Clinical trial results:
A Phase 1/2, Open-label, Multicenter Study of the Combination of NKTR-214 and Nivolumab or the Combination of NKTR-214, Nivolumab, and Other Anti-Cancer Therapies in Patients with Select Locally Advanced or Metastatic Solid Tumor Malignancies

Summary

EudraCT number	2016-003543-11
Trial protocol	GB ES BE FR
Global end of trial date	28 April 2022

Results information

Result version number	v1 (current)
This version publication date	04 January 2023
First version publication date	04 January 2023

Trial information

Trial identification

Sponsor protocol code	16-214-02

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02983045
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Nektar Therapeutics
Sponsor organisation address	455 Mission Bay Boulevard South, San Francisco, United States,
Public contact	Clinical Trial Information Desk, Nektar Therapeutics Contact Center, +1 855482 8676, studyinquiry@nektar.com
Scientific contact	Clinical Trial Information Desk, Nektar Therapeutics Contact Center, +1 855482 8676, 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	16 May 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 April 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- To evaluate the safety and tolerability, and define the maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) of NKTR-214 in combination with nivolumab or in combination with nivolumab and other anti-cancer therapies
- To evaluate the efficacy of NKTR-214 in combination with nivolumab or in combination with nivolumab and other anti-cancer therapies by assessing the objective response rate (ORR) by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) at the RP2D

Protection of trial subjects:

NKTR-214 was designed to mitigate the serious toxicities associated with rapid systemic immune activation seen with administration of aldesleukin. The goal of engineering a polyethylene glycolylated form of interleukin-2 that reduces the treatment-limiting toxicities of ldesleukin, i.e., those necessitating in-hospital administration, appears to have been realized with NKTR-214 at the doses tested. The safety profiles of nivolumab and ipilimumab are well characterized and manageable when administered alone or in combination, including regimens where they are administered in combination with additional immuno-oncology products. Nonclinical data as well as clinical experience with high-dose interleukin-2 and checkpoint inhibitor combinations indicate the potential for improvement in therapeutic response compared with either agent given alone. Thus, the potential benefit of combination therapy appears to outweigh the known risks of these agents and warrants clinical investigation.

The detailed and frequent safety monitoring that will be undertaken in this open-label study precludes the necessity for an independent Data Monitoring Committee. A separate Safety Review Committee will meet to review safety data.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 December 2016
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	Poland: 23
Country: Number of subjects enrolled	Spain: 47
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	Belgium: 29
Country: Number of subjects enrolled	France: 14
Country: Number of subjects enrolled	Italy: 35
Country: Number of subjects enrolled	Canada: 27
Country: Number of subjects enrolled	United States: 376

Worldwide total number of subjects	557
EEA total number of subjects	148

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)	310
From 65 to 84 years	245
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

This study was conducted in the US (30 centers); Spain (7 centers); Canada and Italy (5 centers each); Belgium, France, and Poland (4 centers each); and the United Kingdom (2 centers).

Pre-assignment

Screening details:

Adults with select locally advanced or metastatic solid tumor malignancies who had melanoma, renal cell carcinoma, non-small cell lung cancer, urothelial carcinoma, triple-negative breast cancer, hormone receptor positive human epidermal growth factor receptor 2 breast cancer, gastric cancer, colorectal carcinoma or small cell lung cancer

Period 1

Period 1 title	Treatment Period (Baseline) (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Part 1 - Dose Escalation

Arm description:

Dose escalation for the doublet (NKTR-214 + nivolumab)
Part 1 consisted of following 5 treatment cohorts:
NKTR-214 0.006 mg/kg every 3 weeks (q3w) + nivolumab 240 mg every 2 weeks (q2w)
NKTR-214 0.006 mg/kg q2w + nivolumab 240 mg q2w
NKTR-214 0.003 mg/kg q2w + nivolumab 240 mg q2w
NKTR-214 0.006 mg/kg q3w + nivolumab 360 mg q3w
NKTR-214 0.009 mg/kg q3w + nivolumab 360 mg q3w
NKTR-214 + nivolumab were administered on Day 1 (±3 days) of each treatment cycle

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

Dosage and administration details:

Dosage Level 1: 0.006 mg/kg every 3 weeks
Dosage Level 2: 0.006 mg/kg every 2 weeks
Dosage Level 3: 0.003 mg/kg every 2 weeks
Dosage Level 4: 0.006 mg/kg every 3 weeks
Dosage Level 5: 0.009 mg/kg every 3 weeks

Investigational medicinal product name	Nivolumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in vial
Routes of administration	Intravenous use

Dosage and administration details:

Dosage level 1: 240 mg every 2 weeks
Dosage level 2: 240 mg every 2 weeks
Dosage level 3: 240 mg every 2 weeks
Dosage level 4: 360 mg every 3 weeks
Dosage level 5: 360 mg every 3 weeks

Arm title	Part 2 - Dose Expansion

Arm description:

Dose expansion for the doublet (NKTR-214 + nivolumab ± chemotherapy)
The recommended Phase 2 dose determined in Part 1 (NKTR-214 0.006 mg/kg every 3 weeks + nivolumab 360 mg every 3 weeks) was administered on Day 1 (± 3 days) of each treatment cycle with or without chemotherapy.

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

Dosage and administration details:

0.006 mg/kg every 3 weeks

Investigational medicinal product name	Nivolumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in vial
Routes of administration	Intravenous use

Dosage and administration details:

360 mg every 3 weeks

Investigational medicinal product name	Chemotherapy
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The dose determined in Part 1 (NKTR-214 0.006 mg/kg every 3 weeks + nivolumab 360 mg every 3 weeks) was administered on Day 1 (± 3 days) of each treatment cycle with or without chemotherapy. Chemotherapy treatment was as follows:

Cohorts 3d.1:
Cisplatin 75 mg/m2 or carboplatin area under the concentration-time curve 5 + pemetrexed 500 mg/m2 every 3 weeks × 4 cycles then pemetrexed every 3 weeks

Cohort 3e:
paclitaxel 200 mg/m2 every 3 weeks or nab-paclitaxel 100 mg/m2 on Days 1, 8, and 15 of each 21-day cycle × 4 cycles with carboplatin AUC 6 every 3 weeks × 4 cycles or cisplatin 75 mg/m2 every 3 weeks × 4 cycles

Patients were premedicated with folic acid, vitamin B12, and glucocorticoids according to local guidelines for pemetrexed.

Arm title	Part 3 - Schedule Finding

Arm description:

Schedule finding for the triplet (NKTR-214 + nivolumab + ipilimumab)

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

Dosage and administration details:

- Schedule 1:
NKTR-214: 0.006 mg/kg every 3 weeks
Nivolumab: 360 mg every 3 weeks
Ipilimumab: 1 mg/kg every 6 weeks with the NKTR-214 and nivolumab doublet combination starting at Cycle 1 Day 1

- Schedule 2:
NKTR-214: 0.006 mg/kg every 3 weeks
Nivolumab: 1 mg/kg every 3 weeks
Ipilimumab: 3 mg/kg every 3 weeks x 4 doses

- Schedule 3:
NKTR-214: 0.006 mg/kg every 3 weeks
Nivolumab: 3 mg/kg every 3 weeks
Ipilimumab: 1 mg/kg every 3 weeks x 4 doses

Investigational medicinal product name	Nivolumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in vial
Routes of administration	Intravenous use

Dosage and administration details:

- Schedule 1:
NKTR-214: 0.006 mg/kg every 3 weeks
Nivolumab: 360 mg every 3 weeks
Ipilimumab: 1 mg/kg every 6 weeks with the NKTR-214 and nivolumab doublet combination starting at Cycle 1 Day 1

- Schedule 2:
NKTR-214: 0.006 mg/kg every 3 weeks
Nivolumab: 1 mg/kg every 3 weeks
Ipilimumab: 3 mg/kg every 3 weeks x 4 doses

- Schedule 3:
NKTR-214: 0.006 mg/kg every 3 weeks
Nivolumab: 3 mg/kg every 3 weeks
Ipilimumab: 1 mg/kg every 3 weeks x 4 doses

Investigational medicinal product name	Ipilimumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in vial
Routes of administration	Intravenous use

Dosage and administration details:

- Schedule 1:
NKTR-214: 0.006 mg/kg every 3 weeks
Nivolumab: 360 mg every 3 weeks
Ipilimumab: 1 mg/kg every 6 weeks with the NKTR-214 and nivolumab doublet combination starting at Cycle 1 Day 1

- Schedule 2:
NKTR-214: 0.006 mg/kg every 3 weeks
Nivolumab: 1 mg/kg every 3 weeks
Ipilimumab: 3 mg/kg every 3 weeks x 4 doses

- Schedule 3:
NKTR-214: 0.006 mg/kg every 3 weeks
Nivolumab: 3 mg/kg every 3 weeks
Ipilimumab: 1 mg/kg every 3 weeks x 4 doses

Arm title	Part 4 - Dose Expansion

Arm description:

Dose expansion for the triplet (NKTR-214 + nivolumab + ipilimumab)

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

Dosage and administration details:

- Schedule 1:
NKTR-214: 0.006 mg/kg every 3 weeks
Nivolumab: 360 mg every 3 weeks
Ipilimumab: 1 mg/kg every 6 weeks

- Schedule 2:
NKTR-214: 0.006 mg/kg every 3 weeks
Nivolumab: 3 mg/kg every 3 weeks
Ipilimumab: 1 mg/kg every 3 weeks x 4 doses

Investigational medicinal product name	Nivolumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in vial
Routes of administration	Intravenous use

Dosage and administration details:

- Schedule 1:
NKTR-214: 0.006 mg/kg every 3 weeks
Nivolumab: 360 mg every 3 weeks
Ipilimumab: 1 mg/kg every 6 weeks

- Schedule 2:
NKTR-214: 0.006 mg/kg every 3 weeks
Nivolumab: 3 mg/kg every 3 weeks
Ipilimumab: 1 mg/kg every 3 weeks x 4 doses

Investigational medicinal product name	Ipilimumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in vial
Routes of administration	Intravenous use

Dosage and administration details:

- Schedule 1:
NKTR-214: 0.006 mg/kg every 3 weeks
Nivolumab: 360 mg every 3 weeks
Ipilimumab: 1 mg/kg every 6 weeks

- Schedule 2:
NKTR-214: 0.006 mg/kg every 3 weeks
Nivolumab: 3 mg/kg every 3 weeks
Ipilimumab: 1 mg/kg every 3 weeks x 4 doses

Number of subjects in period 1	Part 1 - Dose Escalation	Part 2 - Dose Expansion	Part 3 - Schedule Finding
Started	38	476	24
Completed	0	0	0
Not completed	38	476	24
Adverse event, serious fatal	-	17	2
Consent withdrawn by subject	2	29	1
Physician decision	2	8	1
Adverse event, non-fatal	9	39	4
Maximal response	7	33	4
Progressive disease by RECIST	16	322	10

Progressive disease clinical progression	2	28	2

Number of subjects in period 1	Part 4 - Dose Expansion
Started	19
Completed	0
Not completed	19
Adverse event, serious fatal	-
Consent withdrawn by subject	1
Physician decision	-
Adverse event, non-fatal	6
Maximal response	1
Progressive disease by RECIST	9
Progressive disease clinical progression	2

Baseline characteristics

Reporting groups	
Reporting group title	Part 1 - Dose Escalation
Reporting group description:	
Dose escalation for the doublet (NKTR-214 + nivolumab) Part 1 consisted of following 5 treatment cohorts: NKTR-214 0.006 mg/kg every 3 weeks (q3w) + nivolumab 240 mg every 2 weeks (q2w) NKTR-214 0.006 mg/kg q2w + nivolumab 240 mg q2w NKTR-214 0.003 mg/kg q2w + nivolumab 240 mg q2w NKTR-214 0.006 mg/kg q3w + nivolumab 360 mg q3w NKTR-214 0.009 mg/kg q3w + nivolumab 360 mg q3w NKTR-214 + nivolumab were administered on Day 1 (±3 days) of each treatment cycle	
Reporting group title	Part 2 - Dose Expansion
Reporting group description:	
Dose expansion for the doublet (NKTR-214 + nivolumab ± chemotherapy) The recommended Phase 2 dose determined in Part 1 (NKTR-214 0.006 mg/kg every 3 weeks + nivolumab 360 mg every 3 weeks) was administered on Day 1 (± 3 days) of each treatment cycle with or without chemotherapy.	
Reporting group title	Part 3 - Schedule Finding
Reporting group description:	
Schedule finding for the triplet (NKTR-214 + nivolumab + ipilimumab)	
Reporting group title	Part 4 - Dose Expansion
Reporting group description:	
Dose expansion for the triplet (NKTR-214 + nivolumab + ipilimumab)	

Reporting group values	Part 1 - Dose Escalation	Part 2 - Dose Expansion	Part 3 - Schedule Finding
Number of subjects	38	476	24
Age categorical Units: Subjects			
Adults (18-64 years)	30	253	15
Adults (65-74 years)	8	162	7
Adults (75 years and older)	0	61	2
Age continuous Units: years			
arithmetic mean	58.5	62.1	61.2
standard deviation	± 9.40	± 11.48	± 9.35
Gender categorical Units: Subjects			
Female	8	207	1
Male	30	269	23
Race Units: Subjects			
White	36	413	20
Black or African American	2	16	2
Asian	0	13	0
American Indian or Alaska Native	0	2	0
Other	0	23	2
Multiple	0	1	0
Not reported	0	0	0
Missing	0	8	0

Ethnicity Units: Subjects			
Not Hispanic or Latino	33	413	19
Hispanic or Latino	4	35	5
Not reported	0	13	0
Unknown	1	13	0
Missing	0	2	0
Region Units: Subjects			
US/Canada	38	322	24
Europe	0	154	0
Eastern Cooperative Oncology Group (ECOG) Scale Units: Subjects			
ECOG Score 0	26	221	17
ECOG Score 1	12	254	7
ECOG Score greater than 1	0	0	0
Missing	0	1	0
Smoking history Units: Subjects			
Current	1	53	2
Former	3	240	11
Never	1	164	11
Unknown	33	19	0
Weight Units: kilograms			
arithmetic mean	91.04	79.52	94.30
standard deviation	± 18.826	± 18.822	± 19.749
Body mass index Units: kilogram(s)/square metre			
arithmetic mean	29.41	27.24	29.87
standard deviation	± 4.851	± 5.433	± 4.786

Reporting group values	Part 4 - Dose Expansion	Total	
Number of subjects	19	557	
Age categorical Units: Subjects			
Adults (18-64 years)	12	310	
Adults (65-74 years)	6	183	
Adults (75 years and older)	1	64	
Age continuous Units: years			
arithmetic mean	59.1		
standard deviation	± 12.63	-	
Gender categorical Units: Subjects			
Female	5	221	
Male	14	336	
Race Units: Subjects			
White	17	486	

Black or African American	0	20	
Asian	0	13	
American Indian or Alaska Native	0	2	
Other	2	27	
Multiple	0	1	
Not reported	0	0	
Missing	0	8	
Ethnicity Units: Subjects			
Not Hispanic or Latino	15	480	
Hispanic or Latino	2	46	
Not reported	0	13	
Unknown	2	16	
Missing	0	2	
Region Units: Subjects			
US/Canada	19	403	
Europe	0	154	
Eastern Cooperative Oncology Group (ECOG) Scale Units: Subjects			
ECOG Score 0	12	276	
ECOG Score 1	7	280	
ECOG Score greater than 1	0	0	
Missing	0	1	
Smoking history Units: Subjects			
Current	1	57	
Former	8	262	
Never	10	186	
Unknown	0	52	
Weight Units: kilograms			
arithmetic mean	85.49		
standard deviation	± 16.686	-	
Body mass index Units: kilogram(s)/square metre			
arithmetic mean	29.39		
standard deviation	± 5.418	-	

End points

End points reporting groups

Reporting group title	Part 1 - Dose Escalation
Reporting group description:	
Dose escalation for the doublet (NKTR-214 + nivolumab) Part 1 consisted of following 5 treatment cohorts: NKTR-214 0.006 mg/kg every 3 weeks (q3w) + nivolumab 240 mg every 2 weeks (q2w) NKTR-214 0.006 mg/kg q2w + nivolumab 240 mg q2w NKTR-214 0.003 mg/kg q2w + nivolumab 240 mg q2w NKTR-214 0.006 mg/kg q3w + nivolumab 360 mg q3w NKTR-214 0.009 mg/kg q3w + nivolumab 360 mg q3w NKTR-214 + nivolumab were administered on Day 1 (±3 days) of each treatment cycle	
Reporting group title	Part 2 - Dose Expansion
Reporting group description:	
Dose expansion for the doublet (NKTR-214 + nivolumab ± chemotherapy) The recommended Phase 2 dose determined in Part 1 (NKTR-214 0.006 mg/kg every 3 weeks + nivolumab 360 mg every 3 weeks) was administered on Day 1 (± 3 days) of each treatment cycle with or without chemotherapy.	
Reporting group title	Part 3 - Schedule Finding
Reporting group description:	
Schedule finding for the triplet (NKTR-214 + nivolumab + ipilimumab)	
Reporting group title	Part 4 - Dose Expansion
Reporting group description:	
Dose expansion for the triplet (NKTR-214 + nivolumab + ipilimumab)	
Subject analysis set title	Part 1: Cohort 1
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
NKTR-214 0.006 mg/kg every 3 weeks + Nivolumab 240 mg every 2 weeks	
Subject analysis set title	Part 1: Cohort 2
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
NKTR-214 0.006 mg/kg every 2 weeks + Nivolumab 240 mg every 2 weeks	
Subject analysis set title	Part 1: Cohort 3
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
NKTR-214 0.003 mg/kg every 2 weeks + Nivolumab 240 mg every 2 weeks	
Subject analysis set title	Part 1: Cohort 4
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
NKTR-214 0.006 mg/kg every 3 weeks + Nivolumab 360 mg every 3 weeks	
Subject analysis set title	Part 1: Cohort 5
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
NKTR-214 0.009 mg/kg every 3 weeks + Nivolumab 360 mg every 3 weeks	
Subject analysis set title	Part 3: Schedule 1
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants assigned to schedule 1 dosing: NKTR-214 0.006 mg/kg every 3 weeks and Nivolumab: 360 mg every 3 weeks plus Ipilimumab 1 mg/kg every 6 weeks	
Subject analysis set title	Part 3: Schedule 2
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants assigned to schedule 2 dosing:
NKTR-214 0.006 mg/kg every 3 weeks and Nivolumab: 1 mg/kg every 3 weeks x 4 doses plus Ipilimumab 3 mg/kg every 3 weeks x 4 doses, followed by a maintenance dose of NKTR-214 0.006 mg/kg every 3 weeks plus Nivolumab 360 mg every 3 weeks

Subject analysis set title	Part 3: Schedule 3
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants assigned to schedule 3 dosing:
NKTR-214 0.006 mg/kg every 3 weeks and Nivolumab: 3 mg/kg every 3 weeks x 4 doses plus Ipilimumab 1 mg/kg every 3 weeks x 4 doses, followed by a maintenance dose of NKTR-214 0.006 mg/kg every 3 weeks plus Nivolumab 360 mg every 3 weeks

Primary: Part 1: Incidence of dose-limiting toxicity (DLT) during the DLT evaluation window

End point title	Part 1: Incidence of dose-limiting toxicity (DLT) during the DLT evaluation window[1]

End point description:

Part 1 of the study was a dose-escalation phase that evaluated the safety and tolerability and defined the maximum tolerated dose or recommended Phase 2 dose of the NKTR-214/nivolumab doublet across 5 dosage/schedule levels. The results presented are for the DLT Population.

End point type	Primary

End point timeframe:

Includes DLTs that occurred within the DLT window of at least 21 days after the first dose of study treatment (28 days for every 2 weeks dosing; 21 days for every 3 weeks dosing). Patients were counted only once under each preferred term.

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: No statistical analysis was performed for this endpoint.

End point values	Part 1: Cohort 1	Part 1: Cohort 2	Part 1: Cohort 3	Part 1: Cohort 4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	4	3	3	24
Units: number of participants				
At least 1 DLT	0	0	0	0
Metabolism and Nutrition Disorders: Acidosis	0	0	0	0
Metabolism and Nutrition Disorders: Hyperglycaemia	0	0	0	0
Vascular Disorders: Hypotension	0	0	0	0

End point values	Part 1: Cohort 5			
Subject group type	Subject analysis set			
Number of subjects analysed	3			
Units: number of participants				
At least 1 DLT	2			
Metabolism and Nutrition Disorders: Acidosis	1			
Metabolism and Nutrition Disorders: Hyperglycaemia	1			
Vascular Disorders: Hypotension	1			

Statistical analyses

No statistical analyses for this end point

Primary: Part 3: Incidence of dose-limiting toxicity (DLT) during the DLT evaluation window

End point title	Part 3: Incidence of dose-limiting toxicity (DLT) during the DLT evaluation window[2]

End point description:

Part 3 of the study was a schedule finding phase to establish the recommended phase 2 dosing schedules for Part 4 and assess the safety and tolerability for the NKTR-214/nivolumab/ipilimumab triplet combination. The results presented are for the DLT Population.

End point type	Primary

End point timeframe:

Dose-limiting toxicities (DLTs) were assessed during a 3-week (21-day) DLT evaluation period beginning with the first dose of ipilimumab.

Notes:

[2] - 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: No statistical analysis was performed for this endpoint.

End point values	Part 3: Schedule 1	Part 3: Schedule 2	Part 3: Schedule 3	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	10	8	6	
Units: number of participants				
Patients with at least one event	1	1	1	
Endocrine disorders: Adrenal insufficiency	0	1	0	
Endocrine disorders: Hyperthyroidism	0	0	1	
Metabolism and nutrition disorders: Hyponatraemia	1	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Part 2: Objective Response Rate

End point title	Part 2: Objective Response Rate[3][4]

End point description:

Response Evaluable Population presented, based on BICR assessment.
Overall response rate = complete response + partial response

End point type	Primary

End point timeframe:

Tumor assessment at Screening then every 8 weeks (± 7 days) from Cycle 1 Day 1 and end of treatment (unless scan done within 4 weeks).

Notes:

[3] - 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: No statistical analysis was performed for this endpoint.

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoints are presented by individual reporting groups.

End point values	Part 2 - Dose Expansion			
Subject group type	Reporting group			
Number of subjects analysed	429			
Units: participants				
Objective Response Rate	64			

Statistical analyses

No statistical analyses for this end point

Primary: Part 4: Objective Response Rate

End point title	Part 4: Objective Response Rate[5][6]

End point description:

Response Evaluable Population presented, based on BICR assessment.
Overall response rate = complete response + partial response

End point type	Primary

End point timeframe:

Tumor assessment at Screening then every 8 weeks (± 7 days) from Cycle 1 Day 1 and end of treatment (unless scan done within 4 weeks).

Notes:

[5] - 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: No statistical analysis was performed for this endpoint.

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoints are presented by individual reporting groups.

End point values	Part 4 - Dose Expansion			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: participants				
Objective Response Rate	3			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded from the time of first study drug(s) administration until 100 days after the last dose of all study drug(s).

Adverse event reporting additional description:

Adverse event and toxicity grades were determined according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Safety Population

Reporting group description:

All patients who received at least 1 dose (or partial dose) of study drug.

Serious adverse events	Safety Population		
Total subjects affected by serious adverse events			
subjects affected / exposed	248 / 557 (44.52%)		
number of deaths (all causes)	318		
number of deaths resulting from adverse events	10		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	4 / 557 (0.72%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 10		
Tumour haemorrhage			
subjects affected / exposed	2 / 557 (0.36%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 10		
Bladder cancer			
subjects affected / exposed	1 / 557 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 10		
Intracranial tumour haemorrhage			

subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 10			
Metastases to central nervous system				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 10			
Oesophageal squamous cell carcinoma				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 10			
Squamous cell carcinoma				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 10			
Vascular disorders				
Hypotension				
subjects affected / exposed	16 / 557 (2.87%)			
occurrences causally related to treatment / all	15 / 19			
deaths causally related to treatment / all	0 / 10			
Embolism				
subjects affected / exposed	6 / 557 (1.08%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 10			
Superior vena cava syndrome				
subjects affected / exposed	3 / 557 (0.54%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 10			
Hypertension				
subjects affected / exposed	2 / 557 (0.36%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 10			
Deep vein thrombosis				

subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 10			
Vena cava thrombosis				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 10			
Venous thrombosis				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 10			
General disorders and administration site conditions				
Pyrexia				
subjects affected / exposed	18 / 557 (3.23%)			
occurrences causally related to treatment / all	17 / 21			
deaths causally related to treatment / all	0 / 10			
Pain				
subjects affected / exposed	4 / 557 (0.72%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 10			
Fatigue				
subjects affected / exposed	3 / 557 (0.54%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 10			
Malaise				
subjects affected / exposed	3 / 557 (0.54%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 10			
Non-cardiac chest pain				
subjects affected / exposed	3 / 557 (0.54%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 10			
Asthenia				

subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 10			
Chills				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 10			
Face oedema				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 10			
General physical health deterioration				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 10			
Influenza like illness				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 10			
Oedema peripheral				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 10			
Immune system disorders				
Cytokine release syndrome				
subjects affected / exposed	2 / 557 (0.36%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 10			
Contrast media allergy				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 10			
Reproductive system and breast disorders				

Pelvic pain				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 10			
Respiratory, thoracic and mediastinal disorders				
Dyspnoea				
subjects affected / exposed	15 / 557 (2.69%)			
occurrences causally related to treatment / all	3 / 15			
deaths causally related to treatment / all	0 / 10			
Pleural effusion				
subjects affected / exposed	8 / 557 (1.44%)			
occurrences causally related to treatment / all	1 / 10			
deaths causally related to treatment / all	0 / 10			
Pneumonitis				
subjects affected / exposed	6 / 557 (1.08%)			
occurrences causally related to treatment / all	6 / 7			
deaths causally related to treatment / all	1 / 10			
Pulmonary embolism				
subjects affected / exposed	5 / 557 (0.90%)			
occurrences causally related to treatment / all	1 / 5			
deaths causally related to treatment / all	0 / 10			
Chronic obstructive pulmonary disease				
subjects affected / exposed	4 / 557 (0.72%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 10			
Respiratory failure				
subjects affected / exposed	4 / 557 (0.72%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 10			
Haemoptysis				
subjects affected / exposed	2 / 557 (0.36%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 10			

Hypoxia				
subjects affected / exposed	2 / 557 (0.36%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 10			
Pneumothorax				
subjects affected / exposed	2 / 557 (0.36%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 10			
Pulmonary oedema				
subjects affected / exposed	2 / 557 (0.36%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 10			
Acute respiratory failure				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 10			
Bronchial obstruction				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 10			
Bronchospasm				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 10			
Cough				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 10			
Diaphragmatic spasm				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 10			
Laryngeal inflammation				

subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 10			
Pulmonary haemorrhage				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 10			
Psychiatric disorders				
Confusional state				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 10			
Hallucination				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 10			
Insomnia				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 10			
Mental status changes				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 10			
Investigations				
Blood creatinine increased				
subjects affected / exposed	2 / 557 (0.36%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 10			
Alanine aminotransferase increased				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 10			
Aspartate aminotransferase				

increased			
subjects affected / exposed	1 / 557 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 10		
Neutrophil count decreased			
subjects affected / exposed	1 / 557 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 10		
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	4 / 557 (0.72%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	0 / 10		
Fall			
subjects affected / exposed	2 / 557 (0.36%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 10		
Subdural haematoma			
subjects affected / exposed	2 / 557 (0.36%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 10		
Craniocerebral injury			
subjects affected / exposed	1 / 557 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 10		
Multiple fractures			
subjects affected / exposed	1 / 557 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 10		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	13 / 557 (2.33%)		
occurrences causally related to treatment / all	4 / 13		
deaths causally related to treatment / all	0 / 10		

Pericardial effusion				
subjects affected / exposed	3 / 557 (0.54%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 10			
Cardiac arrest				
subjects affected / exposed	2 / 557 (0.36%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	1 / 10			
Myocarditis				
subjects affected / exposed	2 / 557 (0.36%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 10			
Acute coronary syndrome				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 10			
Acute myocardial infarction				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 10			
Angina pectoris				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 10			
Arrhythmia supraventricular				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 10			
Atrial flutter				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 10			
Cardiac failure acute				

subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 10			
Cardio-respiratory arrest				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 10			
Myocardial infarction				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 10			
Pericarditis				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 10			
Supraventricular tachycardia				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 10			
Ventricular tachycardia				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 10			
Nervous system disorders				
Cerebrovascular accident				
subjects affected / exposed	10 / 557 (1.80%)			
occurrences causally related to treatment / all	6 / 10			
deaths causally related to treatment / all	1 / 10			
Embolic stroke				
subjects affected / exposed	3 / 557 (0.54%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 10			
Headache				

subjects affected / exposed	3 / 557 (0.54%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 10		
Dizziness			
subjects affected / exposed	2 / 557 (0.36%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 10		
Brain oedema			
subjects affected / exposed	1 / 557 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 10		
Cerebral infarction			
subjects affected / exposed	1 / 557 (0.18%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 10		
Encephalopathy			
subjects affected / exposed	1 / 557 (0.18%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 10		
Facial paralysis			
subjects affected / exposed	1 / 557 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 10		
Hydrocephalus			
subjects affected / exposed	1 / 557 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 10		
Myasthenia gravis			
subjects affected / exposed	1 / 557 (0.18%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 10		
Seizure			

subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 10			
Somnolence				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 10			
Spinal cord compression				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 10			
Syncope				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 10			
Vasogenic cerebral oedema				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 10			
Blood and lymphatic system disorders				
Anaemia				
subjects affected / exposed	5 / 557 (0.90%)			
occurrences causally related to treatment / all	0 / 10			
deaths causally related to treatment / all	0 / 10			
Eosinophilia				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 10			
Hypereosinophilic syndrome				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 10			
Microcytic anaemia				

subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 10			
Eye disorders				
Visual impairment				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 10			
Gastrointestinal disorders				
Nausea				
subjects affected / exposed	6 / 557 (1.08%)			
occurrences causally related to treatment / all	3 / 7			
deaths causally related to treatment / all	0 / 10			
Vomiting				
subjects affected / exposed	6 / 557 (1.08%)			
occurrences causally related to treatment / all	1 / 6			
deaths causally related to treatment / all	0 / 10			
Diarrhoea				
subjects affected / exposed	5 / 557 (0.90%)			
occurrences causally related to treatment / all	1 / 5			
deaths causally related to treatment / all	0 / 10			
Abdominal pain				
subjects affected / exposed	4 / 557 (0.72%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 10			
Pancreatitis				
subjects affected / exposed	2 / 557 (0.36%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 10			
Colitis				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 10			
Diverticulum intestinal haemorrhagic				

subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 10			
Dysphagia				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 10			
Enterocolitis				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 10			
Faecaloma				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 10			
Gastrointestinal haemorrhage				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 10			
Gastrooesophageal reflux disease				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 10			
Haematemesis				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 10			
Large intestinal obstruction				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 10			
Large intestine perforation				

subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 10			
Oesophageal stenosis				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 10			
Rectal haemorrhage				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 10			
Small intestinal obstruction				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 10			
Upper gastrointestinal haemorrhage				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 10			
Hepatobiliary disorders				
Autoimmune hepatitis				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 10			
Hepatic function abnormal				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 10			
Skin and subcutaneous tissue disorders				
Drug reaction with eosinophilia and systemic symptoms				
subjects affected / exposed	2 / 557 (0.36%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 10			

Rash erythematous				
subjects affected / exposed	2 / 557 (0.36%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 10			
Angioedema				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 10			
Erythema				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 10			
Pemphigoid				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 10			
Renal and urinary disorders				
Acute kidney injury				
subjects affected / exposed	9 / 557 (1.62%)			
occurrences causally related to treatment / all	5 / 9			
deaths causally related to treatment / all	0 / 10			
Autoimmune nephritis				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 10			
Haematuria				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 10			
Hydronephrosis				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 10			
Nephrolithiasis				

subjects affected / exposed	1 / 557 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 10		
Obstructive uropathy			
subjects affected / exposed	1 / 557 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 10		
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	3 / 557 (0.54%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	1 / 10		
Hyperthyroidism			
subjects affected / exposed	2 / 557 (0.36%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 10		
Autoimmune hypothyroidism			
subjects affected / exposed	1 / 557 (0.18%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 10		
Hypophysitis			
subjects affected / exposed	1 / 557 (0.18%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 10		
Hypothyroidism			
subjects affected / exposed	1 / 557 (0.18%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 10		
Thyroiditis			
subjects affected / exposed	1 / 557 (0.18%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 10		
Musculoskeletal and connective tissue disorders			

Back pain				
subjects affected / exposed	5 / 557 (0.90%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 10			
Flank pain				
subjects affected / exposed	3 / 557 (0.54%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 10			
Pain in extremity				
subjects affected / exposed	3 / 557 (0.54%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 10			
Arthralgia				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 10			
Groin pain				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 10			
Musculoskeletal chest pain				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 10			
Myalgia				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 10			
Myositis				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 10			
Pain in jaw				

subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 10			
Pathological fracture				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 10			
Rhabdomyolysis				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 10			
Spinal pain				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 10			
Infections and infestations				
Pneumonia				
subjects affected / exposed	12 / 557 (2.15%)			
occurrences causally related to treatment / all	0 / 15			
deaths causally related to treatment / all	0 / 10			
Urinary tract infection				
subjects affected / exposed	8 / 557 (1.44%)			
occurrences causally related to treatment / all	0 / 8			
deaths causally related to treatment / all	0 / 10			
Sepsis				
subjects affected / exposed	7 / 557 (1.26%)			
occurrences causally related to treatment / all	0 / 8			
deaths causally related to treatment / all	0 / 10			
Cellulitis				
subjects affected / exposed	3 / 557 (0.54%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 10			
Bronchitis				

subjects affected / exposed	2 / 557 (0.36%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 10			
Corona virus infection				
subjects affected / exposed	2 / 557 (0.36%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 10			
Infectious pleural effusion				
subjects affected / exposed	2 / 557 (0.36%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 10			
Lower respiratory tract infection				
subjects affected / exposed	2 / 557 (0.36%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 10			
Respiratory tract infection				
subjects affected / exposed	2 / 557 (0.36%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 10			
Abscess soft tissue				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 10			
Bronchopulmonary aspergillosis				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 10			
Bursitis infective staphylococcal				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 10			
Device related infection				

subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 10			
Device related sepsis				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 10			
Gastroenteritis				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 10			
Herpes zoster				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 10			
Lower respiratory tract infection viral				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 10			
Lung infection				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 10			
Systemic infection				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 10			
Urosepsis				
subjects affected / exposed	1 / 557 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 10			
Metabolism and nutrition disorders				
Hyponatraemia				

subjects affected / exposed	9 / 557 (1.62%)		
occurrences causally related to treatment / all	6 / 11		
deaths causally related to treatment / all	0 / 10		
Dehydration			
subjects affected / exposed	7 / 557 (1.26%)		
occurrences causally related to treatment / all	5 / 8		
deaths causally related to treatment / all	0 / 10		
Hypercalcaemia			
subjects affected / exposed	3 / 557 (0.54%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 10		
Hyperglycaemia			
subjects affected / exposed	3 / 557 (0.54%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 10		
Acidosis			
subjects affected / exposed	1 / 557 (0.18%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 10		
Failure to thrive			
subjects affected / exposed	1 / 557 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 10		
Hyperkalaemia			
subjects affected / exposed	1 / 557 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 10		

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

Non-serious adverse events	Safety Population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	549 / 557 (98.56%)		
Vascular disorders			
Hypotension			
subjects affected / exposed	99 / 557 (17.77%)		
occurrences (all)	150		
Hypertension			
subjects affected / exposed	33 / 557 (5.92%)		
occurrences (all)	49		
Flushing			
subjects affected / exposed	32 / 557 (5.75%)		
occurrences (all)	39		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	304 / 557 (54.58%)		
occurrences (all)	741		
Pyrexia			
alternative assessment type: Non-systematic			
subjects affected / exposed	278 / 557 (49.91%)		
occurrences (all)	697		
Influenza like illness			
alternative assessment type: Non-systematic			
subjects affected / exposed	175 / 557 (31.42%)		
occurrences (all)	582		
Chills			
subjects affected / exposed	158 / 557 (28.37%)		
occurrences (all)	289		
Oedema peripheral			
subjects affected / exposed	122 / 557 (21.90%)		
occurrences (all)	175		
Asthenia			
subjects affected / exposed	73 / 557 (13.11%)		
occurrences (all)	111		
Face oedema			

subjects affected / exposed	43 / 557 (7.72%)		
occurrences (all)	112		
Malaise			
subjects affected / exposed	31 / 557 (5.57%)		
occurrences (all)	61		
Non-cardiac chest pain			
subjects affected / exposed	31 / 557 (5.57%)		
occurrences (all)	37		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	155 / 557 (27.83%)		
occurrences (all)	247		
Dyspnoea			
subjects affected / exposed	117 / 557 (21.01%)		
occurrences (all)	144		
Nasal congestion			
subjects affected / exposed	80 / 557 (14.36%)		
occurrences (all)	168		
Oropharyngeal pain			
subjects affected / exposed	45 / 557 (8.08%)		
occurrences (all)	56		
Dysphonia			
subjects affected / exposed	33 / 557 (5.92%)		
occurrences (all)	37		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	71 / 557 (12.75%)		
occurrences (all)	103		
Investigations			
Weight decreased			
subjects affected / exposed	76 / 557 (13.64%)		
occurrences (all)	80		
Blood creatinine increased			
subjects affected / exposed	32 / 557 (5.75%)		
occurrences (all)	39		
Injury, poisoning and procedural complications			

Infusion related reaction			
subjects affected / exposed	37 / 557 (6.64%)		
occurrences (all)	51		
Nervous system disorders			
Headache			
subjects affected / exposed	105 / 557 (18.85%)		
occurrences (all)	165		
Dizziness			
subjects affected / exposed	102 / 557 (18.31%)		
occurrences (all)	153		
Dysgeusia			
subjects affected / exposed	42 / 557 (7.54%)		
occurrences (all)	81		
Paraesthesia			
subjects affected / exposed	35 / 557 (6.28%)		
occurrences (all)	36		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	55 / 557 (9.87%)		
occurrences (all)	61		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	239 / 557 (42.91%)		
occurrences (all)	569		
Diarrhoea			
subjects affected / exposed	174 / 557 (31.24%)		
occurrences (all)	336		
Vomiting			
subjects affected / exposed	148 / 557 (26.57%)		
occurrences (all)	260		
Constipation			
subjects affected / exposed	123 / 557 (22.08%)		
occurrences (all)	155		
Dry mouth			
subjects affected / exposed	71 / 557 (12.75%)		
occurrences (all)	90		
Abdominal pain			

subjects affected / exposed	67 / 557 (12.03%)		
occurrences (all)	86		
Dyspepsia			
subjects affected / exposed	45 / 557 (8.08%)		
occurrences (all)	67		
Stomatitis			
subjects affected / exposed	39 / 557 (7.00%)		
occurrences (all)	45		
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	228 / 557 (40.93%)		
occurrences (all)	340		
Rash			
subjects affected / exposed	154 / 557 (27.65%)		
occurrences (all)	245		
Rash maculo-papular			
subjects affected / exposed	104 / 557 (18.67%)		
occurrences (all)	157		
Dry skin			
subjects affected / exposed	92 / 557 (16.52%)		
occurrences (all)	106		
Erythema			
subjects affected / exposed	56 / 557 (10.05%)		
occurrences (all)	64		
Rash pruritic			
subjects affected / exposed	29 / 557 (5.21%)		
occurrences (all)	38		
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	89 / 557 (15.98%)		
occurrences (all)	91		
Hyperthyroidism			
subjects affected / exposed	32 / 557 (5.75%)		
occurrences (all)	33		
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	151 / 557 (27.11%)		
occurrences (all)	276		
Myalgia			
subjects affected / exposed	98 / 557 (17.59%)		
occurrences (all)	204		
Back pain			
subjects affected / exposed	89 / 557 (15.98%)		
occurrences (all)	104		
Pain in extremity			
subjects affected / exposed	57 / 557 (10.23%)		
occurrences (all)	69		
Musculoskeletal pain			
subjects affected / exposed	43 / 557 (7.72%)		
occurrences (all)	57		
Muscular weakness			
subjects affected / exposed	33 / 557 (5.92%)		
occurrences (all)	35		
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	39 / 557 (7.00%)		
occurrences (all)	61		
Upper respiratory tract infection			
subjects affected / exposed	36 / 557 (6.46%)		
occurrences (all)	42		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	210 / 557 (37.70%)		
occurrences (all)	378		
Dehydration			
subjects affected / exposed	50 / 557 (8.98%)		
occurrences (all)	62		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 December 2016	In alignment with a new development partner (BMS), the study design, including objectives and endpoints, was modified to evaluate NKTR-214 and nivolumab only. Thus, treatment regimens were revised (eg, removed pembrolizumab and atezolizumab [never opened for enrollment], added an NKTR-214 every 2 week dosing schedule, nivolumab dosing changed from weight-based to a flat 240-mg dose every 2 weeks), the UCC tumor type was removed, and the entry criteria were updated. Decreased the duration of nivolumab infusion. Cohort decisions about timing of enrollment, dose level, and dose frequency would be based on evolving clinical data from an ongoing NKTR-214 monotherapy and nivolumab combination therapy studies conducted by the Sponsor and the development partner, respectively. Dose-limiting toxicitywindows were defined and the end of treatment visit was extended.
29 March 2017	Added new immunotherapy naïve cohorts for urothelial carcinoma and triple-negative breast cancer as well as patient populations that were either relapsed or refractory to checkpoint inhibition for the treatment of melanoma, renal cell carcinoma, and non-small cell lung cancer resulting in 8 expansion cohorts across 5 tumor types. Added 3 dose escalation cohorts to evaluate nivolumab at a 360 mg every 3 week dosing schedule. Revised the entry criteria based on feedback from Investigators, Safety Review Committee, and EU requirements; revised the dose-limiting toxicity criteria; added intravenous hydration to Cycle 1 Days 1 and 2 and recommended ≥ 2 L per day of oral hydration on Days 3 to 5 of Cycle 1 and Days 1-5 of Cycle 2 and beyond. Clarified timing of tumor biopsy.
03 April 2017	Removed 2 dosing cohorts from Part 1 per FDA guidance: • NKTR-214 0.003 mg/kg every 3 weeks + nivolumab 360 mg every 3 weeks • NKTR-214 0.003 mg/kg every 2 weeks + nivolumab 240 mg every 2 weeks
22 June 2017	Added the rationale for the Safety Review Committee-approved recommended Phase 2 dose for Part 2, clarified the entry criteria, and updated the IV hydration guidelines with minimum volume requirements (≥ 1 L) and intravenous hydration on Day 1 of all cycles.
05 December 2017	Changed Part 2 cohorts to create more homogenous patient populations and added a new cohort for urothelial carcinoma. Added Part 3 (schedule finding) and Part 4 (dose expansion) to assess the safety, tolerability, and efficacy of the triplet combination (NKTR-214 + nivolumab + ipilimumab) in renal cell carcinoma first-line and non-small cell lung cancer first-line. Thus, the objectives, endpoints, entry criteria, schedule of events, statistical methods (including analysis sets) were updated. Extended the duration of NKTR-214 infusion to reduce the incidence of infusion reactions and increase tolerability, capped the continuation of treatment in patients with confirmed complete response at 2 years, modified the dose-limiting toxicity criteria, updated the reasons for end of treatment, allowed prophylaxis for flu-like symptoms and/or rash/pruritus, and decreased the duration of stable disease for clinical benefit rate to ≥ 7 weeks.

18 June 2018	Added 11 cohorts across new and existing tumor types in Part 2, added 5 cohorts (3 non-small cell lung cancer, 2 triple-negative breast cancer) in which the doublet was administered with the chemotherapy, added 5 cohorts to allow for administrative reclassification of previously enrolled patients by the Sponsor, and patient eligibility criteria were adjusted. Added tumor types, associated entry criteria, and dosing schedules for the triplet regimen in Parts 3 and 4. Clarified the exploratory objectives. Added that investigator could administer intravenous fluid on Day 2 of Cycle 2 and beyond if deemed necessary. The following cohorts were closed to enrollment: • Part 2 (n = 7) – Cohorts 1a and 2a (enrolled a sufficient number of patients); Cohorts 1e, 2c, 3i, 4c, and 5d (represent the 5 aforementioned cohorts that were added for administrative reclassification of previously enrolled patients) • Part 4 (n = 1) – Cohort 10a.1
11 February 2020	The study was closed to further patient screening and enrollment. All active patients continued treatment and follow-up per protocol. Previously closed cohorts (including some that never enrolled patients, see Section 9.1.2.2) included all cohorts in Part 1; Cohorts 1a, 1b, 2a, 3b, 3f, 3g, 4a, 5a, 7, and 9 in Part 2; schedule 1 renal cell carcinoma (10a.1) in Parts 3 and 4. Several cohorts in Part 2 were previously closed via administrative letter (29 March 2019) because registration would not be pursued (1c, 1d, 6a, 6b, 8a, 8b), enrollment was met (2b, 3c, 4b), or the cohort never opened (9 [clinical study results of nivolumab in SCLC showed no advantage in overall survival]). Part 4 Cohort 12a.3 (melanoma), and Cohorts 5b and 5c were also closed. The protocol was updated with the results of a comprehensive review of cerebrovascular accident-related safety information across the NKTR-214 clinical development program after 3 patients receiving the triplet therapy had serious adverse events (SAEs) of cerebrovascular accident (1 fatal) in the current study. Added safety measures to mitigate the risk of cerebrovascular accident: cerebrovascular accident elevated to adverse event (AE) of special interest; cerebrovascular accident AE management algorithm to evaluate cardiac and neurologic events and provide a standard set of tests for evaluation and follow-up of cerebrovascular accident events; and implemented preventative measures (eg, increased monitoring of renal function; delay treatment if renal parameters not met; and contact patients after Cycles 1 and 2 to reinforce hydration guidelines and assess for symptomatology and compliance). Redefined required reporting period for AEs and SAEs as the time of first study drug(s) administration until 100 days after the last dose of all study drug(s).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported