Clinical trial results:
A randomized phase IIb study evaluating immunogenic chemotherapy combined with ipilimumab and nivolumab in patients with metastatic hormone receptor positive breast cancer

Summary

EudraCT number	2017-000220-10
Trial protocol	NO BE
Global end of trial date	11 May 2022

Results information

Result version number	v1 (current)
This version publication date	30 October 2024
First version publication date	30 October 2024
Summary attachment (see zip file)	Published article (Andresen et al. JITC 2024.pdf)

Trial information

Trial identification

Sponsor protocol code	ICON-CA209-9FN

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03409198
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Oslo University Hospital, Department of Oncology
Sponsor organisation address	Ullernchausseen 70, Oslo, Norway, 0379
Public contact	Jon Amund Kyte , Oslo University Hospital, Department of Oncology, +47 97569619, jonky@ous-hf.no
Scientific contact	Jon Amund Kyte , Oslo University Hospital, Department of Oncology, +47 97569619, jonky@ous-hf.no

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	20 January 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 May 2022
Global end of trial reached?	Yes
Global end of trial date	11 May 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Co-primary objectives:
Assessment of toxicity of combined treatment with ipilimumab, nivolumab, pegylated liposomal doxorubicin and cyclophosphamide (ipi/nivo plus chemotherapy).
Assessment of clinical response: Progression-free survival (PFS) in ipi/nivo-chemo group compared to the chemo-only group.

Protection of trial subjects:

The trial was conducted according to the guidelines of Good Clinical Practice and the principles of the World Medical Association’s Declaration of Helsinki. All patients provided written informed consent.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 February 2018
Long term follow-up planned	Yes
Long term follow-up rationale	Scientific research, Safety
Long term follow-up duration	4 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 16
Country: Number of subjects enrolled	Norway: 66
Worldwide total number of subjects	82
EEA total number of subjects	82

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)	65
From 65 to 84 years	17
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Eighty-two subjects were recruited at 5 academic hospitals in Norway and Belgium; Oslo University Hospital (n= 48), CHU UCL Namur (n= 13), Stavanger University Hospital (n= 9), Kristiansand Hospital (n= 9) and Institut Jules Bordet (n= 3).

Pre-assignment

Screening details:

A total of 106 patients were assessed for eligibility in the trial. Eighty-two patients were randomized and started allocated therapy and was included in the full analysis set population.

Period 1

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

Arms

Are arms mutually exclusive?	No
Arm title	Chemotherapy-only

Arm description:

Pegylated liposomal doxorubicin plus cyclophosphamide

Arm type	Active comparator
Investigational medicinal product name	Pegylated liposomal doxorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Pegylated liposomal doxorubicin 20/m2 i.v. every 2nd week. An upper limit of 44mg per dose was applied to patients with a body surface area >2.2 m2.

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Cyclophosphamide tablets 50 mg per day, daily as continuous treatment for every 2nd cycle (i.e. first 2 weeks of each 4 week period)

Arm title	Ipi/nivo plus chemotherapy

Arm description:

Ipilimumab plus nivolumab plus pegylated liposomal doxorubicin plus cyclophosphamide

Arm type	Experimental
Investigational medicinal product name	Nivolumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Nivolumab 240 mg administered intravenously every 2nd week until disease progression or for a maximum of 24 months

Investigational medicinal product name	Ipilimumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Ipilimumab 1mg/kg administered intravenously every 6th week until disease progression or for a maximum of 24 months

Investigational medicinal product name	Pegylated liposomal doxorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Pegylated liposomal doxorubicin 20/m2 i.v. every 2nd week. An upper limit of 44mg per dose was applied to patients with a body surface area >2.2 m2.

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Cyclophosphamide tablets 50 mg per day, daily as continuous treatment for every 2nd cycle (i.e. first 2 weeks of each 4 week period)

Arm title	Ipi/nivo-only (cross-over)

Arm description:

Ipilimumab plus nivolumab without chemotherapy (cross-over from chemo-only)

Arm type	Experimental
Investigational medicinal product name	Nivolumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Nivolumab 240 mg administered intravenously every 2nd week until disease progression or for a maximum of 24 months

Investigational medicinal product name	Ipilimumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Ipilimumab 1mg/kg administered intravenously every 6th week until disease progression or for a maximum of 24 months

Number of subjects in period 1	Chemotherapy-only	Ipi/nivo plus chemotherapy	Ipi/nivo-only (cross-over)
Started	33	49	16
Completed	1	1	0
Not completed	32	48	16
Adverse event, serious fatal	-	1	-
Patient withdrawal	1	-	-
Adverse event, non-fatal	1	6	-
Sponsors decision	1	1	-
Lack of efficacy	29	40	16

Baseline characteristics

Reporting groups	
Reporting group title	Chemotherapy-only
Reporting group description:	
Pegylated liposomal doxorubicin plus cyclophosphamide	
Reporting group title	Ipi/nivo plus chemotherapy
Reporting group description:	
Ipilimumab plus nivolumab plus pegylated liposomal doxorubicin plus cyclophosphamide	
Reporting group title	Ipi/nivo-only (cross-over)
Reporting group description:	
Ipilimumab plus nivolumab without chemotherapy (cross-over from chemo-only)	

Reporting group values	Chemotherapy-only	Ipi/nivo plus chemotherapy	Ipi/nivo-only (cross-over)
Number of subjects	33	49	16
Age categorical Units: Subjects			
Adults (18-64 years)	26	39	15
From 65-84 years	7	10	1
Age continuous Units: years			
median	55	53	56
full range (min-max)	37 to 74	36 to 75	39 to 73
Gender categorical Units: Subjects			
Female	33	48	16
Male	0	1	0
ECOG performance status Units: Subjects			
ECOG 0	18	19	11
ECOG 1	15	30	5
De novo metastatic disease Units: Subjects			
Yes	9	9	4
No	24	40	12
Bone metastases Units: Subjects			
Yes	28	45	14
No	5	4	2
Liver metastases Units: Subjects			
Yes	28	36	15
No	5	13	1
Lung metastases Units: Subjects			
Yes	6	18	3
No	27	31	13
>3 sites of metastases			

Units: Subjects			
Yes	9	14	4
No	24	35	12
Previous CDK4/6 inhibitor Units: Subjects			
Yes	30	44	15
No	3	5	1
PD-L1 expression			
PD-L1 expression was assessed by immunohistochemistry on prestudy formalin-fixed paraffin-embedded (FFPE) sections by the VENTANA SP142 assay (Roche Diagnostics, Rotkreuz, Switzerland). Forty-five patients had more than one biopsy assessed and were categorized as PD-L1+ if any of the biopsies were positive.			
Units: Subjects			
Positive	10	19	5
Negative	20	28	11
Missing	3	2	0
PAM50 subtype			
Gene expression data were used to determine the intrinsic molecular subtype using the nCounter BC360 assay (NanoString Technologies, Seattle, USA). Analysis was performed on bulk RNA isolated from prestudy FFPE sections. In patients with more than one sample analyzed, the profile was based on the most recent sample.			
Units: Subjects			
Luminal A	6	9	3
Luminal B	21	34	11
HER2 enriched	3	4	1
Basal	0	1	0
Missing	3	1	1

Reporting group values	Total		
Number of subjects	82		
Age categorical Units: Subjects			
Adults (18-64 years)	65		
From 65-84 years	17		
Age continuous Units: years median full range (min-max)	- -		
Gender categorical Units: Subjects			
Female	81		
Male	1		
ECOG performance status Units: Subjects			
ECOG 0	37		
ECOG 1	45		
De novo metastatic disease Units: Subjects			
Yes	18		
No	64		
Bone metastases Units: Subjects			
Yes	73		

No	9		
Liver metastases Units: Subjects			
Yes	64		
No	18		
Lung metastases Units: Subjects			
Yes	24		
No	58		
>3 sites of metastases Units: Subjects			
Yes	23		
No	59		
Previous CDK4/6 inhibitor Units: Subjects			
Yes	74		
No	8		
PD-L1 expression			
PD-L1 expression was assessed by immunohistochemistry on prestudy formalin-fixed paraffin-embedded (FFPE) sections by the VENTANA SP142 assay (Roche Diagnostics, Rotkreuz, Switzerland). Forty-five patients had more than one biopsy assessed and were categorized as PD-L1+ if any of the biopsies were positive.			
Units: Subjects			
Positive	29		
Negative	48		
Missing	5		
PAM50 subtype			
Gene expression data were used to determine the intrinsic molecular subtype using the nCounter BC360 assay (NanoString Technologies, Seattle, USA). Analysis was performed on bulk RNA isolated from prestudy FFPE sections. In patients with more than one sample analyzed, the profile was based on the most recent sample.			
Units: Subjects			
Luminal A	15		
Luminal B	55		
HER2 enriched	7		
Basal	1		
Missing	4		

Subject analysis sets

Subject analysis set title	Chemo-only per-protocol population
Subject analysis set type	Per protocol
Subject analysis set description: Patients evaluated for response and received the equivalent of ≥2 treatment cycles	
Subject analysis set title	Ipi/nivo plus chemotherapy per-protocol population
Subject analysis set type	Per protocol
Subject analysis set description: Patients evaluated for tumor response and received the equivalent of ≥ 2 treatment cycles	

Reporting group values	Chemo-only per-protocol population	Ipi/nivo plus chemotherapy per-protocol population	
Number of subjects	31	47	

Age categorical Units: Subjects			
Adults (18-64 years)	25	37	
From 65-84 years	6	10	
Age continuous Units: years			
median	55	53	
full range (min-max)	37 to 74	36 to 75	
Gender categorical Units: Subjects			
Female	31	46	
Male	0	1	
ECOG performance status Units: Subjects			
ECOG 0	17	18	
ECOG 1	14	29	
De novo metastatic disease Units: Subjects			
Yes	9	8	
No	22	39	
Bone metastases Units: Subjects			
Yes	27	43	
No	4	4	
Liver metastases Units: Subjects			
Yes	27	34	
No	4	13	
Lung metastases Units: Subjects			
Yes	4	17	
No	27	30	
>3 sites of metastases Units: Subjects			
Yes	9	13	
No	22	34	
Previous CDK4/6 inhibitor Units: Subjects			
Yes	29	42	
No	2	5	
PD-L1 expression			
PD-L1 expression was assessed by immunohistochemistry on prestudy formalin-fixed paraffin-embedded (FFPE) sections by the VENTANA SP142 assay (Roche Diagnostics, Rotkreuz, Switzerland). Forty-five patients had more than one biopsy assessed and were categorized as PD-L1+ if any of the biopsies were positive.			
Units: Subjects			
Positive	10	19	
Negative	18	26	
Missing	3	2	
PAM50 subtype			
Gene expression data were used to determine the intrinsic molecular subtype using the nCounter BC360 assay (NanoString Technologies, Seattle, USA). Analysis was performed on bulk RNA isolated from			

prestudy FFPE sections. In patients with more than one sample analyzed, the profile was based on the most recent sample.			
Units: Subjects			
Luminal A	6	9	
Luminal B	19	32	
HER2 enriched	3	4	
Basal	0	1	
Missing	3	1	

End points

End points reporting groups

Reporting group title	Chemotherapy-only
Reporting group description: Pegylated liposomal doxorubicin plus cyclophosphamide	
Reporting group title	Ipi/nivo plus chemotherapy
Reporting group description: Ipilimumab plus nivolumab plus pegylated liposomal doxorubicin plus cyclophosphamide	
Reporting group title	Ipi/nivo-only (cross-over)
Reporting group description: Ipilimumab plus nivolumab without chemotherapy (cross-over from chemo-only)	
Subject analysis set title	Chemo-only per-protocol population
Subject analysis set type	Per protocol
Subject analysis set description: Patients evaluated for response and received the equivalent of ≥2 treatment cycles	
Subject analysis set title	Ipi/nivo plus chemotherapy per-protocol population
Subject analysis set type	Per protocol
Subject analysis set description: Patients evaluated for tumor response and received the equivalent of ≥ 2 treatment cycles	

Primary: Progression-free survival, per-protocol population

End point title	Progression-free survival, per-protocol population
End point description: PFS in the per-protocol population. PFS is, defined as the time from randomization to the occurrence of disease progression or death from any cause, whichever occurs first. Data for patients without disease progression or death will be censored at the last tumor assessment date. Data for patients with a PFS event who missed two or more assessments scheduled immediately prior to the date of the PFS event will be censored at the last tumor assessment prior to the missed visits. If no tumor assessment was performed after randomization, data will be censored at the date of randomization +1 day. Clinical deterioration without objective radiological evidence will not be considered as documented disease progression. Comparison between treatment arms will also be given by HR for disease progression or death using a Cox proportional hazards model.	
End point type	Primary
End point timeframe: Until data cut-off 20 JAN 2023	

End point values	Chemo-only per-protocol population	Ipi/nivo plus chemotherapy per-protocol population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	31	47		
Units: Months				
median (confidence interval 95%)	3.6 (1.8 to 9.0)	5.1 (3.4 to 6.5)		

Statistical analyses

Statistical analysis title	Cox proportional hazards model
Comparison groups	Ipi/nivo plus chemotherapy per-protocol population v Chemo-only per-protocol population
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Cox proportional hazard
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.59
upper limit	1.51

Secondary: Progression-free survival, full analysis set population

End point title	Progression-free survival, full analysis set population[1]

End point description:

PFS in the full analysis set population.
PFS is, defined as the time from randomization to the occurrence of disease progression or death from any cause, whichever occurs first. Data for patients without disease progression or death will be censored at the last tumor assessment date. Data for patients with a PFS event who missed two or more assessments scheduled immediately prior to the date of the PFS event will be censored at the last tumor assessment prior to the missed visits. If no tumor assessment was performed after randomization, data will be censored at the date of randomization +1 day. Clinical deterioration without objective radiological evidence will not be considered as documented disease progression. Comparison between treatment arms will also be given by HR for disease progression or death using a Cox proportional hazards model.

End point type	Secondary

End point timeframe:

Until data cut-off 20 JAN 2023

Notes:

[1] - 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: The arms are not mutually exclusive because of cross-over for a subset of patients (16/33) from the chemo-only arm to the separate ipi/nivo-only arm. Progression-free survival for the ipi/nivo-only cross-over arm is reported separately.

End point values	Chemotherapy-only	Ipi/nivo plus chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	49		
Units: Months				
median (confidence interval 95%)	3.6 (1.8 to 9.0)	5.1 (3.4 to 6.5)		

Statistical analyses

Statistical analysis title	Cox proportional hazards model
Comparison groups	Chemotherapy-only v Ipi/nivo plus chemotherapy

Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Cox proportional hazard
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.59
upper limit	1.51

Secondary: Overall survival, per-protocol population

End point title	Overall survival, per-protocol population

End point description:

Overall survival (OS) in the per-protocol population.
OS will be calculated from time of randomization until death. Patients alive at the time of data analysis will be treated as censored. OS will be estimated by the Kaplan Meier method.

End point type	Secondary

End point timeframe:

Until data cut-off 20 JAN 2023

End point values	Chemo-only per-protocol population	Ipi/nivo plus chemotherapy per-protocol population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	31	47		
Units: Months				
median (confidence interval 95%)	19.9 (13.8 to 28.7)	19.7 (12.5 to 24.9)		

Statistical analyses

Statistical analysis title	Cox proportional hazards model
Comparison groups	Chemo-only per-protocol population v Ipi/nivo plus chemotherapy per-protocol population
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Cox proportional hazard
Point estimate	1.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	1.67

Secondary: Overall survival, full analysis set population

End point title	Overall survival, full analysis set population[2]

End point description:

End point type	Secondary

End point timeframe:

Until data cut-off 20 JAN 2023.

Notes:

[2] - 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: The arms are not mutually exclusive because of cross-over for a subset of patients (16/33) from the chemo-only arm to the separate ipi/nivo-only arm. Overall survival for the ipi/nivo-only cross-over arm is reported separately.

End point values	Chemotherapy-only	Ipi/nivo plus chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	49		
Units: Months				
median (confidence interval 95%)	19.7 (13.8 to 28.7)	19.5 (10.4 to 24.8)		

Statistical analyses

Statistical analysis title	Cox proportional hazards model

Statistical analysis description:

Overall survival (OS) in the full analysis set population.
OS will be calculated from time of randomization until death. Patients alive at the time of data analysis will be treated as censored. OS will be estimated by the Kaplan Meier method.

Comparison groups	Chemotherapy-only v Ipi/nivo plus chemotherapy
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Cox proportional hazard
Point estimate	1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	1.71

Secondary: Objective tumor response rate, per-protocol population

End point title	Objective tumor response rate, per-protocol population

End point description:

The number of patients with an objective response (CR or PR) in the per-protocol population of each treatment arm assessed by RECIST v1.1.

End point type	Secondary

End point timeframe:

Until data cut-off 20 JAN 2023.

End point values	Chemo-only per-protocol population	Ipi/nivo plus chemotherapy per-protocol population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	31	47		
Units: Subjects				
Complete or partial response	9	15		
Non-response	22	32		

Statistical analyses

No statistical analyses for this end point

Secondary: Objective tumor response rate, full analysis set population

End point title	Objective tumor response rate, full analysis set population[3]

End point description:

The number of patients with an objective response (CR or PR) in the full analysis set population of each treatment arm assessed by RECIST v1.1.

End point type	Secondary

End point timeframe:

Until data cut-off 20 JAN 2023.

Notes:

[3] - 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: The arms are not mutually exclusive because of cross-over for a subset of patients (16/33) from the chemo-only arm to the separate ipi/nivo-only arm. Objective tumor response rate for the ipi/nivo-only cross-over arm is reported separately.

End point values	Chemotherapy-only	Ipi/nivo plus chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	49		
Units: Subjects				
Complete or partial response	9	15		
Non-response	24	34		

Statistical analyses

No statistical analyses for this end point

Secondary: Durable response rate, per-protocol population

End point title	Durable response rate, per-protocol population

End point description:

Durable response rate (DRR) in the per protocol population, defined as the proportion of patients with an objective tumor response lasting at least 6 months, according to RECIST v1.1.

End point type	Secondary

End point timeframe:

Until data cut-off 20 JAN 2023.

End point values	Chemo-only per-protocol population	Ipi/nivo plus chemotherapy per-protocol population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	31	47		
Units: Subjects				
Durable response	6	6		
Non-durable response	25	41		

Statistical analyses

No statistical analyses for this end point

Secondary: Durable response rate, full analysis set population

End point title	Durable response rate, full analysis set population[4]

End point description:

Durable response rate (DRR) in the full analysis set population, defined as the proportion of patients with an objective tumor response lasting at least 6 months, according to RECIST v1.1.

End point type	Secondary

End point timeframe:

Until data cut-off 20 JAN 2023.

Notes:

[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: The arms are not mutually exclusive because of cross-over for a subset of patients (16/33) from the chemo-only arm to the separate ipi/nivo-only arm. Durable response rate for the ipi/nivo-only cross-over arm is reported separately.

End point values	Chemotherapy-only	Ipi/nivo plus chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	49		
Units: Subjects				
Durable response	6	6		
Non-durable response	27	43		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical benefit rate, per-protocol population

End point title	Clinical benefit rate, per-protocol population

End point description:

Clinical benefit (CB) is defined as the proportion of patients in the analyzed population with best overall response "PR" or "CR", or with stable disease (SD) lasting at least until the 6 month evaluation (performed at week 24 +/- 10 days). This means that patients where PD was first recorded at the 6 month evaluation will be considered to have clinical benefit.

End point type	Secondary

End point timeframe:

Until data cut-off 20 JAN 2023.

End point values	Chemo-only per-protocol population	Ipi/nivo plus chemotherapy per-protocol population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	31	47		
Units: Subjects				
CB	15	26		
Non-CB	16	21		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical benefit rate, full analysis set population

End point title	Clinical benefit rate, full analysis set population[5]

End point description:

Clinical benefit (CB) is defined as the proportion of patients in the analyzed population with best overall response "PR" or "CR", or with stable disease (SD) lasting at least until the 6 month evaluation (performed at week 24 +/- 10 days). This means that patients where PD was first recorded at the 6 month evaluation will be considered to have clinical benefit.

End point type	Secondary

End point timeframe:

Until data cut-off 20 JAN 2023.

Notes:

[5] - 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: The arms are not mutually exclusive because of cross-over for a subset of patients (16/33) from the chemo-only arm to the separate ipi/nivo-only arm. Clinical benefit rate for the ipi/nivo-only cross-over arm is reported separately.

End point values	Chemotherapy-only	Ipi/nivo plus chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	49		
Units: Subjects				
CB	15	26		
Non-CB	18	23		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response, per-protocol population

End point title	Duration of response, per-protocol population

End point description:

Duration of response is defined as the interval from response was first documented (CR or PR) to either progression of disease or death from any cause, whichever comes first.

End point type	Secondary

End point timeframe:

Until data cut-off 20 JAN 2023.

End point values	Chemo-only per-protocol population	Ipi/nivo plus chemotherapy per-protocol population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	31	47		
Units: Months				
median (inter-quartile range (Q1-Q3))	7.4 (3.7 to 11.3)	5.5 (2.8 to 10.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response, full analysis set population

End point title	Duration of response, full analysis set population[6]

End point description:

Duration of response is defined as the interval from response was first documented (CR or PR) to either progression of disease or death from any cause, whichever comes first.

End point type	Secondary

End point timeframe:

Until data cut-off 20 JAN 2023.

Notes:

[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: The arms are not mutually exclusive because of cross-over for a subset of patients (16/33) from the chemo-only arm to the separate ipi/nivo-only arm. Duration of response for the ipi/nivo-only cross-over arm is reported separately.

End point values	Chemotherapy-only	Ipi/nivo plus chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	49		
Units: Months				
median (inter-quartile range (Q1-Q3))	7.4 (3.7 to 11.3)	5.5 (2.8 to 10.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival, ipi/nivo-only (cross-over)

End point title	Progression-free survival, ipi/nivo-only (cross-over)[7]

End point description:

PFS in the cross-over arm is, defined as the time from "Day 1/Cycle 1" to the occurrence of disease progression or death from any cause, whichever occurs first. Data for patients without disease progression or death will be censored at the last tumor assessment date. Data for patients with a PFS event who missed two or more assessments scheduled immediately prior to the date of the PFS event will be censored at the last tumor assessment prior to the missed visits. If no tumor assessment was performed after start of therapy, data will be censored at the "Day 1/Cycle 1" date +1 day. Clinical deterioration without objective radiological evidence will not be considered as documented disease progression.

End point type	Secondary

End point timeframe:

Until data cut-off 20 JAN 2023

Notes:

[7] - 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: The arms are not mutually exclusive because of cross-over for a subset of patients (16/33) from the chemo-only arm to the separate ipi/nivo-only arm. Progression-free survival for the ipi/nivo-chemo and chemo-only arms in the main trial is reported separately.

End point values	Ipi/nivo-only (cross-over)			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: Months				
median (inter-quartile range (Q1-Q3))	1.9 (1.6 to 5.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival, ipi/nivo-only (cross-over)

End point title	Overall survival, ipi/nivo-only (cross-over)[8]

End point description:

Overall survival (OS) will be calculated from time of "Day 1/Cycle 1"until death. Patients alive at the time of data analysis will be treated as censored.

End point type	Secondary

End point timeframe:

Until data cut-off 20 JAN 2023

Notes:

[8] - 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: The arms are not mutually exclusive because of cross-over for a subset of patients (16/33) from the chemo-only arm to the separate ipi/nivo-only arm. Overall survival for the ipi/nivo-chemo and chemo-only arms in the main trial is reported separately.

End point values	Ipi/nivo-only (cross-over)			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: Months				
median (inter-quartile range (Q1-Q3))	22.9 (16.5 to 28.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Objective tumor response rate, ipi/nivo-only (cross-over)

End point title	Objective tumor response rate, ipi/nivo-only (cross-over)[9]

End point description:

The number of patients with an objective response (CR or PR) assessed by RECIST v1.1.

End point type	Secondary

End point timeframe:

Until data cut-off 20 JAN 2023

Notes:

[9] - 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: The arms are not mutually exclusive because of cross-over for a subset of patients (16/33) from the chemo-only arm to the separate ipi/nivo-only arm. Objective tumor response rate for the ipi/nivo-chemo and chemo-only arms in the main trial is reported separately.

End point values	Ipi/nivo-only (cross-over)			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: Subjects				
Complete or partial response	3			
Non-response	13			

Statistical analyses

No statistical analyses for this end point

Secondary: Durable response rate, ipi/nivo-only (cross-over)

End point title	Durable response rate, ipi/nivo-only (cross-over)[10]

End point description:

Durable response rate, defined as the proportion of patients with an objective tumor response lasting at least 6 months, according to RECIST v1.1.

End point type	Secondary

End point timeframe:

Until data cut-off 20 JAN 2023.

Notes:

[10] - 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: The arms are not mutually exclusive because of cross-over for a subset of patients (16/33) from the chemo-only arm to the separate ipi/nivo-only arm. Durable response rate for the ipi/nivo-chemo and chemo-only arms in the main trial is reported separately.

End point values	Ipi/nivo-only (cross-over)			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: Subjects				
Durable response	2			
No durable response	14			

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical benefit rate, ipi/nivo-only (cross-over)

End point title	Clinical benefit rate, ipi/nivo-only (cross-over)[11]

End point description:

Clinical benefit (CB) is defined as the proportion of patients in the analyzed population with best overall response "PR" or "CR", or with stable disease (SD) lasting at least until the 6 month evaluation (performed at week 24 +/- 10 days). This means that patients where PD was first recorded at the 6 month evaluation will be considered to have clinical benefit.

End point type	Secondary

End point timeframe:

Until data cut-off 20 JAN 2023

Notes:

[11] - 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: The arms are not mutually exclusive because of cross-over for a subset of patients (16/33) from the chemo-only arm to the separate ipi/nivo-only arm. Clinical benefit rate for the ipi/nivo-chemo and chemo-only arms in the main trial is reported separately.

End point values	Ipi/nivo-only (cross-over)			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: Subjects				
Clinical benefit	4			
No clinical benefit	12			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response, ipi/nivo-only (cross-over)

End point title	Duration of response, ipi/nivo-only (cross-over)[12]

End point description:

Duration of response is defined as the interval from response was first documented (CR or PR) to either progression of disease or death from any cause, whichever comes first.

End point type	Secondary

End point timeframe:

Until data cut-off 20 JAN 2023.

Notes:

[12] - 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: The arms are not mutually exclusive because of cross-over for a subset of patients (16/33) from the chemo-only arm to the separate ipi/nivo-only arm. Duration of response for the ipi/nivo-chemo and chemo-only arms in the main trial is reported separately.

End point values	Ipi/nivo-only (cross-over)			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: Months				
median (inter-quartile range (Q1-Q3))	7.0 (3.7 to 10.8)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From 21 FEB 2018 until data cut-off 20 JAN 2023.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups	
Reporting group title	Chemotherapy-only
Reporting group description: -	
Reporting group title	Ipi/nivo plus chemotherapy
Reporting group description: -	
Reporting group title	Ipi/nivo-only (cross-over)
Reporting group description: -	

Serious adverse events	Chemotherapy-only	Ipi/nivo plus chemotherapy	Ipi/nivo-only (cross-over)
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 33 (39.39%)	31 / 49 (63.27%)	5 / 16 (31.25%)
number of deaths (all causes)	28	39	12
number of deaths resulting from adverse events	0	2	0
General disorders and administration site conditions			
Death			
subjects affected / exposed	0 / 33 (0.00%)	1 / 49 (2.04%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pyrexia			
subjects affected / exposed	2 / 33 (6.06%)	6 / 49 (12.24%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 2	5 / 7	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 33 (0.00%)	1 / 49 (2.04%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			

Dyspnea			
subjects affected / exposed	0 / 33 (0.00%)	1 / 49 (2.04%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 33 (0.00%)	2 / 49 (4.08%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 33 (0.00%)	1 / 49 (2.04%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Delirium			
subjects affected / exposed	0 / 33 (0.00%)	0 / 49 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fracture			
subjects affected / exposed	0 / 33 (0.00%)	2 / 49 (4.08%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infusion related reaction			
subjects affected / exposed	2 / 33 (6.06%)	1 / 49 (2.04%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	2 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haemorrhage			
subjects affected / exposed	1 / 33 (3.03%)	2 / 49 (4.08%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procedural pain			
subjects affected / exposed	1 / 33 (3.03%)	1 / 49 (2.04%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Procedural pneumothorax			
subjects affected / exposed	0 / 33 (0.00%)	1 / 49 (2.04%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Conduction disorder			
subjects affected / exposed	1 / 33 (3.03%)	0 / 49 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	1 / 33 (3.03%)	0 / 49 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Neuropathy peripheral			
subjects affected / exposed	0 / 33 (0.00%)	2 / 49 (4.08%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peroneal nerve palsy			
subjects affected / exposed	0 / 33 (0.00%)	1 / 49 (2.04%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression			
subjects affected / exposed	0 / 33 (0.00%)	1 / 49 (2.04%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	1 / 33 (3.03%)	0 / 49 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile neutropenia			

subjects affected / exposed	1 / 33 (3.03%)	2 / 49 (4.08%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	1 / 1	2 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 33 (0.00%)	1 / 49 (2.04%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	0 / 33 (0.00%)	1 / 49 (2.04%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 33 (0.00%)	2 / 49 (4.08%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 33 (0.00%)	1 / 49 (2.04%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 33 (0.00%)	1 / 49 (2.04%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 33 (0.00%)	1 / 49 (2.04%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatitis			
subjects affected / exposed	0 / 33 (0.00%)	3 / 49 (6.12%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	3 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			

Rash			
subjects affected / exposed	0 / 33 (0.00%)	1 / 49 (2.04%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Nephritis			
subjects affected / exposed	0 / 33 (0.00%)	1 / 49 (2.04%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 33 (0.00%)	1 / 49 (2.04%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypophysitis			
subjects affected / exposed	0 / 33 (0.00%)	2 / 49 (4.08%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Secondary adrenocortical insufficiency			
subjects affected / exposed	0 / 33 (0.00%)	3 / 49 (6.12%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thyroiditis			
subjects affected / exposed	0 / 33 (0.00%)	1 / 49 (2.04%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 33 (0.00%)	1 / 49 (2.04%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			

subjects affected / exposed	0 / 33 (0.00%)	1 / 49 (2.04%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bacterial infection			
subjects affected / exposed	0 / 33 (0.00%)	1 / 49 (2.04%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			
subjects affected / exposed	0 / 33 (0.00%)	1 / 49 (2.04%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	0 / 33 (0.00%)	1 / 49 (2.04%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	0 / 33 (0.00%)	6 / 49 (12.24%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	2 / 33 (6.06%)	1 / 49 (2.04%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	2 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 33 (3.03%)	3 / 49 (6.12%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 33 (0.00%)	1 / 49 (2.04%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			

subjects affected / exposed	0 / 33 (0.00%)	0 / 49 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Type 1 diabetes mellitus			
subjects affected / exposed	0 / 33 (0.00%)	2 / 49 (4.08%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 4 %

Non-serious adverse events	Chemotherapy-only	Ipi/nivo plus chemotherapy	Ipi/nivo-only (cross-over)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	33 / 33 (100.00%)	49 / 49 (100.00%)	15 / 16 (93.75%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	1 / 33 (3.03%)	0 / 49 (0.00%)	1 / 16 (6.25%)
occurrences (all)	2	0	1
Vascular disorders			
Flushing			
subjects affected / exposed	1 / 33 (3.03%)	2 / 49 (4.08%)	0 / 16 (0.00%)
occurrences (all)	1	2	0
Hypertension			
subjects affected / exposed	0 / 33 (0.00%)	2 / 49 (4.08%)	0 / 16 (0.00%)
occurrences (all)	0	2	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	16 / 33 (48.48%)	27 / 49 (55.10%)	6 / 16 (37.50%)
occurrences (all)	21	28	6
Influenza like illness			
subjects affected / exposed	1 / 33 (3.03%)	2 / 49 (4.08%)	1 / 16 (6.25%)
occurrences (all)	1	2	1
Oedema			
subjects affected / exposed	2 / 33 (6.06%)	4 / 49 (8.16%)	0 / 16 (0.00%)
occurrences (all)	2	4	0
Pyrexia			

subjects affected / exposed	0 / 33 (0.00%)	2 / 49 (4.08%)	3 / 16 (18.75%)
occurrences (all)	0	2	3
Immune system disorders			
Immunisation reaction			
subjects affected / exposed	0 / 33 (0.00%)	0 / 49 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Mycotic allergy			
subjects affected / exposed	0 / 33 (0.00%)	0 / 49 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			
Vulvovaginal discomfort			
subjects affected / exposed	1 / 33 (3.03%)	2 / 49 (4.08%)	0 / 16 (0.00%)
occurrences (all)	1	3	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 33 (9.09%)	4 / 49 (8.16%)	1 / 16 (6.25%)
occurrences (all)	3	4	1
Dyspnoea			
subjects affected / exposed	0 / 33 (0.00%)	3 / 49 (6.12%)	0 / 16 (0.00%)
occurrences (all)	0	3	0
Oropharyngeal pain			
subjects affected / exposed	2 / 33 (6.06%)	0 / 49 (0.00%)	0 / 16 (0.00%)
occurrences (all)	2	0	0
Pleural effusion			
subjects affected / exposed	0 / 33 (0.00%)	2 / 49 (4.08%)	0 / 16 (0.00%)
occurrences (all)	0	5	0
Pneumonitis			
subjects affected / exposed	0 / 33 (0.00%)	3 / 49 (6.12%)	1 / 16 (6.25%)
occurrences (all)	0	3	1
Rhinitis			
subjects affected / exposed	3 / 33 (9.09%)	0 / 49 (0.00%)	1 / 16 (6.25%)
occurrences (all)	3	0	1
Psychiatric disorders			
Depression			
subjects affected / exposed	3 / 33 (9.09%)	0 / 49 (0.00%)	0 / 16 (0.00%)
occurrences (all)	4	0	0

Insomnia			
subjects affected / exposed	1 / 33 (3.03%)	7 / 49 (14.29%)	1 / 16 (6.25%)
occurrences (all)	1	7	1
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 33 (0.00%)	2 / 49 (4.08%)	2 / 16 (12.50%)
occurrences (all)	0	2	2
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 33 (0.00%)	1 / 49 (2.04%)	1 / 16 (6.25%)
occurrences (all)	0	1	1
Ejection fraction decreased			
subjects affected / exposed	2 / 33 (6.06%)	3 / 49 (6.12%)	0 / 16 (0.00%)
occurrences (all)	2	4	0
Haemoglobin decreased			
subjects affected / exposed	5 / 33 (15.15%)	4 / 49 (8.16%)	0 / 16 (0.00%)
occurrences (all)	9	5	0
Lipase increased			
subjects affected / exposed	0 / 33 (0.00%)	2 / 49 (4.08%)	0 / 16 (0.00%)
occurrences (all)	0	2	0
Lymphocyte count decreased			
subjects affected / exposed	15 / 33 (45.45%)	32 / 49 (65.31%)	0 / 16 (0.00%)
occurrences (all)	23	35	0
Neutrophil count decreased			
subjects affected / exposed	10 / 33 (30.30%)	11 / 49 (22.45%)	1 / 16 (6.25%)
occurrences (all)	29	20	1
Platelet count decreased			
subjects affected / exposed	0 / 33 (0.00%)	4 / 49 (8.16%)	0 / 16 (0.00%)
occurrences (all)	0	4	0
Weight decreased			
subjects affected / exposed	1 / 33 (3.03%)	2 / 49 (4.08%)	1 / 16 (6.25%)
occurrences (all)	1	2	1
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	2 / 33 (6.06%)	3 / 49 (6.12%)	0 / 16 (0.00%)
occurrences (all)	3	4	0
Procedural pain			

subjects affected / exposed	1 / 33 (3.03%)	1 / 49 (2.04%)	1 / 16 (6.25%)
occurrences (all)	1	1	1
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	0 / 33 (0.00%)	2 / 49 (4.08%)	0 / 16 (0.00%)
occurrences (all)	0	3	0
Headache			
subjects affected / exposed	4 / 33 (12.12%)	3 / 49 (6.12%)	0 / 16 (0.00%)
occurrences (all)	4	3	0
Neuropathy peripheral			
subjects affected / exposed	6 / 33 (18.18%)	3 / 49 (6.12%)	0 / 16 (0.00%)
occurrences (all)	6	3	0
Urinary incontinence			
subjects affected / exposed	0 / 33 (0.00%)	2 / 49 (4.08%)	0 / 16 (0.00%)
occurrences (all)	0	2	0
Ear and labyrinth disorders			
Ear discomfort			
subjects affected / exposed	1 / 33 (3.03%)	3 / 49 (6.12%)	0 / 16 (0.00%)
occurrences (all)	1	3	0
Tinnitus			
subjects affected / exposed	1 / 33 (3.03%)	0 / 49 (0.00%)	1 / 16 (6.25%)
occurrences (all)	1	0	1
Vertigo			
subjects affected / exposed	2 / 33 (6.06%)	8 / 49 (16.33%)	1 / 16 (6.25%)
occurrences (all)	2	9	1
Eye disorders			
Conjunctivitis			
subjects affected / exposed	2 / 33 (6.06%)	2 / 49 (4.08%)	1 / 16 (6.25%)
occurrences (all)	2	2	1
Periorbital oedema			
subjects affected / exposed	0 / 33 (0.00%)	2 / 49 (4.08%)	0 / 16 (0.00%)
occurrences (all)	0	2	0
Visual impairment			
subjects affected / exposed	3 / 33 (9.09%)	0 / 49 (0.00%)	0 / 16 (0.00%)
occurrences (all)	3	0	0
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	7 / 33 (21.21%)	8 / 49 (16.33%)	1 / 16 (6.25%)
occurrences (all)	10	10	1
Colitis			
subjects affected / exposed	0 / 33 (0.00%)	0 / 49 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Constipation			
subjects affected / exposed	18 / 33 (54.55%)	16 / 49 (32.65%)	0 / 16 (0.00%)
occurrences (all)	20	21	0
Diarrhoea			
subjects affected / exposed	1 / 33 (3.03%)	13 / 49 (26.53%)	3 / 16 (18.75%)
occurrences (all)	1	14	6
Dysphagia			
subjects affected / exposed	3 / 33 (9.09%)	1 / 49 (2.04%)	0 / 16 (0.00%)
occurrences (all)	3	1	0
Gastrooesophageal reflux disease			
subjects affected / exposed	3 / 33 (9.09%)	7 / 49 (14.29%)	0 / 16 (0.00%)
occurrences (all)	3	10	0
Haemorrhoids			
subjects affected / exposed	0 / 33 (0.00%)	2 / 49 (4.08%)	0 / 16 (0.00%)
occurrences (all)	0	2	0
Nausea			
subjects affected / exposed	16 / 33 (48.48%)	25 / 49 (51.02%)	2 / 16 (12.50%)
occurrences (all)	20	29	2
Stomatitis			
subjects affected / exposed	12 / 33 (36.36%)	20 / 49 (40.82%)	2 / 16 (12.50%)
occurrences (all)	18	35	3
Toothache			
subjects affected / exposed	2 / 33 (6.06%)	0 / 49 (0.00%)	0 / 16 (0.00%)
occurrences (all)	2	0	0
Vomiting			
subjects affected / exposed	1 / 33 (3.03%)	3 / 49 (6.12%)	0 / 16 (0.00%)
occurrences (all)	2	3	0
Hepatobiliary disorders			
Hepatitis			

subjects affected / exposed	0 / 33 (0.00%)	0 / 49 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Hepatocellular injury			
subjects affected / exposed	1 / 33 (3.03%)	1 / 49 (2.04%)	0 / 16 (0.00%)
occurrences (all)	1	2	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	4 / 33 (12.12%)	8 / 49 (16.33%)	0 / 16 (0.00%)
occurrences (all)	4	8	0
Nail disorder			
subjects affected / exposed	1 / 33 (3.03%)	2 / 49 (4.08%)	0 / 16 (0.00%)
occurrences (all)	1	3	0
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	10 / 33 (30.30%)	16 / 49 (32.65%)	0 / 16 (0.00%)
occurrences (all)	11	16	0
Pruritus			
subjects affected / exposed	2 / 33 (6.06%)	3 / 49 (6.12%)	5 / 16 (31.25%)
occurrences (all)	2	3	5
Rash			
subjects affected / exposed	13 / 33 (39.39%)	28 / 49 (57.14%)	6 / 16 (37.50%)
occurrences (all)	17	33	7
Skin fissures			
subjects affected / exposed	3 / 33 (9.09%)	1 / 49 (2.04%)	0 / 16 (0.00%)
occurrences (all)	4	2	0
Xeroderma			
subjects affected / exposed	2 / 33 (6.06%)	1 / 49 (2.04%)	2 / 16 (12.50%)
occurrences (all)	2	1	2
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 33 (0.00%)	4 / 49 (8.16%)	0 / 16 (0.00%)
occurrences (all)	0	5	0
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 33 (0.00%)	10 / 49 (20.41%)	1 / 16 (6.25%)
occurrences (all)	0	10	1
Hypophysitis			

subjects affected / exposed	0 / 33 (0.00%)	0 / 49 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Hypothyroidism			
subjects affected / exposed	1 / 33 (3.03%)	23 / 49 (46.94%)	2 / 16 (12.50%)
occurrences (all)	1	23	2
Secondary adrenocortical insufficiency			
subjects affected / exposed	0 / 33 (0.00%)	0 / 49 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	1 / 33 (3.03%)	2 / 49 (4.08%)	0 / 16 (0.00%)
occurrences (all)	1	2	0
Back pain			
subjects affected / exposed	3 / 33 (9.09%)	1 / 49 (2.04%)	0 / 16 (0.00%)
occurrences (all)	3	1	0
Muscle spasms			
subjects affected / exposed	1 / 33 (3.03%)	3 / 49 (6.12%)	0 / 16 (0.00%)
occurrences (all)	1	3	0
Musculoskeletal pain			
subjects affected / exposed	2 / 33 (6.06%)	11 / 49 (22.45%)	5 / 16 (31.25%)
occurrences (all)	5	14	6
Neck pain			
subjects affected / exposed	2 / 33 (6.06%)	0 / 49 (0.00%)	0 / 16 (0.00%)
occurrences (all)	2	0	0
Pain in extremity			
subjects affected / exposed	1 / 33 (3.03%)	0 / 49 (0.00%)	2 / 16 (12.50%)
occurrences (all)	1	0	2
Infections and infestations			
Epstein-Barr virus infection			
subjects affected / exposed	0 / 33 (0.00%)	0 / 49 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Lung infection			
subjects affected / exposed	0 / 33 (0.00%)	3 / 49 (6.12%)	0 / 16 (0.00%)
occurrences (all)	0	3	0
Oral candidiasis			

subjects affected / exposed	0 / 33 (0.00%)	3 / 49 (6.12%)	0 / 16 (0.00%)
occurrences (all)	0	5	0
Skin infection			
subjects affected / exposed	3 / 33 (9.09%)	5 / 49 (10.20%)	0 / 16 (0.00%)
occurrences (all)	3	8	0
Tooth infection			
subjects affected / exposed	2 / 33 (6.06%)	3 / 49 (6.12%)	0 / 16 (0.00%)
occurrences (all)	2	3	0
Upper respiratory tract infection			
subjects affected / exposed	6 / 33 (18.18%)	7 / 49 (14.29%)	1 / 16 (6.25%)
occurrences (all)	8	8	1
Urinary tract infection			
subjects affected / exposed	2 / 33 (6.06%)	10 / 49 (20.41%)	0 / 16 (0.00%)
occurrences (all)	3	16	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 33 (9.09%)	4 / 49 (8.16%)	1 / 16 (6.25%)
occurrences (all)	3	4	1
Hyperglycaemia			
subjects affected / exposed	3 / 33 (9.09%)	2 / 49 (4.08%)	0 / 16 (0.00%)
occurrences (all)	3	2	0
Hypokalaemia			
subjects affected / exposed	0 / 33 (0.00%)	4 / 49 (8.16%)	0 / 16 (0.00%)
occurrences (all)	0	4	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 December 2019	Adjustment of inclusion and excusion criteria. Adjustment of the per-protocol population criteria including specification of the full analysis set population. Specification of planned statistical analyses.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/38242720