Clinical trial results:
A Phase 2, Randomized, Double-Blind Study of Pembrolizumab (MK-3475) plus Epacadostat (INCB024360) Versus Pembrolizumab plus Placebo as First-Line Treatment in Patients with Metastatic Non-Small Cell Lung Cancer Expressing High Levels of PD-L1

Summary

EudraCT number	2017-001841-28
Trial protocol	GB DK EE ES PL IT
Global end of trial date	09 November 2020

Results information

Result version number	v1 (current)
This version publication date	16 December 2021
First version publication date	16 December 2021

Trial information

Trial identification

Sponsor protocol code	KEYNOTE-654-05/ECHO-305-05

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Incyte Corporation
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	09 November 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 November 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to evaluate the efficacy and safety of pembrolizumab plus epacadostat compared to pembrolizumab plus placebo as first-line treatment in participants with metastatic non-small cell lung cancer (NSCLC) expressing high levels of programmed cell death ligand 1 (PD-L1).

Protection of trial subjects:

This study was conducted in conformance with applicable country or local requirements regarding ethical committee review, informed consent, and other statutes or regulations regarding the protection of the rights and welfare of human participants in biomedical research.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 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: 2
Country: Number of subjects enrolled	Canada: 12
Country: Number of subjects enrolled	Switzerland: 7
Country: Number of subjects enrolled	Denmark: 7
Country: Number of subjects enrolled	Spain: 16
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Ireland: 1
Country: Number of subjects enrolled	Israel: 7
Country: Number of subjects enrolled	Italy: 5
Country: Number of subjects enrolled	Japan: 29
Country: Number of subjects enrolled	Korea, Republic of: 10
Country: Number of subjects enrolled	Malaysia: 8
Country: Number of subjects enrolled	Poland: 3
Country: Number of subjects enrolled	Russian Federation: 6
Country: Number of subjects enrolled	Turkey: 14
Country: Number of subjects enrolled	Ukraine: 12
Country: Number of subjects enrolled	United States: 14
Worldwide total number of subjects	154
EEA total number of subjects	32

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)	71
From 65 to 84 years	80
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

A total of 154 participants were randomized in 1:1 to either combination (Pembrolizumab+Epacadostat) and control (Pembrolizumab+Placebo) groups. As of Amendment 05, study design was changed to unblinded, open-label, and single-arm (epacadostat and placebo were removed).

Pre-assignment

Screening details:

A total of 154 participants were randomized and 152 participants received study treatment.

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, Carer, Data analyst

Arms

Are arms mutually exclusive?	Yes
Arm title	Pembrolizumab + Epacadostat

Arm description:

Participants received pembrolizumab 200 mg as an intravenous (IV) infusion, every three weeks (Q3W) starting on Day 1 of each cycle for up to 35 administrations in combination with epacadostat 100 mg orally, twice daily. Epacodostat administration was discontinued after the implementation of protocol amendment 05.

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:

100mg twice a day

Investigational medicinal product name	pembroluzimab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

200mg every 3 weeks

Arm title	Pembrolizumab + Placebo

Arm description:

Participants received pembrolizumab 200 mg by IV infusion, Q3W starting on Day 1 of each cycle for up to 35 administrations in combination with matching placebo orally, twice daily. Placebo administration was discontinued after the implementation of protocol amendment 05.

Arm type	Active comparator
Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details: 100mg twice a day	
Investigational medicinal product name	pembroluzimab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:
200mg every 3 weeks

Number of subjects in period 1	Pembrolizumab + Epacadostat	Pembrolizumab + Placebo
Started	77	77
Completed	46	40
Not completed	31	37
Adverse event, serious fatal	21	28
Physician decision	7	6
Consent withdrawn by subject	3	1
Study terminated by sponsor	-	1
Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Pembrolizumab + Epacadostat
Reporting group description:	
Participants received pembrolizumab 200 mg as an intravenous (IV) infusion, every three weeks (Q3W) starting on Day 1 of each cycle for up to 35 administrations in combination with epacadostat 100 mg orally, twice daily. Epacodostat administration was discontinued after the implementation of protocol amendment 05.	
Reporting group title	Pembrolizumab + Placebo
Reporting group description:	
Participants received pembrolizumab 200 mg by IV infusion, Q3W starting on Day 1 of each cycle for up to 35 administrations in combination with matching placebo orally, twice daily. Placebo administration was discontinued after the implementation of protocol amendment 05.	

Reporting group values	Pembrolizumab + Epacadostat	Pembrolizumab + Placebo	Total
Number of subjects	77	77	154
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)	40	31	71
From 65-84 years	36	44	80
85 years and over	1	2	3
Age Continuous Units: years			
arithmetic mean	63.7	66.9	
standard deviation	± 9.5	± 10.1	-
Sex: Female, Male Units:			
Female	24	18	42
Male	53	59	112
Race/Ethnicity, Customized Units: Subjects			
Asian	25	23	48
White	52	54	106
Race/Ethnicity, Customized Units: Subjects			
Hispanic Or Latino	7	4	11
Not Hispanic Or Latino	66	73	139
Not Reported	3	0	3
Unknown	1	0	1

End points

End points reporting groups

Reporting group title	Pembrolizumab + Epacadostat
Reporting group description:	
Participants received pembrolizumab 200 mg as an intravenous (IV) infusion, every three weeks (Q3W) starting on Day 1 of each cycle for up to 35 administrations in combination with epacadostat 100 mg orally, twice daily. Epacodostat administration was discontinued after the implementation of protocol amendment 05.	
Reporting group title	Pembrolizumab + Placebo
Reporting group description:	
Participants received pembrolizumab 200 mg by IV infusion, Q3W starting on Day 1 of each cycle for up to 35 administrations in combination with matching placebo orally, twice daily. Placebo administration was discontinued after the implementation of protocol amendment 05.	

Primary: Objective response rate (ORR) of pembrolizumab plus epacadostat versus pembrolizumab plus placebo

End point title	Objective response rate (ORR) of pembrolizumab plus epacadostat versus pembrolizumab plus placebo
End point description:	
ORR is defined as the proportion of participants who have a confirmed complete response (CR) or partial response (PR) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 based on blinded independent central review (BICR).	
End point type	Primary
End point timeframe:	
Up to approximately 6 months	

End point values	Pembrolizumab + Epacadostat	Pembrolizumab + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	77		
Units: percentage of participants				
number (confidence interval 95%)	32.5 (22.2 to 44.1)	39.0 (28.0 to 50.8)		

Statistical analyses

Statistical analysis title	Stratified Miettinen and Nurminen method
Comparison groups	Pembrolizumab + Epacadostat v Pembrolizumab + Placebo
Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.8
Method	Stratified Miettinen and Nurminen method
Parameter estimate	Difference in Percentages
Point estimate	-6.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.5
upper limit	8.7

Secondary: Progression-free Survival (PFS) of Pembrolizumab + Epacadostat Versus Pembrolizumab + Placebo

End point title	Progression-free Survival (PFS) of Pembrolizumab + Epacadostat Versus Pembrolizumab + Placebo

End point description:

PFS is defined as the time from randomization to the first documented progressive disease per RECIST v1.1 based on BICR or death due to any cause, whichever occurs first.

End point type	Secondary

End point timeframe:

Up to approximately 36 months

End point values	Pembrolizumab + Epacadostat	Pembrolizumab + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	77		
Units: months				
median (confidence interval 95%)	6.7 (4.3 to 8.2)	6.2 (4.3 to 9.9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS) of Pembrolizumab + Epacadostat versus pembrolizumab + Placebo

End point title	Overall survival (OS) of Pembrolizumab + Epacadostat versus pembrolizumab + Placebo

End point description:

OS is defined as the time from randomization to death due to any cause.

End point type	Secondary

End point timeframe:

Up to approximately 36 months

End point values	Pembrolizumab + Epacadostat	Pembrolizumab + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	77		
Units: Months				
median (confidence interval 95%)	9.9999 (0.9999 to 99.999)	9.9999 (0.999999 to 99.9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response (DOR) of Pembrolizumab + Epacadostat Versus Pembrolizumab + Placebo

End point title	Duration of response (DOR) of Pembrolizumab + Epacadostat Versus Pembrolizumab + Placebo

End point description:

DOR is defined as the time from the earliest date of qualifying response until earliest date of disease progression per RECIST v1.1 or death from any cause, whichever comes first.

End point type	Secondary

End point timeframe:

Up to approximately 36 months

End point values	Pembrolizumab + Epacadostat	Pembrolizumab + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	77		
Units: Months				
median (full range (min-max))	6.2 (1.9 to 6.5)	6.66666 (1.9 to 8.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Adverse Events (AEs)

End point title	Number of Participants With Adverse Events (AEs)

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 37 months

End point values	Pembrolizumab + Epacadostat	Pembrolizumab + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	77		
Units: Participants	72	72		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Discontinued Study Drug due to AEs

End point title	Number of Participants Who Discontinued Study Drug due to AEs

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 37 months

End point values	Pembrolizumab + Epacadostat	Pembrolizumab + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	77		
Units: Participants	15	12		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 37 months

Adverse event reporting additional description:

The All Participants as Treated (APaT) population was used for the safety analysis and consisted of all randomized participants who received at least 1 dose of study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22

Reporting groups

Reporting group title	Pembrolizumab + Epacadostat

Reporting group description:

Pembrolizumab + Epacadostat
Participants received pembrolizumab 200 mg as an intravenous (IV) infusion, every three weeks (Q3W) starting on Day 1 of each cycle for up to 35 administrations in combination with epacadostat 100 mg orally, twice daily. Epacodostat administration was discontinued after the implementation of protocol amendment 05.

Reporting group title	Total

Reporting group description:

Total

Reporting group title	Pembrolizumab + Placebo

Reporting group description:

Participants received pembrolizumab 200 mg by IV infusion, Q3W starting on Day 1 of each cycle for up to 35 administrations in combination with matching placebo orally, twice daily. Placebo administration was discontinued after the implementation of protocol amendment 05.

Serious adverse events	Pembrolizumab + Epacadostat	Total	Pembrolizumab + Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	36 / 75 (48.00%)	71 / 152 (46.71%)	35 / 77 (45.45%)
number of deaths (all causes)	23	52	29
number of deaths resulting from adverse events	9	24	15
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon cancer			
subjects affected / exposed	1 / 75 (1.33%)	1 / 152 (0.66%)	0 / 77 (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
High-grade B-cell lymphoma			
subjects affected / exposed	0 / 75 (0.00%)	1 / 152 (0.66%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Malignant neoplasm progression			
subjects affected / exposed	6 / 75 (8.00%)	14 / 152 (9.21%)	8 / 77 (10.39%)
occurrences causally related to treatment / all	0 / 6	0 / 14	0 / 8
deaths causally related to treatment / all	0 / 4	0 / 11	0 / 7
Tumour pseudoprogression			
subjects affected / exposed	1 / 75 (1.33%)	1 / 152 (0.66%)	0 / 77 (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
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 75 (0.00%)	2 / 152 (1.32%)	2 / 77 (2.60%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypovolaemic shock			
subjects affected / exposed	0 / 75 (0.00%)	1 / 152 (0.66%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Peripheral ischaemia			
subjects affected / exposed	0 / 75 (0.00%)	1 / 152 (0.66%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 75 (0.00%)	1 / 152 (0.66%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	1 / 75 (1.33%)	1 / 152 (0.66%)	0 / 77 (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
General physical health deterioration			
subjects affected / exposed	1 / 75 (1.33%)	1 / 152 (0.66%)	0 / 77 (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

Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 75 (0.00%)	1 / 152 (0.66%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Reproductive system and breast disorders			
Priapism			
subjects affected / exposed	0 / 75 (0.00%)	1 / 152 (0.66%)	1 / 77 (1.30%)
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			
Atelectasis			
subjects affected / exposed	2 / 75 (2.67%)	2 / 152 (1.32%)	0 / 77 (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
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 75 (0.00%)	1 / 152 (0.66%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	1 / 75 (1.33%)	1 / 152 (0.66%)	0 / 77 (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
Haemoptysis			
subjects affected / exposed	1 / 75 (1.33%)	2 / 152 (1.32%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Pleural effusion			
subjects affected / exposed	1 / 75 (1.33%)	2 / 152 (1.32%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			

subjects affected / exposed	4 / 75 (5.33%)	6 / 152 (3.95%)	2 / 77 (2.60%)
occurrences causally related to treatment / all	0 / 4	0 / 6	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 75 (1.33%)	1 / 152 (0.66%)	0 / 77 (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
Respiratory failure			
subjects affected / exposed	1 / 75 (1.33%)	2 / 152 (1.32%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Psychiatric disorders			
Fear of death			
subjects affected / exposed	0 / 75 (0.00%)	1 / 152 (0.66%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fibula fracture			
subjects affected / exposed	1 / 75 (1.33%)	1 / 152 (0.66%)	0 / 77 (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
Infusion related reaction			
subjects affected / exposed	0 / 75 (0.00%)	1 / 152 (0.66%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	1 / 75 (1.33%)	1 / 152 (0.66%)	0 / 77 (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
Tibia fracture			
subjects affected / exposed	1 / 75 (1.33%)	1 / 152 (0.66%)	0 / 77 (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

Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 75 (0.00%)	1 / 152 (0.66%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Autoimmune myocarditis			
subjects affected / exposed	0 / 75 (0.00%)	1 / 152 (0.66%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	0 / 75 (0.00%)	1 / 152 (0.66%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	1 / 75 (1.33%)	1 / 152 (0.66%)	0 / 77 (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
Nervous system disorders			
Cerebral ischaemia			
subjects affected / exposed	0 / 75 (0.00%)	1 / 152 (0.66%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	0 / 75 (0.00%)	1 / 152 (0.66%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	1 / 75 (1.33%)	1 / 152 (0.66%)	0 / 77 (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
Polyneuropathy			
subjects affected / exposed	1 / 75 (1.33%)	1 / 152 (0.66%)	0 / 77 (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

Spinal cord compression			
subjects affected / exposed	0 / 75 (0.00%)	1 / 152 (0.66%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 75 (2.67%)	2 / 152 (1.32%)	0 / 77 (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
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	1 / 75 (1.33%)	1 / 152 (0.66%)	0 / 77 (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
Colitis ischaemic			
subjects affected / exposed	1 / 75 (1.33%)	1 / 152 (0.66%)	0 / 77 (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
Constipation			
subjects affected / exposed	1 / 75 (1.33%)	1 / 152 (0.66%)	0 / 77 (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
Ileus			
subjects affected / exposed	0 / 75 (0.00%)	1 / 152 (0.66%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal perforation			
subjects affected / exposed	0 / 75 (0.00%)	1 / 152 (0.66%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Pancreatitis			
subjects affected / exposed	1 / 75 (1.33%)	1 / 152 (0.66%)	0 / 77 (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

Pseudodiverticular disease			
subjects affected / exposed	1 / 75 (1.33%)	1 / 152 (0.66%)	0 / 77 (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
Small intestinal haemorrhage			
subjects affected / exposed	1 / 75 (1.33%)	1 / 152 (0.66%)	0 / 77 (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			
Cholangitis			
subjects affected / exposed	0 / 75 (0.00%)	1 / 152 (0.66%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis sclerosing			
subjects affected / exposed	1 / 75 (1.33%)	1 / 152 (0.66%)	0 / 77 (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
Hepatitis			
subjects affected / exposed	1 / 75 (1.33%)	1 / 152 (0.66%)	0 / 77 (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
Skin and subcutaneous tissue disorders			
Dermatitis exfoliative generalised			
subjects affected / exposed	0 / 75 (0.00%)	1 / 152 (0.66%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 75 (0.00%)	1 / 152 (0.66%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Hypothyroidism			

subjects affected / exposed	1 / 75 (1.33%)	2 / 152 (1.32%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 75 (1.33%)	1 / 152 (0.66%)	0 / 77 (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
Muscular weakness			
subjects affected / exposed	0 / 75 (0.00%)	1 / 152 (0.66%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pathological fracture			
subjects affected / exposed	0 / 75 (0.00%)	1 / 152 (0.66%)	1 / 77 (1.30%)
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			
Cytomegalovirus viraemia			
subjects affected / exposed	0 / 75 (0.00%)	1 / 152 (0.66%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 75 (1.33%)	1 / 152 (0.66%)	0 / 77 (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
Lower respiratory tract infection			
subjects affected / exposed	0 / 75 (0.00%)	1 / 152 (0.66%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	0 / 75 (0.00%)	1 / 152 (0.66%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1

Pneumonia			
subjects affected / exposed	6 / 75 (8.00%)	13 / 152 (8.55%)	7 / 77 (9.09%)
occurrences causally related to treatment / all	0 / 6	0 / 13	0 / 7
deaths causally related to treatment / all	0 / 2	0 / 4	0 / 2
Pyelonephritis			
subjects affected / exposed	1 / 75 (1.33%)	1 / 152 (0.66%)	0 / 77 (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
Septic shock			
subjects affected / exposed	1 / 75 (1.33%)	1 / 152 (0.66%)	0 / 77 (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
Urinary tract infection			
subjects affected / exposed	1 / 75 (1.33%)	1 / 152 (0.66%)	0 / 77 (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
Viral infection			
subjects affected / exposed	0 / 75 (0.00%)	1 / 152 (0.66%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 75 (1.33%)	1 / 152 (0.66%)	0 / 77 (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
Diabetes mellitus			
subjects affected / exposed	1 / 75 (1.33%)	1 / 152 (0.66%)	0 / 77 (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
Hypercalcaemia			
subjects affected / exposed	0 / 75 (0.00%)	1 / 152 (0.66%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			

subjects affected / exposed	1 / 75 (1.33%)	1 / 152 (0.66%)	0 / 77 (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
Hypokalaemia			
subjects affected / exposed	0 / 75 (0.00%)	2 / 152 (1.32%)	2 / 77 (2.60%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
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 + Epacadostat	Total	Pembrolizumab + Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	69 / 75 (92.00%)	136 / 152 (89.47%)	67 / 77 (87.01%)
Vascular disorders			
Hypotension			
subjects affected / exposed	2 / 75 (2.67%)	6 / 152 (3.95%)	4 / 77 (5.19%)
occurrences (all)	2	6	4
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	8 / 75 (10.67%)	14 / 152 (9.21%)	6 / 77 (7.79%)
occurrences (all)	9	17	8
Chest pain			
subjects affected / exposed	5 / 75 (6.67%)	11 / 152 (7.24%)	6 / 77 (7.79%)
occurrences (all)	5	12	7
Chills			
subjects affected / exposed	4 / 75 (5.33%)	5 / 152 (3.29%)	1 / 77 (1.30%)
occurrences (all)	5	7	2
Fatigue			
subjects affected / exposed	9 / 75 (12.00%)	25 / 152 (16.45%)	16 / 77 (20.78%)
occurrences (all)	11	32	21
Oedema peripheral			
subjects affected / exposed	4 / 75 (5.33%)	9 / 152 (5.92%)	5 / 77 (6.49%)
occurrences (all)	6	11	5
Pyrexia			

subjects affected / exposed	7 / 75 (9.33%)	15 / 152 (9.87%)	8 / 77 (10.39%)
occurrences (all)	8	16	8
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	7 / 75 (9.33%)	15 / 152 (9.87%)	8 / 77 (10.39%)
occurrences (all)	9	17	8
Dyspnoea			
subjects affected / exposed	10 / 75 (13.33%)	20 / 152 (13.16%)	10 / 77 (12.99%)
occurrences (all)	13	26	13
Haemoptysis			
subjects affected / exposed	6 / 75 (8.00%)	13 / 152 (8.55%)	7 / 77 (9.09%)
occurrences (all)	6	13	7
Productive cough			
subjects affected / exposed	4 / 75 (5.33%)	6 / 152 (3.95%)	2 / 77 (2.60%)
occurrences (all)	4	6	2
Psychiatric disorders			
Insomnia			
subjects affected / exposed	6 / 75 (8.00%)	10 / 152 (6.58%)	4 / 77 (5.19%)
occurrences (all)	7	12	5
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	5 / 75 (6.67%)	10 / 152 (6.58%)	5 / 77 (6.49%)
occurrences (all)	5	13	8
Amylase increased			
subjects affected / exposed	8 / 75 (10.67%)	12 / 152 (7.89%)	4 / 77 (5.19%)
occurrences (all)	9	17	8
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 75 (5.33%)	8 / 152 (5.26%)	4 / 77 (5.19%)
occurrences (all)	4	11	7
Blood creatinine increased			
subjects affected / exposed	4 / 75 (5.33%)	11 / 152 (7.24%)	7 / 77 (9.09%)
occurrences (all)	4	12	8
Lipase increased			
subjects affected / exposed	9 / 75 (12.00%)	13 / 152 (8.55%)	4 / 77 (5.19%)
occurrences (all)	9	14	5
Lymphocyte count decreased			

subjects affected / exposed	1 / 75 (1.33%)	5 / 152 (3.29%)	4 / 77 (5.19%)
occurrences (all)	1	8	7
Weight decreased			
subjects affected / exposed	7 / 75 (9.33%)	15 / 152 (9.87%)	8 / 77 (10.39%)
occurrences (all)	7	15	8
Nervous system disorders			
Dizziness			
subjects affected / exposed	5 / 75 (6.67%)	11 / 152 (7.24%)	6 / 77 (7.79%)
occurrences (all)	5	11	6
Dysgeusia			
subjects affected / exposed	4 / 75 (5.33%)	5 / 152 (3.29%)	1 / 77 (1.30%)
occurrences (all)	4	5	1
Headache			
subjects affected / exposed	13 / 75 (17.33%)	17 / 152 (11.18%)	4 / 77 (5.19%)
occurrences (all)	15	19	4
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	7 / 75 (9.33%)	17 / 152 (11.18%)	10 / 77 (12.99%)
occurrences (all)	8	20	12
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	20 / 75 (26.67%)	38 / 152 (25.00%)	18 / 77 (23.38%)
occurrences (all)	23	44	21
Diarrhoea			
subjects affected / exposed	16 / 75 (21.33%)	33 / 152 (21.71%)	17 / 77 (22.08%)
occurrences (all)	30	55	25
Nausea			
subjects affected / exposed	14 / 75 (18.67%)	22 / 152 (14.47%)	8 / 77 (10.39%)
occurrences (all)	16	24	8
Vomiting			
subjects affected / exposed	7 / 75 (9.33%)	13 / 152 (8.55%)	6 / 77 (7.79%)
occurrences (all)	8	14	6
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	5 / 75 (6.67%)	9 / 152 (5.92%)	4 / 77 (5.19%)
occurrences (all)	5	9	4
Pruritus			

subjects affected / exposed	16 / 75 (21.33%)	32 / 152 (21.05%)	16 / 77 (20.78%)
occurrences (all)	21	43	22
Rash			
subjects affected / exposed	15 / 75 (20.00%)	26 / 152 (17.11%)	11 / 77 (14.29%)
occurrences (all)	22	38	16
Rash maculo-papular			
subjects affected / exposed	4 / 75 (5.33%)	11 / 152 (7.24%)	7 / 77 (9.09%)
occurrences (all)	5	13	8
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	8 / 75 (10.67%)	14 / 152 (9.21%)	6 / 77 (7.79%)
occurrences (all)	8	14	6
Hypothyroidism			
subjects affected / exposed	10 / 75 (13.33%)	16 / 152 (10.53%)	6 / 77 (7.79%)
occurrences (all)	11	17	6
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	17 / 75 (22.67%)	27 / 152 (17.76%)	10 / 77 (12.99%)
occurrences (all)	22	34	12
Back pain			
subjects affected / exposed	10 / 75 (13.33%)	18 / 152 (11.84%)	8 / 77 (10.39%)
occurrences (all)	13	24	11
Myalgia			
subjects affected / exposed	2 / 75 (2.67%)	9 / 152 (5.92%)	7 / 77 (9.09%)
occurrences (all)	2	11	9
Pain in extremity			
subjects affected / exposed	5 / 75 (6.67%)	9 / 152 (5.92%)	4 / 77 (5.19%)
occurrences (all)	6	10	4
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	2 / 75 (2.67%)	10 / 152 (6.58%)	8 / 77 (10.39%)
occurrences (all)	2	12	10
Oral candidiasis			
subjects affected / exposed	2 / 75 (2.67%)	6 / 152 (3.95%)	4 / 77 (5.19%)
occurrences (all)	3	9	6
Pneumonia			

subjects affected / exposed	4 / 75 (5.33%)	7 / 152 (4.61%)	3 / 77 (3.90%)
occurrences (all)	4	7	3
Respiratory tract infection			
subjects affected / exposed	5 / 75 (6.67%)	6 / 152 (3.95%)	1 / 77 (1.30%)
occurrences (all)	5	7	2
Upper respiratory tract infection			
subjects affected / exposed	6 / 75 (8.00%)	14 / 152 (9.21%)	8 / 77 (10.39%)
occurrences (all)	6	14	8
Urinary tract infection			
subjects affected / exposed	4 / 75 (5.33%)	10 / 152 (6.58%)	6 / 77 (7.79%)
occurrences (all)	4	14	10
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	17 / 75 (22.67%)	27 / 152 (17.76%)	10 / 77 (12.99%)
occurrences (all)	18	30	12
Hyperglycaemia			
subjects affected / exposed	6 / 75 (8.00%)	8 / 152 (5.26%)	2 / 77 (2.60%)
occurrences (all)	7	9	2
Hyperkalaemia			
subjects affected / exposed	2 / 75 (2.67%)	9 / 152 (5.92%)	7 / 77 (9.09%)
occurrences (all)	5	16	11
Hypokalaemia			
subjects affected / exposed	4 / 75 (5.33%)	9 / 152 (5.92%)	5 / 77 (6.49%)
occurrences (all)	6	13	7
Hyponatraemia			
subjects affected / exposed	6 / 75 (8.00%)	7 / 152 (4.61%)	1 / 77 (1.30%)
occurrences (all)	8	9	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 November 2017	To provide specific dose modification and toxicity management guidelines for myocarditis
06 March 2018	To align HIV and pregnancy testing with regulatory requirements at German sites.
05 April 2018	To align with regulatory requirements at French sites to exclude participants on coumarin based anticoagulants and prohibit coumarin based anticoagulant treatment for participants receiving epacadostat. In addition, to provide specific dose modification and toxicity management guidelines for myocarditis
31 May 2018	Updated Phase 3 design to Phase 2 design, title of protocol and secondary endpoints.
04 March 2019	Data from the final analysis of KEYNOTE-654/ECHO-305 (data cutoff: 10-JAN-2019) indicated that the study did not meet the pre-specified endpoint of improvement in objective response rate (ORR) for the combination of pembrolizumab plus epacadostat compared with pembrolizumab plus placebo. Based upon these data from the final analysis, the Sponsor and MSD implemented this Amendment 05 to direct that all epacadostat and placebo administration stop, and to reflect that the study is no longer blinded.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported