyroidism subjects affected / exposed occurrences (all)	28 / 188 (14.89%) 28		
Hyperthyroidism subjects affected / exposed occurrences (all)	17 / 188 (9.04%) 18		
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	35 / 188 (18.62%)		
occurrences (all)	58		
Back pain			
subjects affected / exposed	23 / 188 (12.23%)		
occurrences (all)	25		
Pain in extremity			
subjects affected / exposed	14 / 188 (7.45%)		
occurrences (all)	14		
Musculoskeletal pain			
subjects affected / exposed	13 / 188 (6.91%)		
occurrences (all)	14		
Myalgia			
subjects affected / exposed	12 / 188 (6.38%)		
occurrences (all)	28		
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	39 / 188 (20.74%)		
occurrences (all)	55		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	58 / 188 (30.85%)		
occurrences (all)	66		
Hyponatraemia			
subjects affected / exposed	13 / 188 (6.91%)		
occurrences (all)	19		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 October 2018	Added additional vital sign measurements, including orthostatic blood pressure measurements predose on Cycle 1 Day 1 and Cycle 1 Day 3, and additional AE measurement on Cycle 1 Day 3 (approximately 48 hours after administration) to allow for closer blood pressure and AE monitoring around the time of maximal hypotension (within 3 to 4 days of NKTR-214 administration). Clarified that permanent discontinuation of study treatment was required for Grade 3 drug-related thrombocytopenia > 7 days or associated with clinically significant bleeding.
07 December 2018	Protocol Amendment 2.0 added a noncomparative, reference chemotherapy arm of gemcitabine and carboplatin (GemCarbo) to inform and confirm the treatment effect and safety in this specific patient population. Under Amendment 2.0, patients were randomized in a 2:1 ratio to receive either NKTR-214 and nivolumab or gemcitabine and carboplatin (GemCarbo). Also, added a cross-over arm to allow patients randomized to GemCarbo to receive NKTR-214 and nivolumab. Added stricter patient entry criteria due to the expected increased toxicity with GemCarbo. Clarified the treatment management guidelines that pertained to GemCarbo (eg, premedication at the first and subsequent administrations, procedures for the GemCarbo arm in case of pregnancy in a female patient or in a female partner of a male patient) and those that pertained to NKTR-214 and nivolumab (eg, hypotension guidelines, blood samples for PK and immunogenicity assessments). Added Exclusion Criterion #3 specifying the tumor must have low PD-L1 expression. Clarified reason for ending treatment: occurrence of an unacceptable, clinically significant AE or non-resolution of clinically significant AE was extended from > 6 to > 8 weeks. Expanded the population by including ECOG performance status of 2 (Inclusion Criterion 6); previously only patients with an ECOG performance status of 0 or 1 were eligible. Added 2 stratification factors to the patient randomization: the presence of liver metastases (yes vs. no) and ECOG performance status (0 or 1 vs. 2).
13 June 2019	Amendment 3.0 removed the GemCarbo arm based on negative feedback from health authorities regarding the utility of the noncomparative GemCarbo arm, especially given that the small sample size in the reference arm was not sufficient to address whether deviation from the historical control (EORTC Study 30986; De Santis 2012) was real or anomaly.

06 February 2020	Added a summary analysis of CVA events conducted across the NKTR-214 clinical program and added mitigation measures for CVA events. Revised treatment discontinuation criteria regarding infusion reactions, adrenal insufficiency, and hypophysitis. Removed the exploratory objective of immune-related RECIST 1.1. Removed radiation therapy from prohibited concomitant medications. Reduced the number of sites and patients to be enrolled. Clarified Inclusion #7 to indicate that a treatment-free interval of > 12 months was required following all chemotherapeutic regimens, not just platinum-based. Clarified NKTR-214 potency, handling, and reconstitution information. Added that dose delay is required if patient had signs or symptoms of systemic infection requiring antibiotic therapy. Clarified classes of antihypertensive medications in Exclusion Criterion #17. Added a new section on the effect of NKTR-214 on clearance of concomitant medication, which reflected the current understanding of drug-drug interaction risks. Revised list of AEs for which additional information would be collected; added atrial fibrillation and deleted hypotension and eosinophilic disorders. Added specification for cycles adjustments if dosing was delayed. Removed drug-induced liver injury as an AE of special interest. Updated urine protein creatinine ratio requirements throughout. Clarified that health-related quality of life to be conducted before other assessments. Added "possibly related" to the definition of causality relationship of AEs. Clarified that hospital admissions only for patient observation not reported as an SAE.
27 May 2021	Extended primary analysis from 6 to 18 months for adequate response duration evaluation. Added guidance for reporting and management of cytokine release syndrome (CRS). Added description of planned hypothesis testing, reflecting modifications to the SAP. Add the option for a rollover study to permit the flexibility to close the study prior to completion of 5 years survival follow-up.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

No Limitations were observed

Notes: