Clinical trial results:
A Phase 1b/2 Study to Evaluate Safety and Clinical Activity of Avelumab in Combination with Bempegaldesleukin (NKTR-214) with or without Talazoparib or Enzalutamide in Participants with Locally Advanced or Metastatic Solid Tumors

Summary

EudraCT number	2019-001358-24
Trial protocol	PL IT ES BE
Global end of trial date	29 September 2020

Results information

Result version number	v1 (current)
This version publication date	08 September 2021
First version publication date	08 September 2021

Trial information

Trial identification

Sponsor protocol code	B9991040

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04052204
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer Inc.
Sponsor organisation address	235 East 42nd Street, New York, NY, United States, 10017-5755
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., Pfizer Inc., +1 8007181021, ClinicalTrails.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., Pfizer Inc., +1 8007181021, ClinicalTrials.gov_Inquiries@pfizer.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	22 January 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 September 2020
Global end of trial reached?	Yes
Global end of trial date	29 September 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary object of this trial was to assess the dose-limiting toxicity (DLT) rate of avelumab in combination with bempegaldesleukin (NKTR-214) (Combination A) to determine the recommended Phase 2 dose (RP2D) for the combinations.

Protection of trial subjects:

This study was conducted in compliance with the ethical principles originated or derived from the Declaration of Helsinki and in compliance with all International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines. All local regulatory requirements were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 December 2019
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Poland: 1
Country: Number of subjects enrolled	Spain: 1
Worldwide total number of subjects	3
EEA total number of subjects	3

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)	2
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

4 subjects screened for this study, 1 of the 4 subjects was a screen failure, 3 subjects were enrolled and received study treatment in Combination A.

Period 1

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

Arms

Arm title	Avelumab + Bempegaldesleukin (NKTR-214) (Combination A)

Arm description:

NKTR-214 was administered prior to avelumab. NKTR-214 0.006 mg/kg was administered intravenously (IV) over 30 minutes every 2 weeks (Q2W). Avelumab 800 mg as a 1-hour IV infusion was administered after the NKTR-214 Q2W, at the investigational site on an outpatient basis on Day 1 and Day 15 of each 28-day cycle. Within the 2-day window, avelumab and NKTR-214 were administered on the same day. Dose reduction of NKTR-214 to 0.003 mg/kg Q2W was triggered if higher than expected toxicity is observed at the higher dose (risk of excessive toxicity ≥ 0.25).

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

Dosage and administration details:

Each subject’s NKTR-214 dose was determined based on the subject’s weight in kilograms on Day 1 of each cycle. NKTR-214 was administered prior to avelumab. NKTR-214 was administered IV over 30 (± 5) minutes every 2 weeks (+/- 2 days).

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

Dosage and administration details:

Avelumab was administered at 800 mg as a 1-hour (-10/+20 minutes) IV infusion starting after the NKTR-214 and talazoparib or enzalutamide (where applicable) was administered, at the investigational site on an outpatient basis on Day 1 and Day 15 of each 28-day cycle.

Number of subjects in period 1	Avelumab + Bempegaldesleukin (NKTR-214) (Combination A)
Started	3
Completed	0
Not completed	3

Death	1
Other	1
Progressive disease	1

Baseline characteristics

Reporting groups	
Reporting group title	Avelumab + Bempegaldesleukin (NKTR-214) (Combination A)
Reporting group description:	
NKTR-214 was administered prior to avelumab. NKTR-214 0.006 mg/kg was administered intravenously (IV) over 30 minutes every 2 weeks (Q2W). Avelumab 800 mg as a 1-hour IV infusion was administered after the NKTR-214 Q2W, at the investigational site on an outpatient basis on Day 1 and Day 15 of each 28-day cycle. Within the 2-day window, avelumab and NKTR-214 were administered on the same day. Dose reduction of NKTR-214 to 0.003 mg/kg Q2W was triggered if higher than expected toxicity is observed at the higher dose (risk of excessive toxicity ≥ 0.25).	

Reporting group values	Avelumab + Bempegaldesleukin (NKTR-214) (Combination A)	Total	
Number of subjects	3	3	
Age Categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	2	2	
From 65-84 years	1	1	
85 years and over	0	0	
Age Continuous Units: years			
median	64.00		
full range (min-max)	56.0 to 65.0	-	
Gender Categorical Units: Subjects			
Female	1	1	
Male	2	2	
Race Units: Subjects			
Black or African American	0	0	
American Indian or Alaska Native	0	0	
Asian	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
White	3	3	
Multiracial	0	0	
Not reported	0	0	

End points

End points reporting groups

Reporting group title	Avelumab + Bempegaldesleukin (NKTR-214) (Combination A)

Reporting group description:

NKTR-214 was administered prior to avelumab. NKTR-214 0.006 mg/kg was administered intravenously (IV) over 30 minutes every 2 weeks (Q2W). Avelumab 800 mg as a 1-hour IV infusion was administered after the NKTR-214 Q2W, at the investigational site on an outpatient basis on Day 1 and Day 15 of each 28-day cycle. Within the 2-day window, avelumab and NKTR-214 were administered on the same day. Dose reduction of NKTR-214 to 0.003 mg/kg Q2W was triggered if higher than expected toxicity is observed at the higher dose (risk of excessive toxicity ≥ 0.25).

Primary: Number of Subjects with Dose Limiting Toxicities (DLT)

End point title	Number of Subjects with Dose Limiting Toxicities (DLT)[1]

End point description:

DLTs were graded according to NCI- CTCAE version 4.03 and coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT) as event category and MedDRA primary system organ class (SOC) body term as Body System category. The DLT-evaluable analysis set was a subset of the safety analysis set and included all enrolled subjects in Phase 1b who received at least one dose of the combination treatment and either experienced DLT during the first cycle (28 days) of treatment, or completed the DLT observation period for the first cycle of treatment without a DLT.

End point type	Primary

End point timeframe:

Cycle 1 of the treatment period (28 days)

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 planned for this endpoint

End point values	Avelumab + Bempegaldesleukin (NKTR-214) (Combination A)			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: Subjects				
Number of Subjects Reported:	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DR)

End point title	Duration of Response (DR)

End point description:

DR was defined, for subjects with a confirmed Objective Response (OR), as the time from the first documentation of OR to the date of first documentation of progressive disease (PD) or death due to any cause. The documentation of PD was defined using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. If a subject had not had an event (PD or death), DR was censored at the date of last

adequate tumor assessment. All subjects treated in combination A who achieved an OR were analyzed.

End point type	Secondary

End point timeframe:

Approximately 8 months (246 days).

End point values	Avelumab + Bempegaldesleukin (NKTR-214) (Combination A)			
Subject group type	Reporting group			
Number of subjects analysed	0[2]			
Units: months				
median (confidence interval 95%)	(to)			

Notes:

[2] - As there were no ORs in the study, no participant met the definition of analysis population.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Tumor Response (TTR)

End point title	Time to Tumor Response (TTR)

End point description:

TTR was defined, for subjects with OR, as the time from the date of first dose of study treatment to the first documentation of objective response (Complete Response or Partial Response) which was subsequently confirmed. All subjects treated in combination A who achieved an OR were analyzed. 99999 indicates that TTR was not analyzed due to no objective responses in the study.

End point type	Secondary

End point timeframe:

Approximately 8 months (246 days).

End point values	Avelumab + Bempegaldesleukin (NKTR-214) (Combination A)			
Subject group type	Reporting group			
Number of subjects analysed	0[3]			
Units: months				
median (full range (min-max))	(to)			

Notes:

[3] - As there were no ORs in the study, no participant met the definition of analysis population.

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS)

End point title	Progression-Free Survival (PFS)

End point description:

Progression-Free Survival (PFS): the time from the date of first dose of study treatment to the date of the first documentation of progressive disease (PD) or death due to any cause, whichever occurs first. PFS data were censored on the date of the last adequate tumor assessment for subjects who did not have an event (PD or death), for subjects who started new anti-cancer therapy prior to an event, or for subjects with an event after two or more missing tumor assessments. Subjects who did not have an adequate baseline tumor assessment or who did not have any adequate post-baseline tumor assessments were censored on the date of first dose of study treatment unless death occurred on or before the time of the second planned tumor assessment, in which case death was considered an event. Two subjects had best overall response of PD and 1 was not evaluable due to early death. One subject died on days 18, another died on day 77. 99999 indicates no summaries of PFS endpoints, because N<= 3.

End point type	Secondary

End point timeframe:

Approximately 8 months (246 days).

End point values	Avelumab + Bempegaldesleukin (NKTR-214) (Combination A)			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as the time from the first dose of study treatment to the date of death due to any cause. Patients last known to be alive were censored at date of last contact. All subjected treated in combination A were analyzed. one subject died 18 after the first dose of treatment, 1 patient did 77 days after first dose of treatment. the 3 subject was censored 191 days after first dose (first dose date 23Mar2020, end of study 29Sep2020). 99999 indicates that there were no summaries of OS endpoints, because N<= 3.

End point type	Secondary

End point timeframe:

Approximately 8 months (246 days)

End point values	Avelumab + Bempegaldesleukin (NKTR-214) (Combination A)			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic (PK) parameters - Cmax and Ctrough for Avelumab and NKTR-214

End point title	Pharmacokinetic (PK) parameters - Cmax and Ctrough for Avelumab and NKTR-214

End point description:

Cmax was defined as the maximum observed plasma concentration at the end of infusion. Ctrough was defined as the predose concentration at the end of dosing interval. The PK parameter analysis set was a subset of the safety analysis set and included subjects who had at least one of the PK parameters of interest for avelumab, NKTR-214, IL-2, talazoparib, enzalutamide, or N-desmethyl-enzalutamide. 99999 indicates that there were no summaries and interpretations of PK results available, because N<=3 in the PK analysis set.

End point type	Secondary

End point timeframe:

Blood samples were collected on Day 1 and Day 15 in Cycle 1 and Cycle 2 for avelumab. Blood samples were collected on Day 1, Day 3, Day 4 and Day 8 in Cycle 1, Day1 and Day 8 in Cycle 2 for NKTR-214.

End point values	Avelumab + Bempegaldesleukin (NKTR-214) (Combination A)			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: ug/mL				
median (confidence interval 95%)	99999 (99999 to 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Positive Anti-Drug Antibody (ADA) Results

End point title	Number of Subjects with Positive Anti-Drug Antibody (ADA) Results

End point description:

ADA against avelumab and NKTR-214 in serum samples was determined and reported separately for ADA never-positive, ADA ever-positive, baseline ADA positive, treatment-boosted ADA, treatment-induced ADA, transient ADA response, Persistent ADA response. For all subjects, blood for ADA samples will be drawn from the contralateral arm of the avelumab and NKTR-214 infusion. The immunogenicity analysis set was a subset of the safety analysis set and included subjects who had at least one ADA/nAb sample collected for avelumab, NKTR-214, or IL-2. 99999 indicates that ADA results were not analyzed for this study due to study termination.

End point type	Secondary

End point timeframe:

Day 1 of Cycle 1, Cycle 2 and end of treatment (EOT).

End point values	Avelumab + Bempegaldesleukin (NKTR-214) (Combination A)			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: Subjects	99999			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Positive Neutralizing Antibody (nAb) Results

End point title	Number of Subjects with Positive Neutralizing Antibody (nAb) Results

End point description:

Samples positive for ADA were analyzed for nAb, nAb in serum samples was determined and reported separately for nAb never-positive, nAb ever-positive, baseline nAb positive, treatment-induced nAb, transient nAb response, persistent nAb response. The immunogenicity analysis set was a subset of the safety analysis set and included subjects who had at least one ADA/nAb sample collected for avelumab, NKTR-214, or IL-2. 99999 indicates that nAb results were not analyzed for this study due to study termination.

End point type	Secondary

End point timeframe:

Day 1 of Cycle 1, Cycle 2, and EOT.

End point values	Avelumab + Bempegaldesleukin (NKTR-214) (Combination A)			
Subject group type	Reporting group			
Number of subjects analysed	3			

Units: Subjects	99999			

Statistical analyses

No statistical analyses for this end point

Secondary: PD-L1 Expression Level in Baseline and On-treatment Tumor Tissue

End point title	PD-L1 Expression Level in Baseline and On-treatment Tumor Tissue

End point description:

PD-L1 expression level in baseline tumor tissue, and in on-treatment tumor tissue was defined as the number of PD-L1 positive cells and/or qualitative assessment of PD-L1 staining on tumor and/or inflammatory cells in regions of interest. PD-L1 expression level in baseline tumor tissue and in on-treatment tumor tissue were under pathological analyses, assisted by image analysis. Subjects were classified as positive or negative according to scoring algorithms and cut-offs established from internal or external sources. The biomarker analysis set for biomarkers that were only measured at screening was a subset of the safety analysis set and included subjects who had at least one baseline biomarker assessment. 99999 indicates that no biomarker data (PD-L1) were analyzed for this study due to early study termination.

End point type	Secondary

End point timeframe:

On-treatment biopsy was required to be collected on Cycle 1 between Days 9 and 14 for subjects in Combination A.

End point values	Avelumab + Bempegaldesleukin (NKTR-214) (Combination A)			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: Subjects	99999			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Treatment-Emergent Adverse Events(TEAEs), Serious TEAEs, TEAEs Leading to Death and Infusion-Related Reactions (IRRs) During On-treatment Period

End point title	Number of Subjects with Treatment-Emergent Adverse Events(TEAEs), Serious TEAEs, TEAEs Leading to Death and Infusion-Related Reactions (IRRs) During On-treatment Period

End point description:

Adverse events (AEs) were any untoward medical occurrences in a subject, temporally associated with the use of study intervention, whether or not considered related to the study intervention. Treatment-

emergent adverse events (TEAEs) were those events with onset dates occurring during the on-treatment period, which was defined as the time from the first dose of study treatment through minimum (30 days + last dose of study treatment). A Serious Adverse Event (SAE) was defined as any untoward medical occurrence that, at any dose: a. Results in death, b. Was life-threatening, c. Required inpatient hospitalization or prolongation of existing hospitalization, d. Resulted in persistent disability/incapacity, e. Was a congenital anomaly/birth defect. Causality to study treatment was determined by the investigator. The safety analysis set included all subjects who received at least one dose of study drug. "Treatment-Related" is abbreviated as "TR" "All-Causality" is abbreviated as "AC"

End point type	Secondary

End point timeframe:

Approximately 6 months (190 days)

End point values	Avelumab + Bempegaldesleukin (NKTR-214) (Combination A)			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: Subjects				
Subjects with AC TEAEs	3			
Subjects with grade ≥ 3 AC TEAEs	2			
Subjects with TR TEAEs	3			
Subjects with grade ≥ 3 TR TEAEs	1			
Subjects with serious AC TEAEs	1			
Subjects with serious TR TEAEs	1			
Subjects with AC TEAEs leading to death	1			
Subjects with TR TEAEs leading to death	1			
Subjects with IRRs	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Laboratory Abnormalities

End point title	Number of Subjects with Laboratory Abnormalities

End point description:

Liver Function Tests of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin (TBILI) were used to assess possible drug induced liver toxicity. The number of subjects with at least one of the following laboratory results were summarized below: 1. (ALT ≥3 × ULN or AST ≥3 × ULN) post-baseline. 2. TBILI ≥2 × ULN post-baseline. 3. (ALP ≤2 × ULN or missing) post-baseline.

End point type	Secondary

End point timeframe:

Day 1, Day 15 of each treatment cycle

End point values	Avelumab + Bempegaldesleukin (NKTR-214) (Combination A)			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: Subjects				
Subjects with at least one NCI-CTCAE Grade ≥3	3			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the subject provided informed consent to a minimum of 90 calendar days after the last administration of the investigational product.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Dose-Finding for Combination A

Reporting group description:

Subjects were administrated 800mg avelumab plus 0.006mg/kg bempegaldesleukin(NKTR-214) intravenous(IV) every 2 weeks (Q2W)

Serious adverse events	Dose-Finding for Combination A		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 3 (33.33%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	1		
General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Dose-Finding for Combination A		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)		
Investigations			
Neutrophil count decreased			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Platelet count increased			

subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Weight decrease			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Fal			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	2		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	7		
Asthenia			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	4		
Influenza like illness			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
General physical health deterioration			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 3 (66.67%)		
occurrences (all)	5		
Musculoskeletal pain			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Myalgia			

subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 6		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	 1 / 3 (33.33%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 June 2019	This amendment is to expand the Dose Limiting Toxicity(DLT) criteria following the feedback received from the FDA during the IND application review.

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.

Only Phase 1b of Combination A was conducted as company terminated this study on 21 May 2020. Termination was not due to a regulatory request or new emerging safety signals. Combination B, C and Phase 2 expansion for Combination A were not tested.

Notes: