

**Clinical trial results:****A Phase 3 Randomized, Double-Blind Clinical Study of Pembrolizumab + Epacadostat vs Pembrolizumab + Placebo as a Treatment for Recurrent or Progressive Metastatic Urothelial Carcinoma in Patients who have Failed a First-Line Platinum-containing Chemotherapy Regimen for Advanced/Metastatic Disease (KEYNOTE-698/ECHO-303)****Summary**

EudraCT number	2017-002310-31
Trial protocol	DE DK GB NL ES HU FR IT
Global end of trial date	27 July 2020

Results information

Result version number	v1 (current)
This version publication date	18 November 2021
First version publication date	18 November 2021

Trial information**Trial identification**

Sponsor protocol code	KEYNOTE-698/ECHO-303
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Incyte
Sponsor organisation address	1801 Augustine Cutoff drive, Wilmington, United States, 19803
Public contact	Study Director, Incyte Corporation, +1 8554633463, medinfo@incyte.com
Scientific contact	Study Director, Incyte Corporation, +1 8554633463, medinfo@incyte.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 July 2020
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	27 July 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study was to evaluate the efficacy and safety of pembrolizumab + epacadostat vs pembrolizumab + placebo as a treatment for recurrent or progressive metastatic urothelial carcinoma in patients who have failed a first-line platinum-containing chemotherapy regimen for advanced/metastatic disease.

Protection of trial subjects:

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator, including, but not limited to, the items outlined below. -Nausea/vomiting: Nausea and vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Subjects should be strongly encouraged to maintain liberal oral fluid intake. -Anti-infectives: Subjects with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating investigator for a given infectious condition, according to standard institutional practice.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 December 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 9
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	Denmark: 6
Country: Number of subjects enrolled	Spain: 11
Country: Number of subjects enrolled	France: 6
Country: Number of subjects enrolled	Ireland: 1
Country: Number of subjects enrolled	Israel: 9
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Japan: 2
Country: Number of subjects enrolled	Korea, Republic of: 5
Country: Number of subjects enrolled	Russian Federation: 9
Country: Number of subjects enrolled	Turkey: 17

Country: Number of subjects enrolled	Taiwan: 4
Country: Number of subjects enrolled	United States: 2
Worldwide total number of subjects	84
EEA total number of subjects	25

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)	33
From 65 to 84 years	50
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 82 centers in 16 countries.

Pre-assignment

Screening details:

Participants were stratified by the Bellmunt score (0 vs 1 vs ≥ 2) and by programmed deathligand 1 expression (combined positive score [CPS] ≥ 10 vs CPS < 10), as assessed by central laboratory, and then randomized 1:1 to either pembrolizumab + epacadostat or pembrolizumab + placebo.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Pembrolizumab 200 mg Q3W + Epacadostat 100 mg BID

Arm description:

Pembrolizumab administered intravenously Day 1 of each cycle every 3 weeks. Epacadostat administered orally twice daily.

Arm type	Experimental
Investigational medicinal product name	epacadostat
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

100 mg

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

Dosage and administration details:

200 mg

Arm title	Pembrolizumab 200 mg Q3W + placebo BID
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Arm description:

Pembrolizumab administered intravenously Day 1 of each cycle every 3 weeks. Matching placebo administered orally twice daily.

Arm type	Placebo
Investigational medicinal product name	pembrolizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intracavernous use

Dosage and administration details:

200 mg

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

Dosage and administration details:

palcebo

Number of subjects in period 1	Pembrolizumab 200 mg Q3W + Epacadostat 100 mg BID	Pembrolizumab 200 mg Q3W + placebo BID
Started	42	42
Intention-to-Treat (ITT)	42	42
All Participants as Treated (APaT)	42	41
Completed	23	28
Not completed	19	14
Adverse event, serious fatal	13	13
Consent withdrawn by subject	3	1
Physician decision	3	-

Baseline characteristics

Reporting groups

Reporting group title	Pembrolizumab 200 mg Q3W + Epacadostat 100 mg BID
Reporting group description:	Pembrolizumab administered intravenously Day 1 of each cycle every 3 weeks. Epacadostat administered orally twice daily.
Reporting group title	Pembrolizumab 200 mg Q3W + placebo BID
Reporting group description:	Pembrolizumab administered intravenously Day 1 of each cycle every 3 weeks. Matching placebo administered orally twice daily.

Reporting group values	Pembrolizumab 200 mg Q3W + Epacadostat 100 mg BID	Pembrolizumab 200 mg Q3W + placebo BID	Total
Number of subjects	42	42	84
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	15	18	33
From 65-84 years	26	24	50
85 years and over	1	0	1
Age Continuous Units: years			
arithmetic mean	67.9	65.2	-
standard deviation	± 8.7	± 10.0	-
Sex: Female, Male Units:			
Female	7	5	12
Male	35	37	72
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	38	37	75
Unknown or Not Reported	4	4	8
Missing	0	1	1
Race/Ethnicity, Customized Units: Subjects			
Asian	5	6	11
White	35	32	67
Missing	2	4	6
Metastasis Status at Screening Units: Subjects			

Metastatic	35	40	75
Advanced/Unresectable	7	2	9

End points

End points reporting groups

Reporting group title	Pembrolizumab 200 mg Q3W + Epacadostat 100 mg BID
Reporting group description:	Pembrolizumab administered intravenously Day 1 of each cycle every 3 weeks. Epacadostat administered orally twice daily.
Reporting group title	Pembrolizumab 200 mg Q3W + placebo BID
Reporting group description:	Pembrolizumab administered intravenously Day 1 of each cycle every 3 weeks. Matching placebo administered orally twice daily.

Primary: Objective response rate (ORR) with pembrolizumab + epacadostat versus pembrolizumab + placebo

End point title	Objective response rate (ORR) with pembrolizumab + epacadostat versus pembrolizumab + placebo ^[1]
End point description:	ORR was defined as the percentage of participants who had a complete response (CR), disappearance of all target lesions or partial response (PR), $\geq 30\%$ decrease in the sum of the longest diameter of target lesions per RECIST v1.1 by investigator determination.
End point type	Primary
End point timeframe:	up to 9 weeks +14 days

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analyses for this end point

End point values	Pembrolizumab 200 mg Q3W + Epacadostat 100 mg BID	Pembrolizumab 200 mg Q3W + placebo BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	42		
Units: percentage of participants				
number (confidence interval 95%)	21.4 (12.49 to 43.26)	9.5 (3.11 to 26.06)		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety and Tolerability of pembrolizumab + epacadostat versus pembrolizumab + placebo as measured by Number of Participants Experiencing Adverse Events (AEs)

End point title	Safety and Tolerability of pembrolizumab + epacadostat versus pembrolizumab + placebo as measured by Number of Participants Experiencing Adverse Events (AEs)
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End point description:

AE is defined as any untoward medical occurrence in a patient or clinical study participant, temporally

associated with the use of study treatment, whether or not considered related to the study treatment.

End point type	Secondary
End point timeframe:	
Up to 8 months	

End point values	Pembrolizumab 200 mg Q3W + Epcadostat 100 mg BID	Pembrolizumab 200 mg Q3W + placebo BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	41		
Units: Participants	42	39		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety and Tolerability of pembrolizumab + epacadostat versus pembrolizumab + placebo as Measured by Number of Participants Discontinuing Study Treatment Due to AE

End point title	Safety and Tolerability of pembrolizumab + epacadostat versus pembrolizumab + placebo as Measured by Number of Participants Discontinuing Study Treatment Due to AE
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End point description:

AE is defined as any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment.

End point type	Secondary
End point timeframe:	
Up to 8 months	

End point values	Pembrolizumab 200 mg Q3W + Epcadostat 100 mg BID	Pembrolizumab 200 mg Q3W + placebo BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	41		
Units: Participants	4	6		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 8 Months

Adverse event reporting additional description:

AE additional description

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	22
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Reporting groups

Reporting group title	Pembrolizumab 200 mg Q3W + Epacadostat 100 mg BID
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Reporting group description:

Pembrolizumab administered intravenously Day 1 of each cycle every 3 weeks. Epacadostat administered orally twice daily.

Reporting group title	Total
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Reporting group description:

Total

Reporting group title	Pembrolizumab Q3W 200 mg + Placebo BID
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Reporting group description:

Pembrolizumab administered intravenously Day 1 of each cycle every 3 weeks. Matching placebo administered orally twice daily.

Serious adverse events	Pembrolizumab 200 mg Q3W + Epacadostat 100 mg BID	Total	Pembrolizumab Q3W 200 mg + Placebo BID
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 42 (52.38%)	38 / 83 (45.78%)	16 / 41 (39.02%)
number of deaths (all causes)	14	32	18
number of deaths resulting from adverse events	7	14	7
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 42 (2.38%)	1 / 83 (1.20%)	0 / 41 (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
Malignant neoplasm progression			
subjects affected / exposed	9 / 42 (21.43%)	15 / 83 (18.07%)	6 / 41 (14.63%)
occurrences causally related to treatment / all	0 / 10	0 / 16	0 / 6
deaths causally related to treatment / all	0 / 6	0 / 12	0 / 6
Squamous cell carcinoma			

subjects affected / exposed	1 / 42 (2.38%)	1 / 83 (1.20%)	0 / 41 (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
General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	1 / 42 (2.38%)	1 / 83 (1.20%)	0 / 41 (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
Immune system disorders			
Haemophagocytic lymphohistiocytosis			
subjects affected / exposed	0 / 42 (0.00%)	1 / 83 (1.20%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	0 / 42 (0.00%)	1 / 83 (1.20%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Bronchitis chronic			
subjects affected / exposed	1 / 42 (2.38%)	1 / 83 (1.20%)	0 / 41 (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
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 42 (2.38%)	1 / 83 (1.20%)	0 / 41 (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
Organising pneumonia			
subjects affected / exposed	1 / 42 (2.38%)	1 / 83 (1.20%)	0 / 41 (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
Pneumonitis			

subjects affected / exposed	1 / 42 (2.38%)	1 / 83 (1.20%)	0 / 41 (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
Pneumonia aspiration			
subjects affected / exposed	1 / 42 (2.38%)	1 / 83 (1.20%)	0 / 41 (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
Pulmonary embolism			
subjects affected / exposed	1 / 42 (2.38%)	1 / 83 (1.20%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Investigations			
Amylase increased			
subjects affected / exposed	1 / 42 (2.38%)	1 / 83 (1.20%)	0 / 41 (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
Injury, poisoning and procedural complications			
Radius fracture			
subjects affected / exposed	0 / 42 (0.00%)	1 / 83 (1.20%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract stoma complication			
subjects affected / exposed	0 / 42 (0.00%)	1 / 83 (1.20%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 42 (2.38%)	1 / 83 (1.20%)	0 / 41 (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
Myocardial infarction			
subjects affected / exposed	1 / 42 (2.38%)	2 / 83 (2.41%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1

Nervous system disorders			
Ataxia			
subjects affected / exposed	1 / 42 (2.38%)	1 / 83 (1.20%)	0 / 41 (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
Hypoxic-ischaemic encephalopathy			
subjects affected / exposed	0 / 42 (0.00%)	1 / 83 (1.20%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral motor neuropathy			
subjects affected / exposed	1 / 42 (2.38%)	1 / 83 (1.20%)	0 / 41 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 42 (2.38%)	2 / 83 (2.41%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diverticular perforation			
subjects affected / exposed	1 / 42 (2.38%)	1 / 83 (1.20%)	0 / 41 (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
Gastrointestinal disorder			
subjects affected / exposed	0 / 42 (0.00%)	1 / 83 (1.20%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	2 / 42 (4.76%)	2 / 83 (2.41%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			

subjects affected / exposed	1 / 42 (2.38%)	1 / 83 (1.20%)	0 / 41 (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
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 42 (2.38%)	1 / 83 (1.20%)	0 / 41 (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
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 42 (0.00%)	1 / 83 (1.20%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic kidney disease			
subjects affected / exposed	0 / 42 (0.00%)	1 / 83 (1.20%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	2 / 42 (4.76%)	3 / 83 (3.61%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydronephrosis			
subjects affected / exposed	1 / 42 (2.38%)	1 / 83 (1.20%)	0 / 41 (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
Urinary retention			
subjects affected / exposed	0 / 42 (0.00%)	1 / 83 (1.20%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bacteraemia			
subjects affected / exposed	1 / 42 (2.38%)	1 / 83 (1.20%)	0 / 41 (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

Bronchitis			
subjects affected / exposed	0 / 42 (0.00%)	1 / 83 (1.20%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 42 (0.00%)	1 / 83 (1.20%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	1 / 42 (2.38%)	1 / 83 (1.20%)	0 / 41 (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
Sepsis			
subjects affected / exposed	1 / 42 (2.38%)	1 / 83 (1.20%)	0 / 41 (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
Urinary tract infection			
subjects affected / exposed	3 / 42 (7.14%)	6 / 83 (7.23%)	3 / 41 (7.32%)
occurrences causally related to treatment / all	0 / 5	0 / 10	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	1 / 42 (2.38%)	1 / 83 (1.20%)	0 / 41 (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

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

Non-serious adverse events	Pembrolizumab 200 mg Q3W + Epacadostat 100 mg BID	Total	Pembrolizumab Q3W 200 mg + Placebo BID
Total subjects affected by non-serious adverse events			
subjects affected / exposed	39 / 42 (92.86%)	74 / 83 (89.16%)	35 / 41 (85.37%)
Investigations			

Amylase increased subjects affected / exposed occurrences (all)	4 / 42 (9.52%) 4	6 / 83 (7.23%) 8	2 / 41 (4.88%) 4
Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	3 / 42 (7.14%) 3	4 / 83 (4.82%) 4	1 / 41 (2.44%) 1
Blood creatinine increased subjects affected / exposed occurrences (all)	4 / 42 (9.52%) 4	7 / 83 (8.43%) 7	3 / 41 (7.32%) 3
Lipase increased subjects affected / exposed occurrences (all)	5 / 42 (11.90%) 10	7 / 83 (8.43%) 14	2 / 41 (4.88%) 4
Weight decreased subjects affected / exposed occurrences (all)	4 / 42 (9.52%) 4	4 / 83 (4.82%) 4	0 / 41 (0.00%) 0
Nervous system disorders Headache subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1	5 / 83 (6.02%) 5	4 / 41 (9.76%) 4
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	11 / 42 (26.19%) 15	20 / 83 (24.10%) 24	9 / 41 (21.95%) 9
Lymphopenia subjects affected / exposed occurrences (all)	3 / 42 (7.14%) 3	5 / 83 (6.02%) 9	2 / 41 (4.88%) 6
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all)	4 / 42 (9.52%) 5	11 / 83 (13.25%) 15	7 / 41 (17.07%) 10
Chest pain subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1	5 / 83 (6.02%) 5	4 / 41 (9.76%) 4
Fatigue subjects affected / exposed occurrences (all)	13 / 42 (30.95%) 13	18 / 83 (21.69%) 18	5 / 41 (12.20%) 5

Oedema peripheral subjects affected / exposed occurrences (all)	3 / 42 (7.14%) 3	4 / 83 (4.82%) 4	1 / 41 (2.44%) 1
Pyrexia subjects affected / exposed occurrences (all)	7 / 42 (16.67%) 7	10 / 83 (12.05%) 10	3 / 41 (7.32%) 3
Gastrointestinal disorders			
Abdominal pain subjects affected / exposed occurrences (all)	6 / 42 (14.29%) 7	8 / 83 (9.64%) 9	2 / 41 (4.88%) 2
Constipation subjects affected / exposed occurrences (all)	14 / 42 (33.33%) 16	20 / 83 (24.10%) 22	6 / 41 (14.63%) 6
Diarrhoea subjects affected / exposed occurrences (all)	9 / 42 (21.43%) 15	13 / 83 (15.66%) 20	4 / 41 (9.76%) 5
Dry mouth subjects affected / exposed occurrences (all)	3 / 42 (7.14%) 3	4 / 83 (4.82%) 5	1 / 41 (2.44%) 2
Dyspepsia subjects affected / exposed occurrences (all)	3 / 42 (7.14%) 3	3 / 83 (3.61%) 3	0 / 41 (0.00%) 0
Nausea subjects affected / exposed occurrences (all)	10 / 42 (23.81%) 12	16 / 83 (19.28%) 22	6 / 41 (14.63%) 10
Vomiting subjects affected / exposed occurrences (all)	6 / 42 (14.29%) 7	10 / 83 (12.05%) 14	4 / 41 (9.76%) 7
Respiratory, thoracic and mediastinal disorders			
Cough subjects affected / exposed occurrences (all)	5 / 42 (11.90%) 5	7 / 83 (8.43%) 7	2 / 41 (4.88%) 2
Skin and subcutaneous tissue disorders			
Pruritus subjects affected / exposed occurrences (all)	8 / 42 (19.05%) 9	12 / 83 (14.46%) 16	4 / 41 (9.76%) 7

Rash			
subjects affected / exposed	9 / 42 (21.43%)	13 / 83 (15.66%)	4 / 41 (9.76%)
occurrences (all)	11	17	6
Rash maculo-papular			
subjects affected / exposed	3 / 42 (7.14%)	3 / 83 (3.61%)	0 / 41 (0.00%)
occurrences (all)	3	3	0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	4 / 42 (9.52%)	5 / 83 (6.02%)	1 / 41 (2.44%)
occurrences (all)	4	5	1
Haematuria			
subjects affected / exposed	8 / 42 (19.05%)	11 / 83 (13.25%)	3 / 41 (7.32%)
occurrences (all)	9	12	3
Renal impairment			
subjects affected / exposed	4 / 42 (9.52%)	5 / 83 (6.02%)	1 / 41 (2.44%)
occurrences (all)	4	5	1
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	4 / 42 (9.52%)	5 / 83 (6.02%)	1 / 41 (2.44%)
occurrences (all)	4	5	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 42 (9.52%)	6 / 83 (7.23%)	2 / 41 (4.88%)
occurrences (all)	4	7	3
Back pain			
subjects affected / exposed	4 / 42 (9.52%)	8 / 83 (9.64%)	4 / 41 (9.76%)
occurrences (all)	4	9	5
Groin pain			
subjects affected / exposed	4 / 42 (9.52%)	4 / 83 (4.82%)	0 / 41 (0.00%)
occurrences (all)	4	4	0
Musculoskeletal pain			
subjects affected / exposed	4 / 42 (9.52%)	6 / 83 (7.23%)	2 / 41 (4.88%)
occurrences (all)	5	7	2
Infections and infestations			
Upper respiratory tract infection			

subjects affected / exposed occurrences (all)	3 / 42 (7.14%) 4	3 / 83 (3.61%) 4	0 / 41 (0.00%) 0
Urinary tract infection subjects affected / exposed occurrences (all)	7 / 42 (16.67%) 13	13 / 83 (15.66%) 22	6 / 41 (14.63%) 9
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	13 / 42 (30.95%) 15	19 / 83 (22.89%) 21	6 / 41 (14.63%) 6
Hyperglycaemia subjects affected / exposed occurrences (all)	4 / 42 (9.52%) 5	4 / 83 (4.82%) 5	0 / 41 (0.00%) 0
Hypoalbuminaemia subjects affected / exposed occurrences (all)	3 / 42 (7.14%) 3	4 / 83 (4.82%) 4	1 / 41 (2.44%) 1
Hyponatraemia subjects affected / exposed occurrences (all)	3 / 42 (7.14%) 3	3 / 83 (3.61%) 3	0 / 41 (0.00%) 0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 December 2017	More frequent pregnancy testing and extend the prohibition of live vaccines to 3 months after the end of treatment
08 March 2018	To align HIV, pregnancy testing, and other modifications with regulatory requirements in Germany
12 June 2018	Enrollment was permanently stopped on 02May2018 as a strategic decision. For participants who are considered to be obtaining ongoing clinical benefit, continued study treatment will be at the discretion of the investigator after a discussion with the participant of the results from KEYNOTE-252/ECHO-301 study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported