



Clinical trial results: PHASE I - II STUDY OF INTRATUMORAL URELUMAB COMBINED WITH NIVOLUMAB IN PATIENTS WITH SOLID TUMORS

Summary

EudraCT number	2017-005106-35
Trial protocol	ES
Global end of trial date	13 January 2022

Results information

Result version number	v1 (current)
This version publication date	13 January 2023
First version publication date	13 January 2023

Trial information

Trial identification

Sponsor protocol code	INTRUST
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03792724
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Clínica Universidad de Navarra (CUN)
Sponsor organisation address	Avenida Pio XII, 36, Pamplona, Spain, 31008
Public contact	UCEC, Clinica Universidad de Navarra, 34 9482554002725, ucicec@unav.es
Scientific contact	UCEC, Clinica Universidad de Navarra, 34 9482554002725, ucicec@unav.es

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	07 July 2022
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	13 January 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- Phase I: to assess the safety and to establish the recommended dose of the combination of intratumoral urelumab administered in combination with systemic nivolumab in patients with advanced solid tumors. Three doses of intratumoral urelumab will be assessed, in combination with systemic nivolumab at standard doses.

- Phase II: to determine the objective response rate of the recommended schedule determined by RECIST and immune response criteria.

Protection of trial subjects:

Study treatment had to be discontinued upon confirmed radiological progression or clinical progression.

Background therapy:

Supportive care for disease-related symptoms was offered to all subjects on the trial.

Use of limited field palliative radiotherapy was allowed at any time during the study except on days where study drugs were administered, as well as one day before or after treatment administration.

Evidence for comparator: -

Actual start date of recruitment	09 April 2019
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	Spain: 40
Worldwide total number of subjects	40
EEA total number of subjects	40

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)	26
From 65 to 84 years	14
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The inclusion of the first patient was on 09/April/2019. The end of recruitment was on 01/February/2021.

Pre-assignment

Screening details:

Screening period: within 30 days after informed consent, patients were evaluated for study eligibility. Participants were tested to determine if they met all the inclusion criteria and none of the exclusion criteria.

40 patients were enrolled in the study, but 9 of them were screening failures and did not receive the study treatment.

Pre-assignment period milestones

Number of subjects started	40
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Number of subjects completed	31
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Pre-assignment subject non-completion reasons

Reason: Number of subjects	Physician decision: 9
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Period 1

Period 1 title	Overall trial (overall period)
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Is this the baseline period?	Yes
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Allocation method	Not applicable
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Blinding used	Not blinded
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Blinding implementation details:

Masking procedures do not apply to this study since it is an open-label clinical trial.

Arms

Are arms mutually exclusive?	Yes
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Arm title	Phase I: Urelumab 1 mg + Nivolumab
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Arm description:

Participants received 1 mg intratumoral Urelumab + intravenous Nivolumab.

Urelumab: three doses of intratumoral urelumab every 4 weeks (Cycle 1, Cycle 3, Cycle 5).

Nivolumab: starting 2 weeks after the first dose of intratumoral urelumab (240 mg for Cycle 2 and at a fixed dose of 480 mg every 4 weeks from Cycle 4 and beyond).

Arm type	Experimental
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Investigational medicinal product name	Urelumab
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Investigational medicinal product code	
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Other name	BMS-663513-01
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Pharmaceutical forms	Concentrate for solution for injection
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Routes of administration	Solution for injection
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Dosage and administration details:

Participants received three doses of intratumoral urelumab every 4 weeks (Cycle 1, Cycle 3, Cycle 5).

Investigational medicinal product name	Nivolumab
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Investigational medicinal product code	
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Other name	BMS-936558-01
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Pharmaceutical forms	Concentrate for solution for infusion
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Routes of administration	Infusion
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Dosage and administration details:

Nivolumab was administered starting 2 weeks after the first dose of intratumoral urelumab as an intravenous infusion at a fixed dose of 240 mg (Cycle 2) and at a fixed dose of 480 mg for Cycle 4 and beyond every 4 weeks. A maximum duration of nivolumab therapy of 18-24 months was suggested.

Arm title	Phase II: Urelumab 8 mg + Nivolumab
Arm description:	
Participants received 8 mg intratumoral Urelumab + intravenous Nivolumab. Urelumab: three doses of intratumoral urelumab every 4 weeks (Cycle 1, Cycle 3, Cycle 5). Nivolumab: starting 2 weeks after the first dose of intratumoral urelumab (240 mg for Cycle 2 and at a fixed dose of 480 mg every 4 weeks from Cycle 4 and beyond).	
Arm type	Experimental
Investigational medicinal product name	Urelumab
Investigational medicinal product code	
Other name	BMS-663513-01
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Solution for injection

Dosage and administration details:

Subjects received three doses of intratumoral urelumab 8 mg every 4 weeks (Cycle 1, Cycle 3, Cycle 5).

Investigational medicinal product name	Nivolumab
Investigational medicinal product code	
Other name	BMS-663513
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Nivolumab was administered starting 2 weeks after the first dose of intratumoral urelumab as an intravenous infusion at a fixed dose of 240 mg for Cycle 2 and at a fixed dose of 480 mg every 4 weeks from Cycle 4 and beyond. A maximum duration of nivolumab therapy of 18-24 months was suggested.

Number of subjects in period 1 ^[1]	Phase I: Urelumab 1 mg + Nivolumab	Phase II: Urelumab 8 mg + Nivolumab
Started	3	28
Completed	0	14
Not completed	3	14
Patient could not come in 4 weeks	-	1
Consent withdrawn by subject	-	1
Will continue treatment in other hospital	-	1
Death	-	6
Progression	1	2
Cannot travel to the site	-	1
Lost to follow-up	2	2

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 40 patients were enrolled in the study, but 9 of them were screening failures and did not receive the study treatment.

Baseline characteristics

Reporting groups

Reporting group title	Phase I: Urelumab 1 mg + Nivolumab
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Reporting group description:

Participants received 1 mg intratumoral Urelumab + intravenous Nivolumab.

Urelumab: three doses of intratumoral urelumab every 4 weeks (Cycle 1, Cycle 3, Cycle 5).

Nivolumab: starting 2 weeks after the first dose of intratumoral urelumab (240 mg for Cycle 2 and at a fixed dose of 480 mg every 4 weeks from Cycle 4 and beyond).

Reporting group title	Phase II: Urelumab 8 mg + Nivolumab
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Reporting group description:

Participants received 8 mg intratumoral Urelumab + intravenous Nivolumab.

Urelumab: three doses of intratumoral urelumab every 4 weeks (Cycle 1, Cycle 3, Cycle 5).

Nivolumab: starting 2 weeks after the first dose of intratumoral urelumab (240 mg for Cycle 2 and at a fixed dose of 480 mg every 4 weeks from Cycle 4 and beyond).

Reporting group values	Phase I: Urelumab 1 mg + Nivolumab	Phase II: Urelumab 8 mg + Nivolumab	Total
Number of subjects	3	28	31
Age categorical			
Age was computed considering the difference in years between the date of birth and the date of the signature of the informed consent form.			
Units: Subjects			
Adults (18-64 years)	1	19	20
From 65-84 years	2	9	11
Age continuous			
Age was computed considering the difference in years between the date of birth and the date of the signature of the informed consent form.			
Units: years			
arithmetic mean	65.67	60.75	
standard deviation	± 12.86	± 10.92	-
Gender categorical			
Units: Subjects			
Female	3	11	14
Male	0	17	17

Subject analysis sets

Subject analysis set title	Phase II: Cohort A
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Subject analysis set type	Per protocol
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Subject analysis set description:

Recruited anti PD1/PDL1 naïve patients presenting tumor types sensitive to PD1/PDL1 blockade. These patients had to be naïve to PD1/PDL1 blockade.

Subject analysis set title	Phase II: Cohort B
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Subject analysis set type	Per protocol
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Subject analysis set description:

Included patients with PD1/PDL1 sensitive tumors that have progressed on previous PD1/ PDL1 blockade.

Reporting group values	Phase II: Cohort A	Phase II: Cohort B	
Number of subjects	20	8	
Age categorical			
Age was computed considering the difference in years between the date of birth and the date of the signature of the informed consent form.			
Units: Subjects			
Adults (18-64 years)	15	4	
From 65-84 years	5	4	
Age continuous			
Age was computed considering the difference in years between the date of birth and the date of the signature of the informed consent form.			
Units: years			
arithmetic mean	58.95	65.25	
standard deviation	± 10.87	± 10.31	
Gender categorical			
Units: Subjects			
Female	8	3	
Male	12	5	

End points

End points reporting groups

Reporting group title	Phase I: Urelumab 1 mg + Nivolumab
Reporting group description: Participants received 1 mg intratumoral Urelumab + intravenous Nivolumab. Urelumab: three doses of intratumoral urelumab every 4 weeks (Cycle 1, Cycle 3, Cycle 5). Nivolumab: starting 2 weeks after the first dose of intratumoral urelumab (240 mg for Cycle 2 and at a fixed dose of 480 mg every 4 weeks from Cycle 4 and beyond).	
Reporting group title	Phase II: Urelumab 8 mg + Nivolumab
Reporting group description: Participants received 8 mg intratumoral Urelumab + intravenous Nivolumab. Urelumab: three doses of intratumoral urelumab every 4 weeks (Cycle 1, Cycle 3, Cycle 5). Nivolumab: starting 2 weeks after the first dose of intratumoral urelumab (240 mg for Cycle 2 and at a fixed dose of 480 mg every 4 weeks from Cycle 4 and beyond).	
Subject analysis set title	Phase II: Cohort A
Subject analysis set type	Per protocol
Subject analysis set description: Recruited anti PD1/PDL1 naïve patients presenting tumor types sensitive to PD1/PDL1 blockade. These patients had to be naïve to PD1/PDL1 blockade.	
Subject analysis set title	Phase II: Cohort B
Subject analysis set type	Per protocol
Subject analysis set description: Included patients with PD1/PDL1 sensitive tumors that have progressed on previous PD1/ PDL1 blockade.	

Primary: Best overall response (BOR)

End point title	Best overall response (BOR) ^[1]
End point description: Best overall response: overall, 3.57% of patients had Partial response, 28.57% Stable disease, 42.86% Pogression and 7.14% Stable disease + progression.	
End point type	Primary
End point timeframe: End of treatment	

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: The analyses performed are descriptive and therefore no statistical analysis can be applied.

End point values	Phase I: Urelumab 1 mg + Nivolumab	Phase II: Urelumab 8 mg + Nivolumab		
	Reporting group	Reporting group		
Subject group type				
Number of subjects analysed	3	25 ^[2]		
Units: Number of patients				
Complete response (CR)	0	0		
Partial response (PR)	1	1		
Stable disease (SD)	1	8		
Progression (PD)	1	12		
Stable disease + progression	0	2		

Notes:

[2] - There are 5 patients without available data

Statistical analyses

No statistical analyses for this end point

Primary: Objective response rate (ORR)

End point title | Objective response rate (ORR)^[3]

End point description:

ORR is defined as the proportion of all treated subjects whose best overall response (BOR) is complete response or partial response.

End point type | Primary

End point timeframe:

End of the treatment

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: The analyses performed are descriptive and therefore no statistical analysis can be applied.

End point values	Phase I: Urelumab 1 mg + Nivolumab	Phase II: Urelumab 8 mg + Nivolumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	28		
Units: Number of patients	1	1		

Statistical analyses

No statistical analyses for this end point

Primary: Dose Limiting toxicities (DLT)

End point title | Dose Limiting toxicities (DLT)^{[4][5]}

End point description:

There were two dose levels for intratumoral urelumab: 1 mg and 8 mg. As no DLTs were observed in the intratumoral urelumab 1 mg level, the dose of intratumoral urelumab was escalated to 8 mg. In addition, as no DLT were observed in the intratumoral urelumab 8 mg level recruitment, in the phase II part continued at that dose until the study was completed.

End point type | Primary

End point timeframe:

The observation period for DTL lasted 6 weeks for each dose level (2 doses of intratumoral urelumab + 2 doses of systemic nivolumab, i.e: it ended before the third dose of urelumab).

Notes:

[4] - 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: The analyses performed are descriptive and therefore no statistical analysis can be applied.

[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: Dose Limiting Toxicities (DLT) were evaluated only in Phase I. There were no DLT in the present study.

End point values	Phase I: Urelumab 1 mg + Nivolumab			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: Dose Limiting Toxicities	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response (DOR)

End point title	Duration of response (DOR)
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End point description:

DOR is defined as time (in weeks) between the date of first radiographic documented objective response and the date of the radiographic disease progression.

End point type	Secondary
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End point timeframe:

Between the date of first radiographic documented objective response and the date of the radiographic disease progression.

End point values	Phase I: Urelumab 1 mg + Nivolumab	Phase II: Urelumab 8 mg + Nivolumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	1		
Units: week				
number (not applicable)	26.20	59.50		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival (PFS)

End point title	Progression-free survival (PFS)
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End point description:

PFS is assessed from the date of inclusion until the date of first sign of disease progression or death due to any cause. Overall, PFS mean was 17.00 and SD was 2.63.

End point type	Secondary
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End point timeframe:

PFS is assessed from the date of inclusion until the date of first sign of disease progression or death due to any cause.

End point values	Phase I: Urelumab 1 mg + Nivolumab	Phase II: Urelumab 8 mg + Nivolumab	Phase II: Cohort A	Phase II: Cohort B
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	3	28	20	8
Units: week				
arithmetic mean (standard error)	21.50 (± 6.72)	16.50 (± 2.81)	18.60 (± 3.75)	11.10 (± 1.93)

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS)

End point title Overall survival (OS)

End point description:

Overall survival (OS) was assessed from the date of inclusion until the date of death due to any cause. Overall, OS mean was 53.10 and SD was 9.45.

End point type Secondary

End point timeframe:

OS was assessed from the date of inclusion until the date of death due to any cause.

End point values	Phase I: Urelumab 1 mg + Nivolumab	Phase II: Urelumab 8 mg + Nivolumab	Phase II: Cohort A	Phase II: Cohort B
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	3	28	20	8
Units: week				
arithmetic mean (standard error)	81.40 (± 0.00)	48.70 (± 10.90)	46.80 (± 10.89)	71.70 (± 9.14)

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of safety results (number of events)

End point title Summary of safety results (number of events)

End point description:

Summary of the safety results related to the count of each type of adverse event for overall patients and by phase and cohort of the study. For Urelumab/Nivolumab related events, AEs whose causal relation is "likely" or "related" were considered. Overall, there were 302 AEs, 28 SAEs, 0 DLT, 7 urelumab related-events, 5 nivolumab-related events and 5 urelumab and nivolumab related events.

End point type Secondary

End point timeframe:

Adverse events were assessed continuously during the study and for a minimum of 100 days following the last dose of study treatment.

End point values	Phase I: Urelumab 1 mg + Nivolumab	Phase II: Urelumab 8 mg + Nivolumab	Phase II: Cohort A	Phase II: Cohort B
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	3	28	20	8
Units: number of events				
Adverse Events (AEs)	26	276	217	59
Serious Adverse Events (SAEs)	0	28	24	4
Dose Limiting Toxicities (DLT)	0	0	0	0
Urelumab-related events	0	7	2	5
Nivolumab-related events	0	5	1	4
Urelumab and nivolumab related events	0	5	1	4

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of safety results (number of patients)

End point title	Summary of safety results (number of patients)
End point description:	Shows the results related to the number of patients within each category. Overall, there were 30 patients with AEs, 14 with SAEs, 0 with DLT, 4 with urelumab related-events, 3 with nivolumab-related events and 3 with urelumab and nivolumab related events.
End point type	Secondary
End point timeframe:	Adverse events were assessed continuously during the study and for a minimum of 100 days following the last dose of study treatment.

End point values	Phase I: Urelumab 1 mg + Nivolumab	Phase II: Urelumab 8 mg + Nivolumab	Phase II: Cohort A	Phase II: Cohort B
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	3	28	20	8
Units: number of patients				
Adverse Events (AEs)	3	28	20	7
Serious Adverse Events (SAEs)	0	14	11	3
Dose Limiting Toxicities (DLT)	0	0	0	0
Urelumab-related events	0	4	2	2
Nivolumab-related events	0	3	1	2
Urelumab and nivolumab related events	0	3	1	2

Statistical analyses

Secondary: Overview of Adverse Events by study phase (number of events within each study phase)

End point title	Overview of Adverse Events by study phase (number of events within each study phase)
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End point description:

Summarizes the results of the number of Adverse Events for overall patients and by phase and cohort

End point type	Secondary
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End point timeframe:

Adverse events were assessed continuously during the study and for a minimum of 100 days following the last dose of study treatment.

End point values	Phase I: Urelumab 1 mg + Nivolumab	Phase II: Urelumab 8 mg + Nivolumab	Phase II: Cohort A	Phase II: Cohort B
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	3	28	20	8
Units: number of events				
Grade: Mild	13	184	141	43
Grade: Moderate	12	83	67	16
Grade: Severe	1	9	9	0
Grade: Life threatening or disabling	0	0	0	0
Grade: Death related to the AE	0	0	0	0
Progression: Death	0	6	0	6
Progression: Persistence of the AE	9	125	110	15
Progression: Recovery with consequences	5	15	14	1
Progression: Recovery without consequences	12	130	93	37
Action taken: None	25	266	209	57
Action taken: Dose reduction of drug	1	1	1	0
Action taken: Dose increase of drug	0	1	1	0
Action taken: Temporary disruption of drug	0	8	6	2
Action taken: Permanent disruption of drug	0	0	0	0
Action taken: Study withdrawal	0	0	0	0
Relation to Urelumab: Not related	22	258	208	50
Relation to Urelumab: Unlikely	1	5	4	1
Relation to Urelumab: Possible	3	7	4	3
Relation to Urelumab: Likely	0	4	0	4
Relation to Urelumab: Related	0	2	1	1
Relation to Nivolumab: Not related	23	260	209	51
Relation to Nivolumab: Unlikely	1	5	4	1
Relation to Nivolumab: Possible	2	7	4	3
Relation to Nivolumab: Likely	0	4	0	4
Relation to Nivolumab: Related	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Overview of Adverse Events by study phase (number of patients within each group)

End point title	Overview of Adverse Events by study phase (number of patients within each group)
End point description:	Presents the results related to the number of patients
End point type	Secondary
End point timeframe:	Adverse events were assessed continuously during the study and for a minimum of 100 days following the last dose of study treatment.

End point values	Phase I: Urelumab 1 mg + Nivolumab	Phase II: Urelumab 8 mg + Nivolumab	Phase II: Cohort A	Phase II: Cohort B
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	3	28		
Units: number of patients				
Grade: Mild	3	26	19	7
Grade: Moderate	3	24	17	7
Grade: Severe	1	6	6	0
Grade: Life threatening or disabling	0	0	0	0
Grade: Death related to the AE	0	0	0	0
Grade: not available	0	0	0	0
Progression: Death	0	1	0	1
Progression: Persistence of the AE	3	22	18	4
Progression: Recovery with consequences	1	8	7	1
Progression: Recovery without consequences	3	24	18	6
Action taken: None	3	27	20	7
Action taken: Dose reduction of drug	1	1	1	0
Action taken: Dose increased of drug	0	1	1	0
Action taken: Temporary disruption of drug	0	6	4	2
Action taken: Permanent disruption of drug	0	0	0	0
Action taken: study withdrawal	0	0	0	0
Relation to Urelumab: Not related	3	27	20	7
Relation to Urelumab: Unlikely	1	5	4	1
Relation to Urelumab: Possible	2	4	2	2
Relation to Urelumab: Likely	0	2	0	2

Relation to Urelumab: Related	0	2	1	1
Relation to Nivolumab: Not related	3	27	20	7
Relation to Nivolumab: Unlikely	1	5	4	1
Relation to Nivolumab: Possible	1	4	2	2
Relation to Nivolumab: Likely	0	2	0	2
Relation to Nivolumab: Related	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Overview of Serious Adverse Events by study phase (number of events within each group).

End point title	Overview of Serious Adverse Events by study phase (number of events within each group).
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End point description:

Summarizes the results of the number of Serious Adverse Events for overall patients and by group

End point type	Secondary
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End point timeframe:

Adverse events were assessed continuously during the study and for a minimum of 100 days following the last dose of study treatment.

End point values	Phase I: Urelumab 1 mg + Nivolumab	Phase II: Urelumab 8 mg + Nivolumab	Phase II: Cohort A	Phase II: Cohort B
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	3	28	20	8
Units: number of events				
Grade: Mild	0	0	0	0
Grade: Moderate	0	6	6	0
Grade: Severe	0	15	13	2
Grade: Life threatening or disabling	0	1	0	1
Grade: Death related to the AE	0	6	5	1
Progression: Death	0	7	6	1
Prgression: Persistence of the AE	0	1	1	0
Progression: Recovery with consequences	0	2	2	0
Progression: Recovery without consequences	0	18	15	3
Action taken: None	0	20	18	2
Action taken: Dose reduction of drug	0	0	0	0
Action taken: Dose increase of drug	0	0	0	0
Action taken: Temporary disruption of drug	0	7	5	2
Action taken: Permanent disruption of drug	0	1	1	0
Action taken: Study withdrawal	0	0	0	0
Relation to Urelumab: Not related	0	23	21	2
Relation to Urelumab: Unlikely	0	0	0	0

Relation to Urelumab: Possible	0	4	2	2
Relation to Urelumab: Likely	0	0	0	0
Relation to Urelumab: Related	0	1	1	0
Relation to Nivolumab: Not related	0	22	20	2
Relation to Nivolumab: Unlikely	0	0	0	0
Relation to Nivolumab: Possible	0	5	3	2
Relation to Nivolumab: Likely	0	0	0	0
Relation to Nivolumab: Related	0	1	1	0

Statistical analyses

No statistical analyses for this end point

Secondary: Overview of Serious Adverse Events by study phase (number of patients within each group).

End point title	Overview of Serious Adverse Events by study phase (number of patients within each group).
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End point description:

Results related to the number of patients

End point type	Secondary
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End point timeframe:

Adverse events were assessed continuously during the study and for a minimum of 100 days following the last dose of study treatment.

End point values	Phase I: Urelumab 1 mg + Nivolumab	Phase II: Urelumab 8 mg + Nivolumab	Phase II: Cohort A	Phase II: Cohort B
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	3	28	20	8
Units: number of patients				
Grade: Mild	0	0	0	0
Grade: Moderate	0	5	5	0
Grade: Severe	0	9	7	2
Grade: Life threatening or disabling	0	1	0	1
Grade: Death related to the AE	0	6	5	1
Progression: Death	0	7	6	1
Progression: Persistence of the AE	0	1	1	0
Progression: Recovery with consequences	0	2	2	0
Progression: Recovery without consequence	0	10	8	2
Action taken: None	0	11	9	2
Action taken: Dose reduction of drug	0	0	0	0
Action taken: Dose increase of drug	0	0	0	0
Action taken: Temporary disruption of drug	0	5	4	1
Action taken: Permanent disruption of drug	0	1	1	0
Action taken: Study withdrawal	0	0	0	0

Relation to Urelumab: Not related	0	12	10	2
Relation to Urelumab: Unlikely	0	0	0	0
Relation to Urelumab: Possible	0	3	2	1
Relation to Urelumab: Likely	0	0	0	0
Relation to Urelumab: Related	0	1	1	0
Relation to Nivolumab: Not related	0	12	10	2
Relation to Nivolumab: Unlikely	0	0	0	0
Relation to Nivolumab: Possible	0	3	2	1
Relation to Nivolumab: Likely	0	0	0	0
Relation to Nivolumab: Related	0	1	1	0

Statistical analyses

No statistical analyses for this end point

Secondary: Overview of Urelumab-related Adverse Events by study phase (number of events within each group).

End point title	Overview of Urelumab-related Adverse Events by study phase (number of events within each group).
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End point description:

Summarizes the results related to the number of Urelumab-related Adverse Events.

Important note. Drug-related AEs are considered when relation with Urelumab is likely or related.

End point type	Secondary
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End point timeframe:

Adverse events were assessed continuously during the study and for a minimum of 100 days following the last dose of study treatment.

End point values	Phase I: Urelumab 1 mg + Nivolumab	Phase II: Urelumab 8 mg + Nivolumab	Phase II: Cohort A	Phase II: Cohort B
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	3	28	20	8
Units: number of events				
Grade: Mild	0	5	1	4
Grade: Moderate	0	2	1	1
Grade: Severe	0	0	0	0
Grade: Life threatening or disabling	0	0	0	0
Grade: Death related to the AE	0	0	0	0
Progression: Death	0	0	0	0
Progression: Persistence of the AE	0	3	0	3
Progression: Recovery with consequences	0	1	1	0
Progression: Recovery without consequence	0	3	1	2
Action taken: None	0	6	1	5
Action taken: Dose reduction of drug	0	0	0	0
Action taken: Dose increase of drug	0	0	0	0

Action taken: Temporary disruption of drug	0	1	1	0
Action taken: Permanent disruption of drug	0	0	0	0
Action taken: Study withdrawal	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Overview of Urelumab-related Adverse Events by study phase (number of patients within each group).

End point title	Overview of Urelumab-related Adverse Events by study phase (number of patients within each group).
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End point description:

Counts the number of patients with Urelumab-related Adverse Events.

Important note. Drug-related AEs are considered when relation with Urelumab is likely or related.

End point type	Secondary
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End point timeframe:

Adverse events were assessed continuously during the study and for a minimum of 100 days following the last dose of study treatment.

End point values	Phase I: Urelumab 1 mg + Nivolumab	Phase II: Urelumab 8 mg + Nivolumab	Phase II: Cohort A	Phase II: Cohort B
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	3	28	20	8
Units: number of patients				
Grade: Mild	0	3	1	2
Grade: Moderate	0	2	1	1
Grade: Severe	0	0	0	0
Grade: Life threatening or disabling	0	0	0	0
Grade: Death related to the AE	0	0	0	0
Progression: Death	0	0	0	0
Progression: Persistence of the AE	0	1	0	1
Progression: Recovery with consequences	0	1	1	0
Progression: Recovery without consequences	0	3	1	2
Action taken: None	0	3	1	2
Action taken: Dose reduction of drug	0	0	0	0
Action taken: Dose increase of drug	0	0	0	0
Action taken: Temporary disruption of drug	0	1	1	0
Action taken: Permanent disruption of drug	0	0	0	0
Action taken: Study withdrawal	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Overview of Nivolumab-related Adverse Events by study phase (number of events within each group).

End point title	Overview of Nivolumab-related Adverse Events by study phase (number of events within each group).
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End point description:

Summarizes the results related to the number of Nivolumab-related Adverse Events

Important note. Drug-related AEs are considered when relation with Nivolumab is likely or related.

End point type	Secondary
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End point timeframe:

Adverse events were assessed continuously during the study and for a minimum of 100 days following the last dose of study treatment.

End point values	Phase I: Urelumab 1 mg + Nivolumab	Phase II: Urelumab 8 mg + Nivolumab	Phase II: Cohort A	Phase II: Cohort B
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	3	28	20	8
Units: number of events				
Grade: Mild	0	3	0	3
Grade: Moderate	0	2	1	1
Grade: Severe	0	0	0	0
Grade: Life threatening or disabling	0	0	0	0
Grade: Death related to the AE	0	0	0	0
Progression: Death	0	0	0	0
Progression: Persistence of the AE	0	3	0	3
Progression: Recovery with consequences	0	1	1	0
Progression: Recovery without consequences	0	1	0	1
Action taken: None	0	4	0	4
Action taken: Dose reduction of drug	0	0	0	0
Action taken: Dose increase of drug	0	0	0	0
Action taken: Temporary disruption of drug	0	1	1	0
Action taken: Permanent disruption of drug	0	0	0	0
Action taken: Study withdrawal	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Overview of Nivolumab-related Adverse Events by study phase (number of patients within each group).

End point title	Overview of Nivolumab-related Adverse Events by study phase (number of patients within each group).
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End point description:

Number of patients with Nivolumab-related Adverse Events.

Important note. Drug-related AEs are considered when relation with Nivolumab is likely or related.

End point type	Secondary
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End point timeframe:

Adverse events were assessed continuously during the study and for a minimum of 100 days following the last dose of study treatment.

End point values	Phase I:	Phase II:	Phase II:	Phase II:
	Urelumab 1 mg + Nivolumab	Urelumab 8 mg + Nivolumab	Cohort A	Cohort B
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	3	28	20	8
Units: number of patients				
Grade: Mild	0	2	0	2
Grade: Moderate	0	2	1	1
Grade: Severe	0	0	0	0
Grade: Life threatening or disabling	0	0	0	0
Grade: Death related to the AE	0	0	0	0
Progression: Death	0	0	0	0
Progression: Persistence of the AE	0	1	0	1
Progression: Recovery with consequences	0	1	1	0
Progression: Recovery without consequences	0	1	0	1
Action taken: None	0	2	0	2
Action taken: Dose reduction of drug	0	0	0	0
Action taken: Dose increase of drug	0	0	0	0
Action taken: Temporary disruption of drug	0	1	1	0
Action taken: Permanent disruption of drug	0	0	0	0
Action taken: Study withdrawal	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: AEs by System Organ Class (SOC) and Preferred Term (PT) (number of patients)

End point title	AEs by System Organ Class (SOC) and Preferred Term (PT) (number of patients) ^[6]
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End point description:

Non-Serious Adverse Events from phase I of the study considering the SOC code, the PT code of the AE.

End point type	Secondary
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End point timeframe:

Adverse events were assessed continuously during the study and for a minimum of 100 days following the last dose of study treatment.

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 endpoint reports statistics for both arms (phase I and phase II), but the adverse effect results reported in the second arm are presented only by cohort.

End point values	Phase I: Urelumab 1 mg + Nivolumab	Phase II: Cohort A	Phase II: Cohort B	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	3	20	8	
Units: number of patients				
Blood and lymphatic system disorders: Anaemia	2	4	2	
Blood and lymphatic system disorders: Leukocytosis	0	1	1	
Blood and lymphatic system disorders: Neutrophilia	0	1	2	
Blood and lymphatic SD: Thrombocytopenia	0	2	0	
Cardiac disorders: Atrial flutter	0	2	0	
Cardiac disorders: Pericardial effusion	0	1	0	
Cardiac disorders: Tachycardia	1	2	3	
Congenital/genetic disorders: Keratosis follicular	0	1	0	
Endocrine disorders: Adrenal insufficiency	0	2	1	
Endocrine disorders: Hypothyroidism	0	3	2	
Gastrointestinal disorders: Abnormal faeces	0	0	1	
Gastrointestinal disorders: Abdominal distension	0	1	0	
Gastrointestinal disorders: Abdominal pain	1	4	0	
Gastrointestinal disorders: Abdominal pain upper	0	1	0	
Gastrointestinal disorders: Ascites	0	1	0	
Gastrointestinal disorders: Constipation	0	8	2	
Gastrointestinal disorders: Diarrhoea	1	4	2	
Gastrointestinal disorders: Flatulence	0	1	0	
Gastrointestinal disorders: Gastritis	0	1	0	
Gastrointestinal disorders: Gastrointestinal pain	1	2	0	
Gastrointestinal: Gastrooesophageal reflux disease	0	1	0	
Gastrointestinal disorders: Nausea	0	4	0	
Gastrointestinal disorders: Pancreatitis	0	1	0	
Gastrointestinal disorders: Rectal haemorrhage	0	1	0	
Gastrointestinal disorders: Vomiting	0	3	2	
General disorders: Application site pain	0	1	0	

General disorders: Asthenia	0	2	0
General disorders: Chest pain	0	1	1
General disorders: Condition aggravated	1	0	0
General disorders: Fatigue	2	13	2
General disorders: Malaise	0	1	0
General disorders: Mucosal inflammation	0	1	0
General disorders: Oedema	1	1	1
General disorders: Pain	0	1	0
General disorders: Pyrexia	0	5	4
General disorders: Sense of oppression	1	0	0
General disorders: Suprapubic pain	0	1	0
Infections and infestations: Adenoviral infection	0	2	0
Infections and infestations: Cellulitis	0	0	1
Infections and infestations: Infection	0	1	0
Infections and infestations: Nasopharyngitis	0	1	0
Infections and infestations: Pneumonia	0	1	0
Infections and infestations: Skin infection	0	0	1
Injury: Craniocerebral injury	0	1	0
Injury: Contusion	0	0	1
Injury: Injury	0	1	0
Injury: Thermal burn	0	1	0
Injury: Upper limb fracture	0	1	0
Investigations: Adjusted calcium increased	0	1	1
Investigations: ALT increased	1	3	1
Investigations: Amylase increased	0	1	0
Investigations: Asp-aminotransferase increased	1	3	2
Investigations: Bleeding time	0	0	1
Investigation: Blood alkalinephosphatase increased	0	1	0
Investigations: Blood bilirubin increased	0	0	1
Investigations: Blood creatinine increased	0	2	0
Investigations: Blood glucose increased	0	2	0
Investigations: Blood LDH increased	0	1	0
Investigations: Blood magnesium decreased	0	2	0
Investigations: Blood TSH decreased	1	0	0
Investigations: Lipase increased	0	1	0
Investigations: Transaminases increased	0	1	0
Investigations: Weight decreased	0	1	1
Metabolism/nutrition disorders: Cachexia	0	1	0
Metabolism/nutrition disorders: Decreased appetite	0	7	2
Metabolism/nutrition disorders: Hyponatraemia	0	1	0
Musculoskeletal disorders: Back pain	0	1	1
Musculoskeletal disorders: Flank pain	2	1	0
Musculoskeletal disorders: Groin pain	0	0	2
Musculoskeletal disorders: joint pain	0	1	0

Musculoskeletal disorders: (M) chest pain	0	1	0
Musculoskeletal disorders: Musculoskeletal pain	0	2	0
Musculoskeletal disorders: Myalgia	0	1	0
Musculoskeletal disorders: Neck pain	0	2	1
Musculoskeletal disorders: Pain in extremity	0	0	1
Musculoskeletal disorders: TMJ syndrome	1	0	0
Neoplasms: Cancer pain	0	1	0
Nervous system disorders: Dizziness	0	2	1
Nervous system disorders: Headache	0	1	0
Nervous system disorders: Hepatic encephalopathy	0	1	0
Nervous system disorders: Myoclonus	0	1	0
Nervous system disorders: Neuralgia	0	1	0
Nervous system disorders: Paraesthesia	0	1	0
Nervous system: Peripheral sensory neuropathy	0	1	0
Nervous system disorders: Seizure	0	1	0
Nervous system disorders: Somnolence	0	2	0
Nervous system disorders: Syncope	0	2	0
Psychiatric disorders: Affect lability	0	1	0
Psychiatric disorders: Anxiety	0	1	0
Psychiatric disorders: Confusional state	0	0	1
Psychiatric disorders: Depressed mood	0	1	0
Psychiatric disorders: Depression	0	5	0
Psychiatric disorders: Insomnia	0	1	0
Psychiatric disorders: Nervousness	0	1	0
Psychiatric : Persistent depressive disorder	0	1	0
Renal and urinary disorders: Nocturia	0	1	0
Renal and urinary disorders: Oliguria	0	0	1
Renal and urinary disorders: Polaquyuria	0	1	0
Renal and urinary disorders: Urinary retention	0	1	0
Reproductive system: Genital dysaesthesia	0	1	0
Reproductive system: Vaginal haemorrhage	0	0	1
Respiratory/thoracic disorders: Cough	0	2	0
Respiratory/thoracic disorders: Dyspnoea	0	1	0
Respiratory/thoracic disorders: Haemoptysis	0	2	0
Respiratory/thoracic disorders: Pneumonia	0	1	0
Respiratory/thoracic disorders: Productive cough	0	1	0
Respiratory/thoracic disorders: Sputum retention	0	2	0
Skin disorders: Cold sweat	0	0	1
Skin disorders: Dermatitis allergic	0	1	0
Skin disorders: Dermatitis contact	0	0	1
Skin disorders: Pruritus	0	0	1

Skin disorders: Psoriasis	0	1	0	
Skin disorders: Skin lesion	0	1	0	
Skin disorders: Wound	0	1	0	
Vascular disorders: Bleeding	0	0	1	
Vascular disorders: Hypertension	0	3	0	
Vascular disorders: Hypotension	0	2	0	
Vascular disorders: Orthostatic hypotension	1	0	0	
Vascular disorders: Superior vena cava syndrome	1	0	0	
Vascular disorders: Thrombosis	1	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: AEs by System Organ Class (SOC) and Preferred Term (PT) (number of events)

End point title	AEs by System Organ Class (SOC) and Preferred Term (PT) (number of events) ^[7]
End point description:	Non-Serious Adverse Events from phase I of the study considering the SOC code, the PT code of the AE
End point type	Secondary
End point timeframe:	During trial and 100 follow up

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 endpoint reports statistics for both arms (phase I and phase II), but the adverse effect results reported in the second arm are presented only by cohort.

End point values	Phase I: Urelumab 1 mg + Nivolumab	Phase II: Cohort A	Phase II: Cohort B	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	3	20	8	
Units: Number of events				
Blood and lymphatic system disorders: Anaemia	5	6	2	
Blood and lymphatic system disorders: Leukocytosis	0	1	1	
Blood and lymphatic system disorders: Neutrophilia	0	1	2	
Blood and lymphatic SD: Thrombocytopenia	0	3	0	
Cardiac disorders: Atrial flutter	0	2	0	
Cardiac disorders: Pericardial effusion	0	1	0	
Cardiac disorders: Tachycardia	1	5	4	
Congenital/genetic disorders: Keratosis follicular	0	1	0	
Endocrine disorders: Adrenal insufficiency	0	4	1	
Endocrine disorders: Hypothyroidism	0	5	2	

Gastrointestinal disorders: Abnormal faeces	0	0	1	
Gastrointestinal disorders: Abdominal distension	0	1	0	
Gastrointestinal disorders: Abdominal pain	1	6	0	
Gastrointestinal disorders: Abdominal pain upper	0	1	0	
Gastrointestinal disorders: Ascites	0	1	0	
Gastrointestinal disorders: Constipation	0	13	2	
Gastrointestinal disorders: Diarrhoea	1	6	3	
Gastrointestinal disorders: Flatulence	0	1	0	
Gastrointestinal disorders: Gastritis	0	2	0	
Gastrointestinal disorders: Gastrointestinal pain	1	2	0	
Gastrointestinal: Gastroesophageal reflux disease	0	1	0	
Gastrointestinal disorders: Nausea	0	5	0	
Gastrointestinal disorders: Pancreatitis	0	2	0	
Gastrointestinal disorders: Rectal haemorrhage	0	1	0	
Gastrointestinal disorders: Vomiting	0	7	3	
General disorders: Application site pain	0	1	0	
General disorders: Asthenia	0	2	0	
General disorders: Chest pain	0	1	2	
General disorders: Condition aggravated	1	0	0	
General disorders: Fatigue	5	16	2	
General disorders: Malaise	0	1	0	
General disorders: Mucosal inflammation	0	1	0	
General disorders: Oedema	1	1	1	
General disorders: Pain	0	1	0	
General disorders: Pyrexia	0	6	7	
General disorders: Sense of oppression	1	0	0	
General disorders: Suprapubic pain	0	1	0	
Infections and infestations: Adenoviral infection	0	2	0	
Infections and infestations: Cellulitis	0	0	1	
Infections and infestations: Infection	0	2	0	
Infections and infestations: Nasopharyngitis	0	1	0	
Infections and infestations: Pneumonia	0	2	0	
Infections and infestations: Skin infection	0	0	1	
Injury: Craniocerebral injury	0	1	0	
Injury: Contusion	0	0	1	
Injury: Injury	0	1	0	
Injury: Thermal burn	0	1	0	
Injury: Upper limb fracture	0	1	0	
Investigations: Adjusted calcium increased	0	1	1	
Investigations: ALT increased	1	3	1	
Investigations: Amylase increased	0	1	0	
Investigations: Asp-aminotransferase increased	1	5	2	
Investigations: Bleeding time	0	0	1	

Investigation: Blood alkalinephosphatase increased	0	2	0
Investigations: Blood bilirubin increased	0	0	1
Investigations: Blood creatinine increased	0	2	0
Investigations: Blood glucose increased	0	2	0
Investigations: Blood LDH increased	0	1	0
Investigations: Blood magnesium decreased	0	2	0
Investigations: Blood TSH decreased	1	0	0
Investigations: Lipase increased	0	1	0
Investigations: Transaminases increased	0	1	0
Investigations: Weight decreased	0	1	1
Metabolism/nutrition disorders: Cachexia	0	1	0
Metabolism/nutrition disorders: Decreased appetite	0	8	2
Metabolism/nutrition disorders: Hyponatraemia	0	1	0
Musculoskeletal disorders: Back pain	0	2	1
Musculoskeletal disorders: Flank pain	2	1	0
Musculoskeletal disorders: Groin pain	0	0	3
Musculoskeletal disorders: joint pain	0	1	0
Musculoskeletal disorders: (M) chest pain	0	1	0
Musculoskeletal disorders: Musculoskeletal pain	0	2	0
Musculoskeletal disorders: Myalgia	0	1	0
Musculoskeletal disorders: Neck pain	0	2	1
Musculoskeletal disorders: Pain in extremity	0	0	1
Musculoskeletal disorders: TMJ syndrome	1	0	0
Neoplasms: Cancer pain	0	1	0
Nervous system disorders: Dizziness	0	2	1
Nervous system disorders: Headache	0	1	0
Nervous system disorders: Hepatic encephalopathy	0	1	0
Nervous system disorders: Myoclonus	0	1	0
Nervous system disorders: Neuralgia	0	1	0
Nervous system disorders: Paraesthesia	0	1	0
Nervous system: Peripheral sensory neuropathy	0	1	0
Nervous system disorders: Seizure	0	1	0
Nervous system disorders: Somnolence	0	2	0
Nervous system disorders: Syncope	0	2	0
Psychiatric disorders: Affect lability	0	1	0
Psychiatric disorders: Anxiety	0	1	0
Psychiatric disorders: Confusional state	0	0	1
Psychiatric disorders: Depressed mood	0	1	0
Psychiatric disorders: Depression	0	6	0
Psychiatric disorders: Insomnia	0	1	0
Psychiatric disorders: Nervousness	0	1	0
Psychiatric : Persistent depressive disorder	0	1	0
Renal and urinary disorders: Nocturia	0	1	0

Renal and urinary disorders: Oliguria	0	0	1	
Renal and urinary disorders: Polaquyuria	0	1	0	
Renal and urinary disorders: Urinary retention	0	1	0	
Reproductive system: Genital dysaesthesia	0	1	0	
Reproductive system: Vaginal haemorrhage	0	0	1	
Respiratory/thoracic disorders: Cough	0	2	0	
Respiratory/thoracic disorders: Dyspnoea	0	1	0	
Respiratory/thoracic disorders: Haemoptysis	0	4	0	
Respiratory/thoracic disorders: Pneumonia	0	1	0	
Respiratory/thoracic disorders: Productive cough	0	1	0	
Respiratory/thoracic disorders: Sputum retention	0	3	0	
Skin disorders: Cold sweat	0	0	1	
Skin disorders: Dermatitis allergic	0	1	0	
Skin disorders: Dermatitis contact	0	0	1	
Skin disorders: Pruritus	0	0	1	
Skin disorders: Psoriasis	0	1	0	
Skin disorders: Skin lesion	0	1	0	
Skin disorders: Wound	0	1	0	
Vascular disorders: Bleeding	0	0	1	
Vascular disorders: Hypertension	0	7	0	
Vascular disorders: Hypotension	0	2	0	
Vascular disorders: Orthostatic hypotension	1	0	0	
Vascular disorders: Superior vena cava syndrome	1	0	0	
Vascular disorders: Thrombosis	1	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Urelumab-related AES by study phase and cohort (Number of patients)

End point title	Number of Urelumab-related AES by study phase and cohort (Number of patients)
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End point description:

List of AEs likely or related to Urelumab

End point type	Secondary
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End point timeframe:

Adverse events were assessed continuously during the study and for a minimum of 100 days following the last dose of study treatment.

End point values	Phase I: Urelumab 1 mg + Nivolumab	Phase II: Urelumab 8 mg + Nivolumab	Phase II: Cohort A	Phase II: Cohort B
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	3	28	20	8
Units: number of patients				
Gastrointestinal disorders: Nausea	0	1	1	0
Gastrointestinal disorders: Diarrhoea	0	1	0	1
General disorders: Pyrexia	0	1	0	1
Investigations: ALT increased	0	1	0	1
Investigations: Asp-aminotransferase increased	0	1	0	1
Investigations: Blood bilirubin increased	0	1	0	1

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Urelumab-related AES by study phase and cohort (number of AEs)

End point title	Number of Urelumab-related AES by study phase and cohort (number of AEs)
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End point description:

List of AEs likely or related to Urelumab

End point type	Secondary
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End point timeframe:

Adverse events were assessed continuously during the study and for a minimum of 100 days following the last dose of study treatment.

End point values	Phase I: Urelumab 1 mg + Nivolumab	Phase II: Urelumab 8 mg + Nivolumab	Phase II: Cohort A	Phase II: Cohort B
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	3	28	20	8
Units: Number of AEs				
Gastrointestinal disorders: Nausea	0	1	1	0
Gastrointestinal disorders: Diarrhoea	0	1	0	1
General disorders: Pyrexia	0	1	0	1
Investigations: ALT increased	0	1	0	1
Investigations: Asp-aminotransferase increased	0	1	0	1
Investigations: Blood bilirubin increased	0	1	0	1

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Nivolumab-related AES by study phase and cohort (number of patients)

End point title	Number of Nivolumab-related AES by study phase and cohort (number of patients)
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End point description:

List of AEs by phase of the study likely or related to Nivolumab

End point type	Secondary
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End point timeframe:

Adverse events were assessed continuously during the study and for a minimum of 100 days following the last dose of study treatment.

End point values	Phase I: Urelumab 1 mg + Nivolumab	Phase II: Urelumab 8 mg + Nivolumab	Phase II: Cohort A	Phase II: Cohort B
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	3	28	20	8
Units: Number of patients				
General disorders: Pyrexia	0	1	0	1
Investigations: ALT increased	0	1	0	1
Investigations: asp-aminotransferase increased	0	1	0	1
Investigations: Blood bilirubin increased	0	1	0	1

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Nivolumab-related AES by study phase and cohort (Number of AEs)

End point title	Number of Nivolumab-related AES by study phase and cohort (Number of AEs)
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End point description:

List of AEs by phase of the study likely or related to Nivolumab

End point type	Secondary
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End point timeframe:

Adverse events were assessed continuously during the study and for a minimum of 100 days following the last dose of study treatment.

End point values	Phase I: Urelumab 1 mg + Nivolumab	Phase II: Urelumab 8 mg + Nivolumab	Phase II: Cohort A	Phase II: Cohort B
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	3	28	20	8
Units: Number of AEs				
General disorders: Pyrexia	0	1	0	1
Investigations: ALT increased	0	1	0	1

Investigations: asp-aminotransferase increased	0	1	0	1
Investigations: Blood bilirubin increased	0	1	0	1

Statistical analyses

No statistical analyses for this end point

Secondary: SAES by study phase and cohort (number of patients)

End point title	SAES by study phase and cohort (number of patients)
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End point description:

There were no SAEs in phase I of the study.

List of SAEs from phase II by cohort

End point type	Secondary
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End point timeframe:

Adverse events were assessed continuously during the study and for a minimum of 100 days following the last dose of study treatment.

End point values	Phase I: Urelumab 1 mg + Nivolumab	Phase II: Urelumab 8 mg + Nivolumab	Phase II: Cohort A	Phase II: Cohort B
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	3	28	20	8
Units: number of patients				
Blood and lymphatic SD: Thrombocytopenia	0	1	0	1
Cardiac disorders: Pericardial effusion	0	1	1	0
Gastrointestinal disorders: Abdominal infection	0	1	1	0
Gastrointestinal disorders: Constipation	0	1	1	0
General disorders: Condition aggravated	0	1	1	0
General disorders: Disease progression	0	4	3	1
General disorders: Pain	0	1	1	0
General disorders: Pyrexia	0	1	1	0
Infections and infestations: Infection	0	2	2	0
Infections and infestations: Pneumonia	0	4	4	0
Injury: Biliary anastomosis complication	0	1	1	0
Injury: Tracheal obstruction	0	1	1	0
Investigations: Transaminases increased	0	2	1	1
Nervous system disorders: Clumsiness	0	1	1	0
Renal and urinary disorders: Renal failure	0	1	1	0
Renal and urinary disorders: Acute kidney injury	0	1	0	1
Respiratory, thoracic disorders: Laryngeal oedema	0	1	1	0
Skin disorders: Rash maculo-papular	0	1	1	0

Statistical analyses

No statistical analyses for this end point

Secondary: SAES by study phase and cohort (number of SAEs)

End point title	SAES by study phase and cohort (number of SAEs)
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End point description:

There were no SAEs in phase I of the study.

List of SAEs from phase II by cohort

End point type	Secondary
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End point timeframe:

Adverse events were assessed continuously during the study and for a minimum of 100 days following the last dose of study treatment.

End point values	Phase I: Urelumab 1 mg + Nivolumab	Phase II: Urelumab 8 mg + Nivolumab	Phase II: Cohort A	Phase II: Cohort B
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	3	28	20	8
Units: Number of SAEs				
Blood and lymphatic SD: Thrombocytopenia	0	1	0	1
Cardiac disorders: Pericardial effusion	0	1	1	0
Gastrointestinal disorders: Abdominal infection	0	1	1	0
Gastrointestinal disorders: Constipation	0	1	1	0
General disorders: Condition aggravated	0	1	1	0
General disorders: Disease progression	0	4	3	1
General disorders: Pain	0	1	1	0
General disorders: Pyrexia	0	1	1	0
Infections and infestations: Infection	0	2	2	0
Infections and infestations: Pneumonia	0	3	3	0
Injury: Biliary anastomosis complication	0	1	1	0
Injury: Tracheal obstruction	0	1	1	0
Investigations: Transaminases increased	0	2	1	1
Nervous system disorders: Clumsiness	0	1	1	0
Renal and urinary disorders: Renal failure	0	1	1	0
Renal and urinary disorders: Acute kidney injury	0	1	0	1
Respiratory, thoracic disorders: Laryngeal oedema	0	1	1	0
Skin disorders: Rash maculo-papular	0	1	1	0

Statistical analyses

No statistical analyses for this end point

Secondary: Urelumab-related SAEs from Phase II by cohort (number of patients)

End point title	Urelumab-related SAEs from Phase II by cohort (number of patients)
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End point description:

There were no SAEs in phase I of the study.

List of SAEs from phase II by cohort that were likely or related to Urelumab.

End point type	Secondary
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End point timeframe:

Adverse events were assessed continuously during the study and for a minimum of 100 days following the last dose of study treatment.

End point values	Phase I: Urelumab 1 mg + Nivolumab	Phase II: Urelumab 8 mg + Nivolumab	Phase II: Cohort A	Phase II: Cohort B
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	3	28	20	8
Units: number of patients				
Investigations: Transaminases increased	0	1	1	0

Statistical analyses

No statistical analyses for this end point

Secondary: Urelumab-related SAEs from Phase II by cohort (number of SAEs)

End point title	Urelumab-related SAEs from Phase II by cohort (number of SAEs)
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End point description:

There were no SAEs in phase I of the study.

List of SAEs from phase II by cohort that were likely or related to Urelumab.

End point type	Secondary
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End point timeframe:

Adverse events were assessed continuously during the study and for a minimum of 100 days following the last dose of study treatment.

End point values	Phase I: Urelumab 1 mg + Nivolumab	Phase II: Urelumab 8 mg + Nivolumab	Phase II: Cohort A	Phase II: Cohort B
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	3	28	20	8
Units: Number of SAEs				
Investigations: Transaminases increased	0	1	1	0

Statistical analyses

No statistical analyses for this end point

Secondary: Nivolumab-related SAEs from Phase II by cohort (number of patients)

End point title	Nivolumab-related SAEs from Phase II by cohort (number of patients)
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End point description:

SAEs from phase II by cohort that were likely or related to Nivolumab

End point type	Secondary
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End point timeframe:

Adverse events were assessed continuously during the study and for a minimum of 100 days following the last dose of study treatment.

End point values	Phase I: Urelumab 1 mg + Nivolumab	Phase II: Urelumab 8 mg + Nivolumab	Phase II: Cohort A	Phase II: Cohort B
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	3	28	20	8
Units: number of patients				
Investigations: Transaminases increased	0	1	1	0

Statistical analyses

No statistical analyses for this end point

Secondary: Nivolumab-related SAEs from Phase II by cohort (number of SAEs)

End point title	Nivolumab-related SAEs from Phase II by cohort (number of SAEs)
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End point description:

SAEs from phase II by cohort that were likely or related to Nivolumab

End point type	Secondary
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End point timeframe:

Adverse events were assessed continuously during the study and for a minimum of 100 days following the last dose of study treatment.

End point values	Phase I: Urelumab 1 mg + Nivolumab	Phase II: Urelumab 8 mg + Nivolumab	Phase II: Cohort A	Phase II: Cohort B
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	3	28	20	8
Units: Number of SAEs				
Investigations: Transaminases increased	0	1	1	0

Statistical analyses

No statistical analyses for this end point

Secondary: AES leading to a temporary or permanent discontinuation of study therapy by organ class (SOC) and Preferred Term (PT) (number of patients)

End point title	AES leading to a temporary or permanent discontinuation of study therapy by organ class (SOC) and Preferred Term (PT) (number of patients)
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End point description:

List of Adverse Events that lead to a temporary or permanent discontinuation of the study therapy by study phase and cohort.

End point type	Secondary
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End point timeframe:

During the clinical trial

End point values	Phase I: Urelumab 1 mg + Nivolumab	Phase II: Urelumab 8 mg + Nivolumab	Phase II: Cohort A	Phase II: Cohort B
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	3	28	20	8
Units: number of patients				
Blood and lymphatic SD: Thrombocytopenia	0	2	1	1
General disorders: Disease progression	0	1	1	0
General disorders: Oedema	0	1	1	0
General disorders: Pyrexia	0	1	1	0
Infections and infestations: Infection	0	1	1	0
Infections and infestations: Pneumonia	0	2	2	0
Infections and infestations: Cellulitis	0	1	0	1
Injury: Biliary anastomosis complication	0	1	1	0
Injury: Craniocerebral injury	0	1	1	0
Injury: Tracheal obstruction	0	1	1	0
Investigations: Bleeding time	0	1	0	1
Investigations: Transaminases increased	0	2	1	1
Respiratory, thoracic disorders: Pneumonia	0	1	1	0

Statistical analyses

No statistical analyses for this end point

Secondary: AES leading to a temporary or permanent discontinuation of study therapy by organ class (SOC) and Preferred Term (PT) (number of AEs)

End point title	AES leading to a temporary or permanent discontinuation of study therapy by organ class (SOC) and Preferred Term (PT) (number of AEs)
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End point description:

List of Adverse Events that lead to a temporary or permanent discontinuation of the study therapy by study phase and cohort.

End point type	Secondary
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End point timeframe:

During the clinical trial

End point values	Phase I: Urelumab 1 mg + Nivolumab	Phase II: Urelumab 8 mg + Nivolumab	Phase II: Cohort A	Phase II: Cohort B
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	3	28	20	8
Units: Number of AEs				
Blood and lymphatic SD: Thrombocytopenia	0	2	1	1
General disorders: Disease progression	0	1	1	0
General disorders: Oedema	0	1	1	0
General disorders: Pyrexia	0	1	1	0
Infections and infestations: Infection	0	1	1	0
Infections and infestations: Pneumonia	0	2	2	0
Infections and infestations: Cellulitis	0	1	0	1
Injury: Biliary anastomosis complication	0	1	1	0
Injury: Craniocerebral injury	0	1	1	0
Injury: Tracheal obstruction	0	1	1	0
Investigations: Bleeding time	0	1	0	1
Investigations: Transaminases increased	0	2	1	1
Respiratory, thoracic disorders: Pneumonia	0	1	1	0

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Regarding safety assessments, adverse events were assessed continuously during the study and for a minimum of 100 days following the last dose of study treatment.

Adverse event reporting additional description:

Evaluated according to the National Cancer Institute (NCI) Common Terminology Criter.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.1
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Reporting groups

Reporting group title	Phase I
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Reporting group description:

Urelumab 1 mg (Cycle 1, Cycle 3) + Nivolumab 240mg (Cycle 2), 480 mg (Cycle 4)

Reporting group title	Phase II Cohort A
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Reporting group description:

Cohort A recruited anti PD1/PDL1 naïve patients presenting tumor types sensitive to PD1/PDL1 blockade.

Reporting group title	Phase II: Cohort B
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Reporting group description:

cohort B included patients with tumors that have progressed on previous PD1/ PDL1 blockade

Serious adverse events	Phase I	Phase II Cohort A	Phase II: Cohort B
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 3 (0.00%)	11 / 20 (55.00%)	3 / 8 (37.50%)
number of deaths (all causes)	0	7	1
number of deaths resulting from adverse events	0	5	1
Investigations			
Transaminases increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Biliary anastomosis complication			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	0 / 8 (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
Tracheal obstruction			

subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	0 / 8 (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
Cardiac disorders			
Pericardial effusion			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	0 / 8 (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
Nervous system disorders			
Clumsiness			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	0 / 8 (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
General disorders and administration site conditions			
Condition aggravated			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	0 / 8 (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
Disease progression			
subjects affected / exposed	0 / 3 (0.00%)	3 / 20 (15.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 3	0 / 1
Pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	0 / 8 (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
Pyrexia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	0 / 8 (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
Pneumonia			
subjects affected / exposed	0 / 3 (0.00%)	4 / 20 (20.00%)	0 / 8 (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

Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 20 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	0 / 8 (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
Constipation			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	0 / 8 (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			
Laryngeal oedema			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	0 / 8 (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
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	0 / 8 (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
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 3 (0.00%)	0 / 20 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	0 / 8 (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			
Infection			

subjects affected / exposed	0 / 3 (0.00%)	2 / 20 (10.00%)	0 / 8 (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

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Phase I	Phase II Cohort A	Phase II: Cohort B
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	20 / 20 (100.00%)	7 / 8 (87.50%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			
Orthostatic hypotension			
subjects affected / exposed	1 / 3 (33.33%)	0 / 20 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Superior vena cava syndrome			
subjects affected / exposed	1 / 3 (33.33%)	0 / 20 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Thrombosis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 20 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Hypertension			
subjects affected / exposed	0 / 3 (0.00%)	3 / 20 (15.00%)	0 / 8 (0.00%)
occurrences (all)	0	7	0
Hypotension			
subjects affected / exposed	0 / 3 (0.00%)	2 / 20 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Bleeding			
subjects affected / exposed	0 / 3 (0.00%)	0 / 20 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Condition aggravated			

subjects affected / exposed	1 / 3 (33.33%)	0 / 20 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Fatigue			
subjects affected / exposed	2 / 3 (66.67%)	13 / 20 (65.00%)	2 / 8 (25.00%)
occurrences (all)	5	16	2
Oedema			
subjects affected / exposed	1 / 3 (33.33%)	1 / 20 (5.00%)	1 / 8 (12.50%)
occurrences (all)	1	1	1
Sense of oppression			
subjects affected / exposed	1 / 3 (33.33%)	0 / 20 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Application site pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Asthenia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 20 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Chest pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	1 / 8 (12.50%)
occurrences (all)	0	1	2
Malaise			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Mucosal inflammation			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Pyrexia			
subjects affected / exposed	0 / 3 (0.00%)	5 / 20 (25.00%)	4 / 8 (50.00%)
occurrences (all)	0	6	7
Suprapubic pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Reproductive system and breast			

disorders			
Genital dysaesthesia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Vaginal haemorrhage			
subjects affected / exposed	0 / 3 (0.00%)	0 / 20 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 3 (0.00%)	2 / 20 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Dyspnoea			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Haemoptysis			
subjects affected / exposed	0 / 3 (0.00%)	2 / 20 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	4	0
Pneumonia aspiration			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Productive cough			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Sputum retention			
subjects affected / exposed	0 / 3 (0.00%)	2 / 20 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	3	0
Psychiatric disorders			
Affect lability			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Anxiety			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Depressed mood			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0

Depression			
subjects affected / exposed	0 / 3 (0.00%)	5 / 20 (25.00%)	0 / 8 (0.00%)
occurrences (all)	0	6	0
Insomnia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Nervousness			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Persistent depressive disorder			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Confusional state			
subjects affected / exposed	0 / 3 (0.00%)	0 / 20 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Investigations			
ALT increased			
subjects affected / exposed	1 / 3 (33.33%)	3 / 20 (15.00%)	1 / 8 (12.50%)
occurrences (all)	1	3	1
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 3 (33.33%)	3 / 20 (15.00%)	2 / 8 (25.00%)
occurrences (all)	1	5	2
Blood thyroid stimulating hormone decreased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 20 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Adjusted calcium decreased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	1 / 8 (12.50%)
occurrences (all)	0	1	1
Amylase increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Blood creatinine increased			

subjects affected / exposed	0 / 3 (0.00%)	2 / 20 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Blood glucose increased			
subjects affected / exposed	0 / 3 (0.00%)	2 / 20 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Blood magnesium decreased			
subjects affected / exposed	0 / 3 (0.00%)	2 / 20 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Lipase increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Transaminases increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Weight decreased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	1 / 8 (12.50%)
occurrences (all)	0	1	1
Bleeding time			
subjects affected / exposed	0 / 3 (0.00%)	0 / 20 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Blood bilirubin increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 20 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Craniocerebral injury			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Injury			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Thermal burn			

subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 20 (5.00%) 1	0 / 8 (0.00%) 0
Upper limb fracture subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 20 (5.00%) 1	0 / 8 (0.00%) 0
Contusion subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 20 (0.00%) 0	1 / 8 (12.50%) 1
Congenital, familial and genetic disorders			
Keratosis follicular subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 20 (5.00%) 1	0 / 8 (0.00%) 0
Cardiac disorders			
Tachycardia subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	2 / 20 (10.00%) 5	3 / 8 (37.50%) 4
Artrial flutter subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	2 / 20 (10.00%) 2	0 / 8 (0.00%) 0
Pericardial effusion subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 20 (5.00%) 1	0 / 8 (0.00%) 0
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	2 / 20 (10.00%) 2	1 / 8 (12.50%) 1
Headache subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 20 (5.00%) 1	0 / 8 (0.00%) 0
Hepatic encephalopathy subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 20 (5.00%) 1	0 / 8 (0.00%) 0
Myoclonus subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 20 (5.00%) 1	0 / 8 (0.00%) 0
Neuralgia			

subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Paraesthesia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Seizure			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Somnolence			
subjects affected / exposed	0 / 3 (0.00%)	2 / 20 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Syncope			
subjects affected / exposed	0 / 3 (0.00%)	2 / 20 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 3 (66.67%)	4 / 20 (20.00%)	2 / 8 (25.00%)
occurrences (all)	5	6	2
Leukocytosis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	1 / 8 (12.50%)
occurrences (all)	0	1	1
Neutrophilia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	2 / 8 (25.00%)
occurrences (all)	0	1	2
Thrombocytopenia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 20 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	3	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 3 (33.33%)	4 / 20 (20.00%)	0 / 8 (0.00%)
occurrences (all)	1	6	0
Diarrhoea			

subjects affected / exposed	1 / 3 (33.33%)	4 / 20 (20.00%)	2 / 8 (25.00%)
occurrences (all)	1	6	3
Gastrointestinal pain			
subjects affected / exposed	1 / 3 (33.33%)	2 / 20 (10.00%)	0 / 8 (0.00%)
occurrences (all)	1	2	0
Abdominal distension			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Abdominal pain upper			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Ascites			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Constipation			
subjects affected / exposed	0 / 3 (0.00%)	8 / 20 (40.00%)	2 / 8 (25.00%)
occurrences (all)	0	13	2
Flatulence			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Gastritis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	0 / 3 (0.00%)	4 / 20 (20.00%)	0 / 8 (0.00%)
occurrences (all)	0	5	0
Pancreatitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Rectal haemorrhage			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Vomiting			

subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	3 / 20 (15.00%) 7	2 / 8 (25.00%) 3
Abnormal faeces subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 20 (0.00%) 0	1 / 8 (12.50%) 1
Skin and subcutaneous tissue disorders			
Dermatitis allergic subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 20 (5.00%) 1	0 / 8 (0.00%) 0
Psoriasis subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 20 (5.00%) 1	0 / 8 (0.00%) 0
Skin lesion subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 20 (5.00%) 1	0 / 8 (0.00%) 0
Wound subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 20 (5.00%) 1	0 / 8 (0.00%) 0
Cold sweat subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 20 (0.00%) 0	1 / 8 (12.50%) 1
Dermatitis contact subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 20 (0.00%) 0	1 / 8 (12.50%) 1
Pruritus subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 20 (0.00%) 0	1 / 8 (12.50%) 1
Renal and urinary disorders			
Nocturia subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 20 (5.00%) 1	0 / 8 (0.00%) 0
Polaquyuria subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 20 (5.00%) 1	0 / 8 (0.00%) 0
Urinary retention			

subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 20 (5.00%) 1	0 / 8 (0.00%) 0
Oliguria subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 20 (0.00%) 0	1 / 8 (12.50%) 1
Endocrine disorders Adrenal insufficiency subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	2 / 20 (10.00%) 4	1 / 8 (12.50%) 1
Hypothyroidism subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	3 / 20 (15.00%) 5	2 / 8 (25.00%) 2
Musculoskeletal and connective tissue disorders Flank pain subjects affected / exposed occurrences (all)	2 / 3 (66.67%) 2	1 / 20 (5.00%) 1	0 / 8 (0.00%) 0
Temporomandibular joint syndrome subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	0 / 20 (0.00%) 0	0 / 8 (0.00%) 0
Back pain subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 20 (5.00%) 2	1 / 8 (12.50%) 1
Joint pain subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 20 (5.00%) 1	0 / 8 (0.00%) 0
Musculoskeletal chest pain subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 20 (5.00%) 1	0 / 8 (0.00%) 0
Musculoskeletal pain subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	2 / 20 (10.00%) 2	0 / 8 (0.00%) 0
Myalgia subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 20 (5.00%) 1	0 / 8 (0.00%) 0
Neck pain			

subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	2 / 20 (10.00%) 2	1 / 8 (12.50%) 1
Groin pain subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 20 (0.00%) 0	2 / 8 (25.00%) 3
Pain in extremity subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 20 (0.00%) 0	1 / 8 (12.50%) 1
Infections and infestations			
Adenoviral upper respiratory infection subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	2 / 20 (10.00%) 2	0 / 8 (0.00%) 0
Infection subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 20 (5.00%) 2	0 / 8 (0.00%) 0
Nasopharyngitis subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 20 (5.00%) 1	0 / 8 (0.00%) 0
Pneumonia subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 20 (5.00%) 2	0 / 8 (0.00%) 0
Cellulitis subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 20 (0.00%) 0	1 / 8 (12.50%) 1
Skin infection subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 20 (0.00%) 0	1 / 8 (12.50%) 1
Metabolism and nutrition disorders			
Cachexia subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 20 (5.00%) 1	0 / 8 (0.00%) 0
Decreased appetite subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	7 / 20 (35.00%) 8	2 / 8 (25.00%) 2
Hyponatraemia			

subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 November 2018	Versión 2.0 Changes in the inclusion criteria Changes in the criteria for permanent treatment discontinuation due to toxicity

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.

Among the limitations of the study, the small sample size of this type of phase I/II study is the main one. The inferential analyses could not be done because available sample size was too small, especially in Phase I.

Notes: