



Clinical trial results:

A Phase III Study of Pembrolizumab (MK-3475) vs. Best Supportive Care as Second-Line Therapy in Subjects With Previously Systemically Treated Advanced Hepatocellular Carcinoma (KEYNOTE-240)

Summary

EudraCT number	2015-004567-36
Trial protocol	IE DE DK HU FR GB PL BE IT
Global end of trial date	22 September 2021

Results information

Result version number	v1 (current)
This version publication date	15 September 2022
First version publication date	15 September 2022

Trial information

Trial identification

Sponsor protocol code	3475-240
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02702401
WHO universal trial number (UTN)	-
Other trial identifiers	JAPIC-CTI: 163456, Merck: KEYNOTE-240

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme LLC
Sponsor organisation address	126 East Lincoln Avenue, P.O. Box 2000, Rahway, NJ, United States, 07065
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme LLC, ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme LLC., ClinicalTrialsDisclosure@merck.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	22 September 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 January 2019
Global end of trial reached?	Yes
Global end of trial date	22 September 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This is a study of pembrolizumab (MK-3475) in participants with previously systemically treated advanced hepatocellular carcinoma (HCC).

The primary objectives of this study are to determine 1) Progression-Free Survival (PFS) and 2) Overall Survival (OS) of pembrolizumab plus best supportive care (BSC) compared with placebo plus BSC. The primary hypotheses of this study are: 1) pembrolizumab plus BSC prolongs PFS per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, assessed by Blinded Independent Central Review compared to placebo plus BSC, and 2) pembrolizumab plus BSC improves OS compared with placebo plus BSC.

Effective with Amendment 4: Upon study completion, participants are discontinued and may be enrolled in a pembrolizumab extension study, if available.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy:

Background therapy will consist of best supportive care and will be administered to all arms in this study. Best supportive care will include pain management and management of other potential complications including ascites per local standards of care.

Evidence for comparator: -

Actual start date of recruitment	26 May 2016
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	Argentina: 2
Country: Number of subjects enrolled	Australia: 11
Country: Number of subjects enrolled	Belgium: 11
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	Chile: 8
Country: Number of subjects enrolled	Colombia: 3
Country: Number of subjects enrolled	Denmark: 5
Country: Number of subjects enrolled	France: 78
Country: Number of subjects enrolled	Germany: 10
Country: Number of subjects enrolled	Hong Kong: 14
Country: Number of subjects enrolled	Hungary: 11

Country: Number of subjects enrolled	Ireland: 3
Country: Number of subjects enrolled	Israel: 8
Country: Number of subjects enrolled	Italy: 7
Country: Number of subjects enrolled	Japan: 59
Country: Number of subjects enrolled	Korea, Republic of: 50
Country: Number of subjects enrolled	Mexico: 7
Country: Number of subjects enrolled	Norway: 6
Country: Number of subjects enrolled	Philippines: 2
Country: Number of subjects enrolled	Poland: 5
Country: Number of subjects enrolled	Russian Federation: 17
Country: Number of subjects enrolled	Taiwan: 27
Country: Number of subjects enrolled	Thailand: 5
Country: Number of subjects enrolled	Turkey: 17
Country: Number of subjects enrolled	United Kingdom: 9
Country: Number of subjects enrolled	United States: 37
Worldwide total number of subjects	413
EEA total number of subjects	136

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)	173
From 65 to 84 years	233
85 years and over	7

Subject disposition

Recruitment

Recruitment details:

Although 278 participants were randomized to receive pembrolizumab and 135 to receive placebo, 1 participant in the placebo group received pembrolizumab in error. The efficacy population included all participants as randomized and the safety population was adjusted to account for actual treatment received (pembrolizumab = 279, placebo = 134).

Pre-assignment

Screening details:

Per protocol, response/progression or adverse events during the second pembrolizumab course were not counted towards efficacy outcome measures or safety outcome measures.

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, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Pembrolizumab + Best Supportive Care

Arm description:

Participants received pembrolizumab 200 mg by intravenous (IV) infusion on Day 1 of each 3-week cycle for up to 35 cycles of treatment PLUS best supportive care (BSC). Participants who complete 35 administrations or achieve a complete response (CR) but progress after discontinuation can initiate a second course of pembrolizumab for up to 17 cycles (approximately 1 additional year).

Arm type	Experimental
Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	
Other name	MK-3475 KEYTRUDA®
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

200 mg on Day 1 of each 3-week cycle.

Arm title	Placebo + Best Supportive Care
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Arm description:

Participants received placebo by IV infusion on Day 1 of each 3-week cycle for up to 35 cycles of treatment PLUS BSC.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

0.90% w/v sodium chloride

Number of subjects in period 1	Pembrolizumab + Best Supportive Care	Placebo + Best Supportive Care
Started	278	135
Treated	278	135
Received second course	7	0
Completed	0	0
Not completed	278	135
Consent withdrawn by subject	15	5
Physician decision	1	2
Death	242	125
Sponsor Decision	19	3
Lost to follow-up	1	-

Baseline characteristics

Reporting groups

Reporting group title	Pembrolizumab + Best Supportive Care
Reporting group description:	
Participants received pembrolizumab 200 mg by intravenous (IV) infusion on Day 1 of each 3-week cycle for up to 35 cycles of treatment PLUS best supportive care (BSC). Participants who complete 35 administrations or achieve a complete response (CR) but progress after discontinuation can initiate a second course of pembrolizumab for up to 17 cycles (approximately 1 additional year).	
Reporting group title	Placebo + Best Supportive Care
Reporting group description:	
Participants received placebo by IV infusion on Day 1 of each 3-week cycle for up to 35 cycles of treatment PLUS BSC.	

Reporting group values	Pembrolizumab + Best Supportive Care	Placebo + Best Supportive Care	Total
Number of subjects	278	135	413
Age categorical			
Units: Participants			
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)	109	64	173
From 65-84 years	164	69	233
85 years and over	5	2	7
Age Continuous			
Units: Years			
arithmetic mean	65.6	64.4	-
standard deviation	± 11.1	± 10.3	
Sex: Female, Male			
Units: Participants			
Female	52	23	75
Male	226	112	338
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	5	1	6
Asian	113	52	165
Native Hawaiian or Other Pacific Islander	1	0	1
Black or African American	13	6	19
White	143	70	213
More than one race	3	5	8
Unknown or Not Reported	0	1	1
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	22	13	35

Not Hispanic or Latino	233	113	346
Unknown or Not Reported	23	9	32
Region of enrollment			
Units: Subjects			
Asia without Japan	67	31	98
European Union	96	43	139
Japan	40	19	59
United States	21	16	37
Others	54	26	80
Macrovascular invasion			
The presence or absence of macrovascular invasion was obtained from case report forms.			
Units: Subjects			
Yes (Present)	36	16	52
No (Absent)	242	119	361
Alpha-fetoprotein level			
Alpha-fetoprotein levels were measured using an enzyme-linked immunosorbent assay (ELISA) and participants were categorized by those having alpha-fetoprotein levels of <200 ng/mL and those having levels of ≥200 ng/mL.			
Units: Subjects			
<200 ng/mL	149	77	226
≥200 ng/mL	129	58	187

End points

End points reporting groups

Reporting group title	Pembrolizumab + Best Supportive Care
Reporting group description: Participants received pembrolizumab 200 mg by intravenous (IV) infusion on Day 1 of each 3-week cycle for up to 35 cycles of treatment PLUS best supportive care (BSC). Participants who complete 35 administrations or achieve a complete response (CR) but progress after discontinuation can initiate a second course of pembrolizumab for up to 17 cycles (approximately 1 additional year).	
Reporting group title	Placebo + Best Supportive Care
Reporting group description: Participants received placebo by IV infusion on Day 1 of each 3-week cycle for up to 35 cycles of treatment PLUS BSC.	
Subject analysis set title	Pembrolizumab + Best Supportive Care
Subject analysis set type	Safety analysis
Subject analysis set description: Participants received pembrolizumab 200 mg by IV infusion on Day 1 of each 3-week cycle for up to 35 cycles of treatment PLUS BSC. Participants who complete 35 administrations or achieve a complete response (CR) but progress after discontinuation can initiate a second course of pembrolizumab for up to 17 cycles (approximately 1 additional year).	
Subject analysis set title	Placebo + Best Supportive Care
Subject analysis set type	Safety analysis
Subject analysis set description: Participants received placebo by IV infusion on Day 1 of each 3-week cycle for up to 35 cycles of treatment PLUS BSC.	

Primary: Progression-Free Survival (PFS) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1)

End point title	Progression-Free Survival (PFS) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1)
End point description: PFS was defined as the time from randomization to the first documented progressive disease (PD) or death due to any cause, whichever occurred first, per RECIST 1.1 as assessed by Blinded Independent Central Review (BICR). PD was defined as ≥20% increase in the sum of diameters of target lesions and an absolute increase of ≥5 mm. The appearance of ≥1 new lesion was also considered PD. If there was no disease progression or death, participants were censored at the date of their last disease assessment. The PFS was analyzed using the product-limit (Kaplan-Meier) method for censored data. Final analyses for PFS was performed for the first pembrolizumab course at protocol specified cut off of 26-Mar-2018. The analysis population included all randomized participants. Participants were included in the treatment group to which they were randomized.	
End point type	Primary
End point timeframe: Through database cutoff date of 26-Mar-2018 (Up to approximately 21 months)	

End point values	Pembrolizumab + Best Supportive Care	Placebo + Best Supportive Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	278	135		
Units: Months				
median (confidence interval 95%)	3.0 (2.8 to 4.1)	2.8 (2.5 to 4.1)		

Statistical analyses

Statistical analysis title	PFS Hazard Ratio
Statistical analysis description: Cox regression model with Efron's method (treatment as covariate) stratified by geographic region, macrovascular invasion and alfa-fetoprotein level	
Comparison groups	Pembrolizumab + Best Supportive Care v Placebo + Best Supportive Care
Number of subjects included in analysis	413
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0186 ^[1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.775
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.609
upper limit	0.987

Notes:

[1] - One-sided p-value stratified by geographic region, macrovascular invasion and alfa-fetoprotein level.

Primary: Overall Survival (OS)

End point title	Overall Survival (OS)
End point description: OS was determined for all participants and was defined as the time from randomization to death due to any cause. Participants were censored at the date of their last follow-up. The OS was analyzed using the product-limit (Kaplan-Meier) method for censored data. Final analyses for OS was performed for the first pembrolizumab course at protocol specified cut off of 02-Jan-2019. The analysis population included all randomized participants. Participants were included in the treatment group to which they were randomized.	
End point type	Primary
End point timeframe: Through database cutoff date of 02-Jan-2019 (Up to approximately 30 months)	

End point values	Pembrolizumab + Best Supportive Care	Placebo + Best Supportive Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	278	135		
Units: Months				
median (confidence interval 95%)	13.9 (11.6 to 16.0)	10.6 (8.3 to 13.5)		

Statistical analyses

Statistical analysis title	OS Hazard Ratio
Statistical analysis description: Cox regression model with Efron's method (treatment as covariate) stratified by geographic region, macrovascular invasion and alfa-fetoprotein level	
Comparison groups	Pembrolizumab + Best Supportive Care v Placebo + Best Supportive Care
Number of subjects included in analysis	413
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0238 ^[2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.781
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.611
upper limit	0.998

Notes:

[2] - One-sided p-value stratified by geographic region, macrovascular invasion and alfa-fetoprotein level.

Secondary: Objective Response Rate (ORR) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1)

End point title	Objective Response Rate (ORR) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1)
End point description: ORR was determined in all participants and was defined as the percentage of participants who had a confirmed Complete Response (CR: Disappearance of all target lesions) or a Partial Response (PR: At least a 30% decrease in the sum of diameters of target lesions) per RECIST 1.1 as assessed by Blinded Independent Central Review (BICR). Participants with missing data were considered non-responders. The ORR was analyzed using the Miettinen & Nurminen method. The percentage of participants who experienced a CR or PR per RECIST 1.1 is presented. Final analyses for ORR was performed for the first pembrolizumab course at protocol specified cut off of 02-Jan-2019. The analysis population included all randomized participants. Participants were included in the treatment group to which they were randomized.	
End point type	Secondary
End point timeframe: Through database cutoff date of 02-Jan-2019 (Up to approximately 30 months)	

End point values	Pembrolizumab + Best Supportive Care	Placebo + Best Supportive Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	278	135		
Units: Percentage of participants				
number (confidence interval 95%)	18.3 (14.0 to 23.4)	4.4 (1.6 to 9.4)		

Statistical analyses

Statistical analysis title	ORR Difference in Percent
Statistical analysis description:	
Miettinen & Nurminen method stratified by geographic region, macrovascular invasion and alfa-fetoprotein level	
Comparison groups	Pembrolizumab + Best Supportive Care v Placebo + Best Supportive Care
Number of subjects included in analysis	413
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in Percent
Point estimate	13.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.7
upper limit	19.5

Secondary: Disease Control Rate (DCR) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1)

End point title	Disease Control Rate (DCR) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1)
End point description:	
DCR was defined as the percentage of participants who had a Complete Response (CR: Disappearance of all target lesions), Partial Response (PR: $\geq 30\%$ decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters), or Stable Disease (SD) per RECIST 1.1 after ≥ 6 weeks as assessed by Blinded Independent Central Review (BICR). The DCR was analyzed using the Miettinen & Nurminen method. The percentage of participants who experienced a CR, PR, or SD is presented. Final analyses for DCR was performed for the first pembrolizumab course at protocol specified cut off of 02-Jan-2019. The analysis population included all randomized participants. Participants were included in the treatment group to which they were randomized.	
End point type	Secondary
End point timeframe:	
Through database cutoff date of 02-Jan-2019 (Up to approximately 30 months)	

End point values	Pembrolizumab + Best Supportive Care	Placebo + Best Supportive Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	278	135		
Units: Percentage of participants				
number (confidence interval 95%)	62.2 (56.2 to 68.0)	53.3 (44.6 to 62.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Progression (TTP) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1)

End point title	Time to Progression (TTP) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1)
End point description:	
TTP was defined as the time from randomization to the first documented disease progression per RECIST 1.1 as assessed by Blinded Independent Central Review (BICR). PD was defined as $\geq 20\%$ increase in the sum of diameters of target lesions and an absolute increase of ≥ 5 mm. The appearance of ≥ 1 new lesion was also considered PD. If there was no documented disease progression, TTP was censored at last tumor assessment date. The TTP was analyzed using the product-limit (Kaplan-Meier) method for censored data. TTP per RECIST 1.1 is presented for all participants. Final analyses for TTP was performed for the first pembrolizumab course at protocol specified cut off of 02-Jan-2019. The analysis population included all randomized participants. Participants were included in the treatment group to which they were randomized.	
End point type	Secondary
End point timeframe:	
Through database cutoff date of 02-Jan-2019 (Up to approximately 30 months)	

End point values	Pembrolizumab + Best Supportive Care	Placebo + Best Supportive Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	278	135		
Units: Months				
median (confidence interval 95%)	3.8 (2.8 to 4.4)	2.8 (1.6 to 2.9)		

Statistical analyses

Statistical analysis title	TTP Hazard Ratio
Statistical analysis description:	
Cox regression model with Efron's method (treatment as covariate) stratified by geographic region, macrovascular invasion and alfa-fetoprotein level	
Comparison groups	Pembrolizumab + Best Supportive Care v Placebo + Best Supportive Care

Number of subjects included in analysis	413
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0011 ^[3]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.688
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	0.877

Notes:

[3] - One-sided p-value stratified by geographic region, macrovascular invasion and alfa-fetoprotein level.

Secondary: Duration of Response (DOR) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1)

End point title	Duration of Response (DOR) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1)
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End point description:

In participants with a Complete Response (CR: disappearance of all target lesions) or Partial Response (PR: $\geq 30\%$ decrease in sum of diameters of target lesions) per RECIST 1.1 by BICR, DOR was the time from first CR/PR until progressive disease (PD: $\geq 20\%$ increase in the sum of diameters and an absolute increase of ≥ 5 mm; appearance of ≥ 1 new lesion is also PD) or death. Participants who did not progress or die at time of analysis were censored at last tumor assessment. Final analysis for DOR was done for the first pembrolizumab course at protocol specified cut off of 02-Jan-2019. The analysis population was all randomized participants who demonstrated at least a partial response. Participants were included in the treatment group to which they were randomized. "9999" indicates median and upper limit were not reached according to the prespecified methodology in the protocol.

End point type	Secondary
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End point timeframe:

From time of first documented evidence of CR or PR through database cutoff date of 02-Jan-2019 (Up to approximately 30 months)

End point values	Pembrolizumab + Best Supportive Care	Placebo + Best Supportive Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	6		
Units: Months				
median (confidence interval 95%)	13.8 (6.9 to 9999)	9999 (2.8 to 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Experienced At Least One Adverse Event (AE)

End point title	Number of Participants Who Experienced At Least One Adverse Event (AE)
End point description:	
An AE was defined as any untoward medical occurrence in a participant given a study treatment and not necessarily have to have a causal relationship with this treatment. An AE can thus be any unfavorable, unintended sign, symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the study treatment or protocol-specified procedure. Also worsening of a pre-existing condition temporally associated with the use of study treatment, was an AE. The number of participants who experienced at least one AE is presented. Final analyses for AE was performed for the first pembrolizumab course at protocol specified cut off of 02-Jan-2019. The analysis population included participants who received ≥ 1 dose of study treatment. Participants were grouped by actual treatment received.	
End point type	Secondary
End point timeframe:	
Through database cutoff date of 02-Jan-2019 (Up to approximately 30 months)	

End point values	Pembrolizumab + Best Supportive Care	Placebo + Best Supportive Care		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	279	134		
Units: Participants	269	121		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Discontinued Study Treatment Due to an Adverse Event (AE)

End point title	Number of Participants Who Discontinued Study Treatment Due to an Adverse Event (AE)
End point description:	
An AE was defined as any untoward medical occurrence in a participant given a study treatment and not necessarily have to have a causal relationship with this treatment. An AE can thus be any unfavorable, unintended sign, symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the study treatment or protocol-specified procedure. Also worsening of a pre-existing condition temporally associated with the use of study treatment, was an AE. The number of participants who discontinued study treatment due to an AE is presented. Final analyses for AE was performed for the first pembrolizumab course at protocol specified cut off of 02-Jan-2019. The analysis population included participants who received ≥ 1 dose of study treatment. Participants were grouped by actual treatment received.	
End point type	Secondary
End point timeframe:	
From Day 1 through end of treatment (Up to approximately 24 months)	

End point values	Pembrolizumab + Best Supportive Care	Placebo + Best Supportive Care		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	279	134		
Units: Participants	48	12		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Through database cutoff date of 22-Sep-2021 (Up to approximately 59.3 months).

Adverse event reporting additional description:

All participants who received ≥ 1 dose of study treatment. Per protocol, MedDRA terms "Neoplasm progression (NP)", "Malignant NP" & "Disease progression" unrelated to study drug are excluded as AEs. Due to a dosing error, the population for all-cause mortality and AEs was adjusted to account for actual treatment received.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	24.0
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Reporting groups

Reporting group title	Pembrolizumab + Best Supportive Care
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Reporting group description:

Participants received pembrolizumab 200 mg by IV infusion on Day 1 of each 3-week cycle for up to 35 cycles of treatment PLUS BSC. Participants who complete 35 administrations or achieve a complete response (CR) but progress after discontinuation can initiate a second course of pembrolizumab for up to 17 cycles (approximately 1 additional year).

Reporting group title	Pembrolizumab Second Course
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Reporting group description:

Participants who completed the first course of up to 35 administrations of pembrolizumab (~2 years) but progressed after discontinuation, initiated a second course of pembrolizumab at the investigator's discretion, at the same dose and schedule at 200 mg IV on Day 1 of each 3-week cycle (Q3W) for up to 17 cycles (up to ~1 year).

Reporting group title	Placebo + Best Supportive Care
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Reporting group description:

Participants received placebo by IV infusion on Day 1 of each 3-week cycle for up to 35 cycles of treatment PLUS BSC.

Serious adverse events	Pembrolizumab + Best Supportive Care	Pembrolizumab Second Course	Placebo + Best Supportive Care
Total subjects affected by serious adverse events			
subjects affected / exposed	106 / 279 (37.99%)	3 / 7 (42.86%)	37 / 134 (27.61%)
number of deaths (all causes)	246	3	124
number of deaths resulting from adverse events	1	1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	1 / 279 (0.36%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric cancer			

subjects affected / exposed	1 / 279 (0.36%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Insulinoma			
subjects affected / exposed	1 / 279 (0.36%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant neoplasm progression			
subjects affected / exposed	1 / 279 (0.36%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Oral neoplasm			
subjects affected / exposed	1 / 279 (0.36%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour haemorrhage			
subjects affected / exposed	0 / 279 (0.00%)	0 / 7 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour rupture			
subjects affected / exposed	1 / 279 (0.36%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	0 / 279 (0.00%)	0 / 7 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	1 / 279 (0.36%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			

Chest pain			
subjects affected / exposed	1 / 279 (0.36%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	1 / 279 (0.36%)	0 / 7 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Fatigue			
subjects affected / exposed	1 / 279 (0.36%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	2 / 279 (0.72%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza like illness			
subjects affected / exposed	0 / 279 (0.00%)	0 / 7 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mucosal inflammation			
subjects affected / exposed	0 / 279 (0.00%)	0 / 7 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	1 / 279 (0.36%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Contrast media allergy			
subjects affected / exposed	1 / 279 (0.36%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal			

disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 279 (0.36%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 279 (0.00%)	0 / 7 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	1 / 279 (0.36%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	3 / 279 (1.08%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	2 / 279 (0.72%)	0 / 7 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleurisy			
subjects affected / exposed	0 / 279 (0.00%)	0 / 7 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	2 / 279 (0.72%)	0 / 7 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	2 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	2 / 279 (0.72%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Psychiatric disorders			
Mental status changes			
subjects affected / exposed	1 / 279 (0.36%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	7 / 279 (2.51%)	0 / 7 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	5 / 7	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	9 / 279 (3.23%)	0 / 7 (0.00%)	4 / 134 (2.99%)
occurrences causally related to treatment / all	5 / 9	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood bilirubin increased			
subjects affected / exposed	8 / 279 (2.87%)	0 / 7 (0.00%)	2 / 134 (1.49%)
occurrences causally related to treatment / all	3 / 8	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatinine increased			
subjects affected / exposed	1 / 279 (0.36%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 279 (0.00%)	0 / 7 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	1 / 279 (0.36%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			

subjects affected / exposed	1 / 279 (0.36%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	1 / 279 (0.36%)	0 / 7 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	1 / 279 (0.36%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ligament sprain			
subjects affected / exposed	1 / 279 (0.36%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar vertebral fracture			
subjects affected / exposed	1 / 279 (0.36%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular procedure complication			
subjects affected / exposed	1 / 279 (0.36%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 279 (0.36%)	0 / 7 (0.00%)	2 / 134 (1.49%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	1 / 279 (0.36%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			

subjects affected / exposed	2 / 279 (0.72%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	1 / 279 (0.36%)	0 / 7 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pericardial effusion			
subjects affected / exposed	0 / 279 (0.00%)	0 / 7 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	1 / 279 (0.36%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	1 / 279 (0.36%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	1 / 279 (0.36%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic encephalopathy			
subjects affected / exposed	1 / 279 (0.36%)	0 / 7 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	1 / 279 (0.36%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			

subjects affected / exposed	0 / 279 (0.00%)	0 / 7 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 279 (1.08%)	0 / 7 (0.00%)	5 / 134 (3.73%)
occurrences causally related to treatment / all	0 / 3	0 / 0	1 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune thrombocytopenia			
subjects affected / exposed	1 / 279 (0.36%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 279 (0.00%)	0 / 7 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Blindness unilateral			
subjects affected / exposed	0 / 279 (0.00%)	0 / 7 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Macular hole			
subjects affected / exposed	1 / 279 (0.36%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal detachment			
subjects affected / exposed	0 / 279 (0.00%)	0 / 7 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal vein occlusion			
subjects affected / exposed	0 / 279 (0.00%)	0 / 7 (0.00%)	1 / 134 (0.75%)
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 distension			
subjects affected / exposed	1 / 279 (0.36%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	1 / 279 (0.36%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	2 / 279 (0.72%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	13 / 279 (4.66%)	0 / 7 (0.00%)	5 / 134 (3.73%)
occurrences causally related to treatment / all	1 / 14	0 / 0	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	2 / 279 (0.72%)	1 / 7 (14.29%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	2 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Constipation			
subjects affected / exposed	1 / 279 (0.36%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	2 / 279 (0.72%)	0 / 7 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticular fistula			
subjects affected / exposed	1 / 279 (0.36%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulum intestinal haemorrhagic			

subjects affected / exposed	1 / 279 (0.36%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer			
subjects affected / exposed	1 / 279 (0.36%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 279 (0.00%)	0 / 7 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroduodenal ulcer			
subjects affected / exposed	1 / 279 (0.36%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 279 (0.00%)	1 / 7 (14.29%)	0 / 134 (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
Gastrointestinal inflammation			
subjects affected / exposed	1 / 279 (0.36%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	1 / 279 (0.36%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal perforation			
subjects affected / exposed	1 / 279 (0.36%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intra-abdominal haemorrhage			

subjects affected / exposed	1 / 279 (0.36%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal varices haemorrhage			
subjects affected / exposed	3 / 279 (1.08%)	0 / 7 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	1 / 279 (0.36%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	3 / 279 (1.08%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Varices oesophageal			
subjects affected / exposed	3 / 279 (1.08%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 279 (0.36%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Autoimmune hepatitis			
subjects affected / exposed	2 / 279 (0.72%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis			
subjects affected / exposed	0 / 279 (0.00%)	0 / 7 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholestasis			

subjects affected / exposed	2 / 279 (0.72%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic cirrhosis			
subjects affected / exposed	2 / 279 (0.72%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hepatic cyst			
subjects affected / exposed	0 / 279 (0.00%)	0 / 7 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic failure			
subjects affected / exposed	2 / 279 (0.72%)	0 / 7 (0.00%)	2 / 134 (1.49%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Hepatic haemorrhage			
subjects affected / exposed	1 / 279 (0.36%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperbilirubinaemia			
subjects affected / exposed	2 / 279 (0.72%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune-mediated hepatitis			
subjects affected / exposed	3 / 279 (1.08%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice			
subjects affected / exposed	1 / 279 (0.36%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice cholestatic			

subjects affected / exposed	1 / 279 (0.36%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Erythema multiforme			
subjects affected / exposed	1 / 279 (0.36%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lichenoid keratosis			
subjects affected / exposed	1 / 279 (0.36%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	3 / 279 (1.08%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	0 / 279 (0.00%)	0 / 7 (0.00%)	1 / 134 (0.75%)
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	1 / 279 (0.36%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Hypophysitis			
subjects affected / exposed	1 / 279 (0.36%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypothyroidism			
subjects affected / exposed	1 / 279 (0.36%)	1 / 7 (14.29%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 279 (0.00%)	0 / 7 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	0 / 279 (0.00%)	1 / 7 (14.29%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bursitis			
subjects affected / exposed	0 / 279 (0.00%)	0 / 7 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar spinal stenosis			
subjects affected / exposed	1 / 279 (0.36%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neck pain			
subjects affected / exposed	0 / 279 (0.00%)	0 / 7 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteochondrosis			
subjects affected / exposed	1 / 279 (0.36%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 279 (0.00%)	1 / 7 (14.29%)	0 / 134 (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
Pathological fracture			
subjects affected / exposed	1 / 279 (0.36%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Polymyalgia rheumatica			
subjects affected / exposed	1 / 279 (0.36%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 279 (0.36%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 279 (0.36%)	0 / 7 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 279 (0.36%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis B			
subjects affected / exposed	0 / 279 (0.00%)	0 / 7 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis C			
subjects affected / exposed	1 / 279 (0.36%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	2 / 279 (0.72%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 279 (0.00%)	0 / 7 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver abscess			

subjects affected / exposed	1 / 279 (0.36%)	0 / 7 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mycobacterial infection			
subjects affected / exposed	1 / 279 (0.36%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	1 / 279 (0.36%)	0 / 7 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Peritonitis bacterial			
subjects affected / exposed	2 / 279 (0.72%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural infection			
subjects affected / exposed	0 / 279 (0.00%)	0 / 7 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	6 / 279 (2.15%)	0 / 7 (0.00%)	3 / 134 (2.24%)
occurrences causally related to treatment / all	0 / 6	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia bacterial			
subjects affected / exposed	1 / 279 (0.36%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia mycoplasmal			
subjects affected / exposed	0 / 279 (0.00%)	0 / 7 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			

subjects affected / exposed	2 / 279 (0.72%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombophlebitis septic			
subjects affected / exposed	1 / 279 (0.36%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	1 / 279 (0.36%)	0 / 7 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 279 (0.36%)	0 / 7 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 279 (0.36%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	1 / 279 (0.36%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus			
subjects affected / exposed	0 / 279 (0.00%)	0 / 7 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	1 / 279 (0.36%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			

subjects affected / exposed	0 / 279 (0.00%)	0 / 7 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	1 / 279 (0.36%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	1 / 279 (0.36%)	0 / 7 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Type 1 diabetes mellitus			
subjects affected / exposed	1 / 279 (0.36%)	0 / 7 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
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 + Best Supportive Care	Pembrolizumab Second Course	Placebo + Best Supportive Care
Total subjects affected by non-serious adverse events			
subjects affected / exposed	240 / 279 (86.02%)	7 / 7 (100.00%)	109 / 134 (81.34%)
Vascular disorders			
Hypertension			
subjects affected / exposed	10 / 279 (3.58%)	0 / 7 (0.00%)	8 / 134 (5.97%)
occurrences (all)	10	0	14
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	26 / 279 (9.32%)	0 / 7 (0.00%)	15 / 134 (11.19%)
occurrences (all)	35	0	17
Fatigue			
subjects affected / exposed	51 / 279 (18.28%)	2 / 7 (28.57%)	31 / 134 (23.13%)
occurrences (all)	60	2	32
Oedema peripheral			

subjects affected / exposed	32 / 279 (11.47%)	1 / 7 (14.29%)	17 / 134 (12.69%)
occurrences (all)	39	1	20
Pyrexia			
subjects affected / exposed	25 / 279 (8.96%)	0 / 7 (0.00%)	15 / 134 (11.19%)
occurrences (all)	27	0	22
Reproductive system and breast disorders			
Penile erythema			
subjects affected / exposed	1 / 279 (0.36%)	1 / 7 (14.29%)	0 / 134 (0.00%)
occurrences (all)	2	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	24 / 279 (8.60%)	1 / 7 (14.29%)	24 / 134 (17.91%)
occurrences (all)	32	1	27
Dyspnoea			
subjects affected / exposed	19 / 279 (6.81%)	0 / 7 (0.00%)	14 / 134 (10.45%)
occurrences (all)	19	0	16
Nasal congestion			
subjects affected / exposed	2 / 279 (0.72%)	1 / 7 (14.29%)	1 / 134 (0.75%)
occurrences (all)	2	1	2
Rhinorrhoea			
subjects affected / exposed	1 / 279 (0.36%)	1 / 7 (14.29%)	3 / 134 (2.24%)
occurrences (all)	1	1	3
Psychiatric disorders			
Sleep disorder			
subjects affected / exposed	1 / 279 (0.36%)	1 / 7 (14.29%)	0 / 134 (0.00%)
occurrences (all)	1	1	0
Insomnia			
subjects affected / exposed	12 / 279 (4.30%)	0 / 7 (0.00%)	8 / 134 (5.97%)
occurrences (all)	12	0	10
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	45 / 279 (16.13%)	0 / 7 (0.00%)	12 / 134 (8.96%)
occurrences (all)	49	0	12
Aspartate aminotransferase increased			

subjects affected / exposed	55 / 279 (19.71%)	0 / 7 (0.00%)	18 / 134 (13.43%)
occurrences (all)	58	0	21
Blood alkaline phosphatase increased			
subjects affected / exposed	20 / 279 (7.17%)	0 / 7 (0.00%)	9 / 134 (6.72%)
occurrences (all)	20	0	9
Gamma-glutamyltransferase increased			
subjects affected / exposed	18 / 279 (6.45%)	0 / 7 (0.00%)	7 / 134 (5.22%)
occurrences (all)	19	0	7
Blood bilirubin increased			
subjects affected / exposed	46 / 279 (16.49%)	0 / 7 (0.00%)	16 / 134 (11.94%)
occurrences (all)	59	0	18
Platelet count decreased			
subjects affected / exposed	13 / 279 (4.66%)	1 / 7 (14.29%)	2 / 134 (1.49%)
occurrences (all)	16	1	2
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	3 / 279 (1.08%)	1 / 7 (14.29%)	0 / 134 (0.00%)
occurrences (all)	3	1	0
Nervous system disorders			
Headache			
subjects affected / exposed	20 / 279 (7.17%)	0 / 7 (0.00%)	5 / 134 (3.73%)
occurrences (all)	23	0	7
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	27 / 279 (9.68%)	0 / 7 (0.00%)	11 / 134 (8.21%)
occurrences (all)	29	0	18
Lymphadenopathy			
subjects affected / exposed	1 / 279 (0.36%)	1 / 7 (14.29%)	1 / 134 (0.75%)
occurrences (all)	1	1	1
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	39 / 279 (13.98%)	0 / 7 (0.00%)	9 / 134 (6.72%)
occurrences (all)	51	0	9
Abdominal pain upper			
subjects affected / exposed	25 / 279 (8.96%)	0 / 7 (0.00%)	10 / 134 (7.46%)
occurrences (all)	27	0	14

Ascites			
subjects affected / exposed	15 / 279 (5.38%)	0 / 7 (0.00%)	8 / 134 (5.97%)
occurrences (all)	15	0	8
Constipation			
subjects affected / exposed	28 / 279 (10.04%)	0 / 7 (0.00%)	15 / 134 (11.19%)
occurrences (all)	33	0	16
Diarrhoea			
subjects affected / exposed	49 / 279 (17.56%)	0 / 7 (0.00%)	20 / 134 (14.93%)
occurrences (all)	74	0	24
Gastrooesophageal reflux disease			
subjects affected / exposed	5 / 279 (1.79%)	1 / 7 (14.29%)	2 / 134 (1.49%)
occurrences (all)	6	1	2
Nausea			
subjects affected / exposed	33 / 279 (11.83%)	0 / 7 (0.00%)	20 / 134 (14.93%)
occurrences (all)	41	0	21
Toothache			
subjects affected / exposed	3 / 279 (1.08%)	1 / 7 (14.29%)	0 / 134 (0.00%)
occurrences (all)	4	1	0
Pneumatosis intestinalis			
subjects affected / exposed	0 / 279 (0.00%)	1 / 7 (14.29%)	0 / 134 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	26 / 279 (9.32%)	0 / 7 (0.00%)	5 / 134 (3.73%)
occurrences (all)	41	0	9
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	53 / 279 (19.00%)	0 / 7 (0.00%)	17 / 134 (12.69%)
occurrences (all)	66	0	18
Rash			
subjects affected / exposed	35 / 279 (12.54%)	0 / 7 (0.00%)	7 / 134 (5.22%)
occurrences (all)	42	0	8
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	2 / 279 (0.72%)	1 / 7 (14.29%)	1 / 134 (0.75%)
occurrences (all)	2	1	1
Endocrine disorders			

Hypothyroidism subjects affected / exposed occurrences (all)	13 / 279 (4.66%) 14	0 / 7 (0.00%) 0	7 / 134 (5.22%) 7
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	33 / 279 (11.83%) 37	0 / 7 (0.00%) 0	17 / 134 (12.69%) 19
Back pain subjects affected / exposed occurrences (all)	29 / 279 (10.39%) 31	0 / 7 (0.00%) 0	13 / 134 (9.70%) 14
Neck pain subjects affected / exposed occurrences (all)	4 / 279 (1.43%) 4	1 / 7 (14.29%) 1	0 / 134 (0.00%) 0
Flank pain subjects affected / exposed occurrences (all)	5 / 279 (1.79%) 8	1 / 7 (14.29%) 1	3 / 134 (2.24%) 3
Infections and infestations			
Herpes zoster subjects affected / exposed occurrences (all)	2 / 279 (0.72%) 2	1 / 7 (14.29%) 1	0 / 134 (0.00%) 0
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	47 / 279 (16.85%) 51	0 / 7 (0.00%) 0	21 / 134 (15.67%) 23
Hyperglycaemia subjects affected / exposed occurrences (all)	12 / 279 (4.30%) 21	0 / 7 (0.00%) 0	7 / 134 (5.22%) 7
Hypoalbuminaemia subjects affected / exposed occurrences (all)	21 / 279 (7.53%) 25	0 / 7 (0.00%) 0	7 / 134 (5.22%) 7

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 March 2016	The primary reason for amendment 1 was removal of health economic assessment (HEA) from patient reported outcomes, removal of the option of including participants without confirmed diagnosis of HCC from inclusion criterion, removal of "target lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions" from inclusion criterion and insertion of clarifying text 'negative for anti-HBs' (Hepatitis B surface antibody) to exclusion criteria. Other primary reasons included updates and corrections to prohibited concomitant medications, supportive care guidelines, participant withdrawal/discontinuation criteria, trial flow charts, investigational products and the appendix.
03 August 2016	The primary reason for amendment 2 was addition of participant eligibility by radiographic diagnosis for HCC and text to change percentage of participants to be enrolled in the specified populations and countries.
16 March 2017	The primary reason for amendment 3 was addition of 2nd interim analysis, updates to show survival status activities taking place throughout the trial and addition of "the trial will be deemed positive if either OS or PFS null hypothesis are rejected" to the primary objectives and hypothesis. Other primary reasons included updates and corrections to survival follow-up phase, dose modification guidelines and survival status.
03 March 2021	The primary reason for amendment 4 was addition of language to include the requirement of roll over of trial participants into an extension trial (if available) when this trial is completed, update to assessment by radiologic imaging from every 6 weeks (Q6W) to every 12 weeks (Q12W) and duration of follow-up phase.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported