



Clinical trial results:

A Phase III Study of Pomalidomide and Low Dose Dexamethasone With or Without Pembrolizumab (MK3475) in Refractory or Relapsed and Refractory Multiple Myeloma (rrMM) (KEYNOTE 183)

Summary

EudraCT number	2015-002509-13
Trial protocol	DE ES NO FR IT
Global end of trial date	16 July 2020

Results information

Result version number	v1 (current)
This version publication date	15 July 2021
First version publication date	15 July 2021

Trial information

Trial identification

Sponsor protocol code	MK-3475-183
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02576977
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme Corp.
Sponsor organisation address	2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com
Scientific contact	Senior Vice President, Global Clinical Development, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com
Sponsor organisation name	Merck Sharp & Dohme Corp.
Sponsor organisation address	2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., 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	16 July 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 July 2018
Global end of trial reached?	Yes
Global end of trial date	16 July 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to compare the efficacy of pomalidomide and low dose dexamethasone with pembrolizumab (MK-3475) to that of pomalidomide and low dose dexamethasone without pembrolizumab in terms of Progression-Free Survival (PFS) in participants with refractory or relapsed and refractory multiple myeloma (rrMM) who have undergone at least 2 lines of prior treatment. The study's 2 primary hypotheses are: 1. Pembrolizumab in combination with pomalidomide and low dose dexamethasone prolongs PFS as assessed by Clinical Adjudication Committee (CAC) blinded central review using International Myeloma Working Group Criteria for Response Assessment in Multiple Myeloma (IMWG criteria) compared to treatment with pomalidomide and low dose dexamethasone standard of care (SOC) alone. 2. Pembrolizumab in combination with pomalidomide and low dose dexamethasone prolongs OS compared to treatment with pomalidomide and low dose dexamethasone (SOC) alone.

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: -

Evidence for comparator: -

Actual start date of recruitment	19 October 2015
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: 5
Country: Number of subjects enrolled	Canada: 4
Country: Number of subjects enrolled	France: 9
Country: Number of subjects enrolled	Germany: 9
Country: Number of subjects enrolled	Israel: 23
Country: Number of subjects enrolled	Italy: 8
Country: Number of subjects enrolled	Japan: 27
Country: Number of subjects enrolled	New Zealand: 25
Country: Number of subjects enrolled	Norway: 12
Country: Number of subjects enrolled	Spain: 21
Country: Number of subjects enrolled	United States: 108

Worldwide total number of subjects	251
EEA total number of subjects	59

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)	110
From 65 to 84 years	137
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

Subject Disposition as per database cutoff date of August 3, 2020.

Note: For administrative reasons (a noncompliant site), one participant in the SOC arm was recorded as "Ongoing in Trial" in the CSR Disposition Table and "Final Disposition Unknown" here.

Pre-assignment

Screening details:

Has a confirmed diagnosis of active multiple myeloma and measurable disease.

Must have undergone prior treatment with ≥ 2 treatment lines of anti-myeloma therapy and must have failed their last line of treatment (disease progression during or within 60 days of completing their last anti-myeloma therapy).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Pembrolizumab+Pomalidomide+Dexamethasone

Arm description:

Participants receive pembrolizumab 200 mg intravenously (IV) on Day 1 every 3 weeks (Q3W) PLUS pomalidomide 4 mg orally (PO) on Days 1 to 21 of each 28-day cycle PLUS dexamethasone 40 mg PO on Days 1, 8, 15 and 22 of each 28-day cycle.

Arm type	Experimental
Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	
Other name	KEYTRUDA® MK-3475 SCH 9000475
Pharmaceutical forms	Concentrate and solvent for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Pembrolizumab 200 mg intravenously (IV) on Day 1 every 3 weeks (Q3W)

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

Dosage and administration details:

Dexamethasone 40 mg PO on Days 1, 8, 15 and 22 of each 28-day cycle.

Investigational medicinal product name	Pomalidomide
Investigational medicinal product code	
Other name	POMALYST®
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Pomalidomide 4 mg orally (PO) on Days 1 to 21 of each 28-day cycle

Arm title	Standard of Care (SOC) Pomalidomide+Dexamethasone
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Arm description:

Participants receive pomalidomide 4 mg PO on Days 1 to 21 of each 28-day cycle PLUS dexamethasone 40 mg PO on Days 1, 8, 15 and 22 of each 28-day cycle.

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

Dosage and administration details:

Dexamethasone 40 mg PO on Days 1, 8, 15 and 22 of each 28-day cycle.

Investigational medicinal product name	Pomalidomide
Investigational medicinal product code	
Other name	POMALYST®
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Pomalidomide 4 mg orally (PO) on Days 1 to 21 of each 28-day cycle

Number of subjects in period 1	Pembrolizumab+Pomalidomide+Dexamethasone	Standard of Care (SOC) Pomalidomide+Dexamethasone
Started	126	125
Treated	122	123
Completed	0	0
Not completed	126	125
Adverse event, serious fatal	73	60
Consent withdrawn by subject	11	11
Adverse event, non-fatal	13	2
Progressive Disease	-	1
Final Disposition Unknown	-	1
Screen failure	1	-
Lost to follow-up	1	-
Study Terminated at Selected Sites	27	50

Baseline characteristics

Reporting groups

Reporting group title	Pembrolizumab+Pomalidomide+Dexamethasone
Reporting group description:	
Participants receive pembrolizumab 200 mg intravenously (IV) on Day 1 every 3 weeks (Q3W) PLUS pomalidomide 4 mg orally (PO) on Days 1 to 21 of each 28-day cycle PLUS dexamethasone 40 mg PO on Days 1, 8, 15 and 22 of each 28-day cycle.	
Reporting group title	Standard of Care (SOC) Pomalidomide+Dexamethasone
Reporting group description:	
Participants receive pomalidomide 4 mg PO on Days 1 to 21 of each 28-day cycle PLUS dexamethasone 40 mg PO on Days 1, 8, 15 and 22 of each 28-day cycle.	

Reporting group values	Pembrolizumab+Pomalidomide+Dexamethasone	Standard of Care (SOC) Pomalidomide+Dexamethasone	Total
Number of subjects	126	125	251
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)	61	49	110
From 65-84 years	63	74	137
85 years and over	2	2	4
Age Continuous Units: Years			
arithmetic mean	65.5	66.4	-
standard deviation	± 9.3	± 10.0	
Sex: Female, Male Units: Participants			
Female	48	46	94
Male	78	79	157
Race (NIH/OMB) Units: Subjects			
Asian	17	12	29
Native Hawaiian or Other Pacific Islander	2	1	3
Black or African American	10	14	24
White	92	95	187
More than one race	1	2	3
Unknown or Not Reported	4	1	5
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	8	5	13
Not Hispanic or Latino	110	117	227

Unknown or Not Reported	8	3	11
Disease Status (Refractory vs. Sensitive to Lenalidomide) Units: Subjects			
Refractory to Lenalidomide	108	108	216
Sensitive to Lenalidomide	18	17	35

End points

End points reporting groups

Reporting group title	Pembrolizumab+Pomalidomide+Dexamethasone
Reporting group description: Participants receive pembrolizumab 200 mg intravenously (IV) on Day 1 every 3 weeks (Q3W) PLUS pomalidomide 4 mg orally (PO) on Days 1 to 21 of each 28-day cycle PLUS dexamethasone 40 mg PO on Days 1, 8, 15 and 22 of each 28-day cycle.	
Reporting group title	Standard of Care (SOC) Pomalidomide+Dexamethasone
Reporting group description: Participants receive pomalidomide 4 mg PO on Days 1 to 21 of each 28-day cycle PLUS dexamethasone 40 mg PO on Days 1, 8, 15 and 22 of each 28-day cycle.	

Primary: Progression Free Survival (PFS) Assessed by Clinical Adjudication Committee (CAC) Blinded Central Review According to the International Myeloma Working Group (IMWG) Response Criteria

End point title	Progression Free Survival (PFS) Assessed by Clinical Adjudication Committee (CAC) Blinded Central Review According to the International Myeloma Working Group (IMWG) Response Criteria
End point description: Progression free survival was defined as the time from randomization to the first documented disease progression, or death due to any cause, whichever occurred first. PFS was assessed by CAC blinded central review according to the IMWG criteria based on the development of new bone lesions or soft tissue plasmacytomas or on a definite increase in the size of existing bone lesions or soft tissue plasmacytomas. Median PFS was calculated from the product-limit (Kaplan-Meier) method for censored data. The analysis population included all randomized participants. Participants were included in the treatment group to which they were randomized. The data cutoff date was July 9, 2018.	
End point type	Primary
End point timeframe: Up to approximately 30 months	

End point values	Pembrolizumab + Pomalidomide + Dexamethasone	Standard of Care (SOC) Pomalidomide + Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	125		
Units: Months				
median (confidence interval 95%)	5.7 (4.5 to 7.5)	7.4 (5.6 to 11.5)		

Statistical analyses

Statistical analysis title	MK-3475 200mg Q3W + SOC vs. Standard of Care
Statistical analysis description: Based on Cox regression model with treatment as a covariate stratified by disease status (refractory vs. sensitive to Lenalidomide) and Lines of previous treatments (two vs. three or more).	

Comparison groups	Pembrolizumab+Pomalidomide+Dexamethasone v Standard of Care (SOC) Pomalidomide+Dexamethasone
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.99324 ^[1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.08
upper limit	2.08

Notes:

[1] - One-sided p-value based on Stratified log-rank test.

Primary: Overall Survival (OS)

End point title	Overall Survival (OS)
End point description:	
Overall survival is defined as the time from randomization to death due to any cause. Participants without documented death at the time of the final analysis were censored at the date of the last follow-up. Median overall survival was calculated from the product-limit (Kaplan-Meier) method for censored data. A value of "9999" indicates that the median, a lower or upper confidence interval were not reached due to an insufficient number of deaths. The analysis population included all randomized participants. Participants were included in the treatment group to which they were randomized. The data cutoff date was August 3, 2020.	
End point type	Primary
End point timeframe:	
Up to approximately 54 months	

End point values	Pembrolizumab +Pomalidomide +Dexamethasone	Standard of Care (SOC) Pomalidomide+Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	125		
Units: Months				
median (confidence interval 95%)	21.0 (14.2 to 29.1)	39.6 (28.5 to 9999)		

Statistical analyses

Statistical analysis title	MK-3475 200mg Q3W + SOC vs. Standard of Care
Statistical analysis description:	
The Hazard Ratio and 95% confidence intervals were based on Cox regression model with treatment as a covariate stratified by disease status (refractory vs. sensitive to Lenalidomide) and Lines of previous treatments (two vs. three or more).	
Comparison groups	Pembrolizumab+Pomalidomide+Dexamethasone v Standard of

	Care (SOC) Pomalidomide+Dexamethasone
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.99989 [2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.32
upper limit	2.55

Notes:

[2] - One-sided p-value based on Stratified log-rank test.

Secondary: Overall Response Rate (ORR) Evaluated According to the IMWG Response Criteria by CAC Blinded Central Review

End point title	Overall Response Rate (ORR) Evaluated According to the IMWG Response Criteria by CAC Blinded Central Review
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End point description:

Disease control rate was based on participants who achieved confirmed sCR, CR, VGPR, PR, minimal response (MR) or have demonstrated stable disease (SD) for at least 12 weeks prior to any evidence of progression. CR = negative immunofixation of serum and urine AND disappearance of any soft tissue plasmacytomas AND <5% plasmacytomas in the bone marrow; sCR=stringent complete response, CR as above PLUS normal serum FLC assay ratio and absence of clonal cells in bone marrow by immunohistochemistry/fluorescence; VGPR = serum and urine M-component detectable by immunofixation but not on electrophoresis OR $\geq 90\%$ reduction in serum M-component plus urine M-component <100 mg/24 hr; PR = $\geq 50\%$ reduction of serum M-protein and reduction in 24-hour urinary M-protein by $\geq 90\%$ or to <200 mg/24 hours. The analysis population included all randomized participants. Participants were included in the treatment group to which they were randomized. The data cutoff date was July 9, 2018.

End point type	Secondary
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End point timeframe:

Up to approximately 30 months

End point values	Pembrolizumab +Pomalidomide +Dexamethasone	Standard of Care (SOC) Pomalidomide+Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	125		
Units: Percentage of participants				
number (confidence interval 95%)	37.3 (28.9 to 46.4)	42.4 (33.6 to 51.6)		

Statistical analyses

Statistical analysis title	MK-3475 200mg Q3W + SOC vs. Standard of Care
Statistical analysis description:	
Based on Miettinen & Nurminen method stratified by disease status (refractory vs. sensitive to Lenalidomide) and Lines of previous treatments (two vs. three or more); If there were no participants in one of the treatment groups involved in a comparison for a particular stratum, then that stratum was excluded from the treatment comparison.	
Comparison groups	Pembrolizumab+Pomalidomide+Dexamethasone v Standard of Care (SOC) Pomalidomide+Dexamethasone
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.79921
Method	Miettinen & Nurminen method
Parameter estimate	Difference in % vs. SOC
Point estimate	-5.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.1
upper limit	6.9

Secondary: Participants Experiencing One or More Adverse Events (AEs)

End point title	Participants Experiencing One or More Adverse Events (AEs)
End point description:	
An adverse event (AE) was defined as any unfavorable and unintended sign including an abnormal laboratory finding, symptom or disease associated with the use of a medical treatment or procedure, regardless of whether it was considered related to the medical treatment or procedure, that occurred during the course of the study. The analysis population consisted of all randomized participants who received at least one dose of study treatment. Participants were included in the treatment group corresponding to the study treatment they actually received. The data cutoff date was August 3, 2020.	
End point type	Secondary
End point timeframe:	
Up to approximately 54 months	

End point values	Pembrolizumab+Pomalidomide+Dexamethasone	Standard of Care (SOC) Pomalidomide+Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	122	123		
Units: Participants	122	119		

Statistical analyses

No statistical analyses for this end point

Secondary: Participants Discontinuing Study Investigational Product Due to an AE

End point title	Participants Discontinuing Study Investigational Product Due to an AE
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End point description:

An adverse event was defined as any unfavorable and unintended sign including an abnormal laboratory finding, symptom or disease associated with the use of a medical treatment or procedure, regardless of whether it was considered related to the medical treatment or procedure, that occurred during the course of the study. The analysis population consisted of all randomized participants who received at least one dose of study treatment. Participants were included in the treatment group corresponding to the study treatment they actually received. The data cutoff date was August 3, 2020.

End point type	Secondary
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End point timeframe:

Up to approximately 54 months

End point values	Pembrolizumab + Pomalidomide + Dexamethasone	Standard of Care (SOC) Pomalidomide+ Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	122	123		
Units: Participants	26	10		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR) Evaluated According to the IMWG Response Criteria by CAC Blinded Central Review

End point title	Disease Control Rate (DCR) Evaluated According to the IMWG Response Criteria by CAC Blinded Central Review
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End point description:

Disease control rate was based on participants who achieved confirmed sCR, CR, VGPR, PR, minimal response (MR) or had demonstrated stable disease (SD) for at least 12 weeks prior to any evidence of progression. CR = negative immunofixation of serum and urine AND disappearance of any soft tissue plasmacytomas AND <5% plasmacytomas in the bone marrow; sCR=stringent complete response, CR as above PLUS normal serum FLC assay ratio and absence of clonal cells in bone marrow by immunohistochemistry/fluorescence; VGPR = serum and urine M-component detectable by immunofixation but not on electrophoresis OR $\geq 90\%$ reduction in serum M-component plus urine M-component <100 mg/24 hr; PR = $\geq 50\%$ reduction of serum M-protein and reduction in 24-hour urinary M-protein by $\geq 90\%$ or to <200 mg/24 hours. The analysis population included all randomized participants. Participants were included in the treatment group to which they were randomized. The data cutoff date was July 9, 2018.

End point type	Secondary
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End point timeframe:

Up to approximately 30 months

End point values	Pembrolizumab + Pomalidomide + Dexamethasone	Standard of Care (SOC) Pomalidomide+ Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	125		
Units: Percentage of participants				
number (confidence interval 95%)	88.1 (81.1 to 93.2)	84.8 (77.3 to 90.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Second Progression Free Survival (PFS2)

End point title	Second Progression Free Survival (PFS2)
End point description:	
PFS2 was defined as the time from randomization to subsequent disease progression after initiation of new anti-cancer therapy, or death from any cause, whichever occurred first, by investigator assessment. PFS was assessed by CAC blinded central review according to the IMWG response criteria based on the development of new bone lesions or soft tissue plasmacytomas or on a definite increase in the size of existing bone lesions or soft tissue plasmacytomas. The analysis population included all randomized participants. Participants were included in the treatment group to which they were randomized. PFS2 was not analyzed or reported due to early termination of the study.	
End point type	Secondary
End point timeframe:	
Up to approximately 30 months	

End point values	Pembrolizumab + Pomalidomide + Dexamethasone	Standard of Care (SOC) Pomalidomide+ Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[3]	0 ^[4]		
Units: Months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[3] - PFS2 was not analyzed or reported due to an early termination of the study.

[4] - PFS2 was not analyzed or reported due to an early termination of the study.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to approximately 54 months

Adverse event reporting additional description:

Cancer progression was not considered an adverse event (AE) unless considered related to study treatment. The analysis population for all-cause mortality was all randomized participants and for adverse events was the treated participants. The data cutoff date was August 3, 2020.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.0
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Reporting groups

Reporting group title	Pembrolizumab+Pomalidomide+Dexamethasone
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Reporting group description:

Participants receive pembrolizumab 200 mg intravenously (IV) on Day 1 every 3 weeks (Q3W) PLUS pomalidomide 4 mg orally (PO) on Days 1 to 21 of each 28-day cycle PLUS dexamethasone 40 mg PO on Days 1, 8, 15 and 22 of each 28-day cycle.

Reporting group title	Standard of Care (SOC) Pomalidomide+Dexamethasone
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Reporting group description:

Participants receive pomalidomide 4 mg PO on Days 1 to 21 of each 28-day cycle PLUS dexamethasone 40 mg PO on Days 1, 8, 15 and 22 of each 28-day cycle.

Serious adverse events	Pembrolizumab+Pomalidomide+Dexamethasone	Standard of Care (SOC) Pomalidomide+Dexamethasone	
Total subjects affected by serious adverse events			
subjects affected / exposed	79 / 122 (64.75%)	57 / 123 (46.34%)	
number of deaths (all causes)	86	64	
number of deaths resulting from adverse events	4	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 122 (0.82%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basosquamous carcinoma of skin			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 122 (0.82%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Colorectal adenocarcinoma alternative dictionary used: MedDRA 21.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 122 (0.82%) 0 / 1 0 / 0	0 / 123 (0.00%) 0 / 0 0 / 0	
Intestinal adenocarcinoma alternative dictionary used: MedDRA 21.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 122 (0.82%) 0 / 1 0 / 0	0 / 123 (0.00%) 0 / 0 0 / 0	
Malignant ascites alternative dictionary used: MedDRA 21.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 122 (0.82%) 0 / 1 0 / 0	0 / 123 (0.00%) 0 / 0 0 / 0	
Squamous cell carcinoma alternative dictionary used: MedDRA 21.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	2 / 122 (1.64%) 0 / 2 0 / 0	1 / 123 (0.81%) 0 / 1 0 / 0	
Squamous cell carcinoma of skin alternative dictionary used: MedDRA 21.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 122 (0.82%) 0 / 1 0 / 0	0 / 123 (0.00%) 0 / 0 0 / 0	
Vascular disorders Aortic stenosis alternative dictionary used: MedDRA 21.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 122 (0.00%) 0 / 0 0 / 0	1 / 123 (0.81%) 0 / 1 0 / 0	
Deep vein thrombosis alternative dictionary used: MedDRA 21.0			

subjects affected / exposed	0 / 122 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 122 (0.82%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 122 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 122 (0.82%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	3 / 122 (2.46%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	1 / 3	0 / 0	
Fatigue			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 122 (0.00%)	2 / 123 (1.63%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
alternative dictionary used: MedDRA 21.0			

subjects affected / exposed	0 / 122 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 122 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	3 / 122 (2.46%)	5 / 123 (4.07%)	
occurrences causally related to treatment / all	1 / 3	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 122 (0.82%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 122 (0.82%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 122 (0.82%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
alternative dictionary used: MedDRA 21.0			

subjects affected / exposed	2 / 122 (1.64%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 122 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 122 (0.82%)	2 / 123 (1.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 122 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 122 (0.82%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 122 (0.82%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 122 (0.82%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumonitis alternative dictionary used: MedDRA 21.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	5 / 122 (4.10%) 5 / 5 0 / 0	0 / 123 (0.00%) 0 / 0 0 / 0	
Pulmonary congestion alternative dictionary used: MedDRA 21.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 122 (0.00%) 0 / 0 0 / 0	1 / 123 (0.81%) 0 / 1 0 / 0	
Pulmonary embolism alternative dictionary used: MedDRA 21.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 122 (0.00%) 0 / 0 0 / 0	4 / 123 (3.25%) 4 / 4 0 / 0	
Pulmonary haemorrhage alternative dictionary used: MedDRA 21.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 122 (0.82%) 0 / 1 0 / 0	0 / 123 (0.00%) 0 / 0 0 / 0	
Psychiatric disorders Delirium alternative dictionary used: MedDRA 21.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 122 (0.00%) 0 / 0 0 / 0	1 / 123 (0.81%) 0 / 1 0 / 0	
Investigations Alanine aminotransferase increased alternative dictionary used: MedDRA 21.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all Aspartate aminotransferase increased	1 / 122 (0.82%) 0 / 1 0 / 0	0 / 123 (0.00%) 0 / 0 0 / 0	

alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 122 (0.82%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	2 / 122 (1.64%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accidental overdose			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 122 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 122 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 122 (0.82%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibula fracture			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 122 (0.82%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
alternative dictionary used: MedDRA 21.0			

subjects affected / exposed	1 / 122 (0.82%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 122 (0.82%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle strain			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 122 (0.82%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural fever			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 122 (0.82%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 122 (0.82%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 122 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
alternative dictionary used: MedDRA 21.0			

subjects affected / exposed	2 / 122 (1.64%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 122 (0.82%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiogenic shock			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 122 (0.82%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	2 / 122 (1.64%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myocarditis			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 122 (0.82%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pericardial haemorrhage			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 122 (0.82%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Supraventricular tachycardia			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 122 (0.82%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Nervous system disorders			
Balance disorder			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 122 (0.82%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central nervous system lesion			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 122 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 122 (0.82%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cerebrovascular accident			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	2 / 122 (1.64%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cognitive disorder			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 122 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
IIIrd nerve disorder			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 122 (0.82%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
alternative dictionary used: MedDRA 21.0			

subjects affected / exposed	0 / 122 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somnolence			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 122 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 122 (0.82%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 122 (0.82%)	4 / 123 (3.25%)	
occurrences causally related to treatment / all	0 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia of malignant disease			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 122 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Disseminated intravascular coagulation			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 122 (0.82%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile bone marrow aplasia			
alternative dictionary used: MedDRA 21.0			

subjects affected / exposed	1 / 122 (0.82%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	4 / 122 (3.28%)	4 / 123 (3.25%)	
occurrences causally related to treatment / all	3 / 4	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 122 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 122 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 122 (0.82%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo positional			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 122 (0.82%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
alternative dictionary used: MedDRA 21.0			

subjects affected / exposed	0 / 122 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Constipation			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 122 (0.82%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 122 (0.82%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 122 (0.82%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 122 (0.82%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 122 (0.82%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth disorder			
alternative dictionary used: MedDRA 21.0			

subjects affected / exposed	1 / 122 (0.82%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 122 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatitis alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 122 (0.82%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Panniculitis alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 122 (0.82%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stevens-Johnson syndrome alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 122 (0.82%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Rash alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 122 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury alternative dictionary used: MedDRA 21.0			

subjects affected / exposed	4 / 122 (3.28%)	4 / 123 (3.25%)	
occurrences causally related to treatment / all	1 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 122 (0.82%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis haemorrhagic alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 122 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	2 / 122 (1.64%)	2 / 123 (1.63%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders Adrenal insufficiency alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 122 (0.82%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders Fracture pain alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 122 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness alternative dictionary used: MedDRA 21.0			

subjects affected / exposed	1 / 122 (0.82%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis of jaw alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 122 (0.82%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 122 (0.82%)	3 / 123 (2.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyarthritis alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 122 (0.82%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Anal abscess alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 122 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis bacterial alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 122 (0.82%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia alternative dictionary used: MedDRA 21.0			

subjects affected / exposed	1 / 122 (0.82%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial infection			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 122 (0.82%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial sepsis			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 122 (0.82%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 122 (0.82%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis bacterial			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 122 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	2 / 122 (1.64%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 122 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Clostridium difficile infection alternative dictionary used: MedDRA 21.0 subjects affected / exposed	1 / 122 (0.82%)	0 / 123 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Escherichia bacteraemia alternative dictionary used: MedDRA 21.0 subjects affected / exposed	0 / 122 (0.00%)	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Genital herpes simplex alternative dictionary used: MedDRA 21.0 subjects affected / exposed	0 / 122 (0.00%)	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Infective exacerbation of chronic obstructive airways disease alternative dictionary used: MedDRA 21.0 subjects affected / exposed	1 / 122 (0.82%)	0 / 123 (0.00%)		
occurrences causally related to treatment / all	0 / 4	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Influenza alternative dictionary used: MedDRA 21.0 subjects affected / exposed	1 / 122 (0.82%)	3 / 123 (2.44%)		
occurrences causally related to treatment / all	0 / 1	0 / 3		
deaths causally related to treatment / all	0 / 0	0 / 0		
Lower respiratory tract infection alternative dictionary used: MedDRA 21.0 subjects affected / exposed	1 / 122 (0.82%)	0 / 123 (0.00%)		
occurrences causally related to treatment / all	1 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Neutropenic sepsis alternative dictionary used: MedDRA 21.0				

subjects affected / exposed	2 / 122 (1.64%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Parainfluenzae virus infection alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 122 (0.82%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parotitis alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 122 (0.82%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	3 / 122 (2.46%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	23 / 122 (18.85%)	17 / 123 (13.82%)	
occurrences causally related to treatment / all	13 / 29	5 / 21	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia bacterial alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 122 (0.82%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia influenzal alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 122 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumonia parainfluenzae viral alternative dictionary used: MedDRA 21.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 122 (0.82%) 0 / 1 0 / 0	0 / 123 (0.00%) 0 / 0 0 / 0		
Pulmonary sepsis alternative dictionary used: MedDRA 21.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 122 (0.82%) 0 / 1 0 / 0	0 / 123 (0.00%) 0 / 0 0 / 0		
Respiratory tract infection alternative dictionary used: MedDRA 21.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 122 (0.82%) 0 / 1 0 / 1	1 / 123 (0.81%) 1 / 1 0 / 0		
Respiratory tract infection viral alternative dictionary used: MedDRA 21.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 122 (0.82%) 0 / 1 0 / 0	0 / 123 (0.00%) 0 / 0 0 / 0		
Rhinovirus infection alternative dictionary used: MedDRA 21.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 122 (0.82%) 0 / 1 0 / 0	0 / 123 (0.00%) 0 / 0 0 / 0		
Sepsis alternative dictionary used: MedDRA 21.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	3 / 122 (2.46%) 2 / 3 0 / 0	3 / 123 (2.44%) 0 / 3 0 / 0		
Septic shock alternative dictionary used: MedDRA 21.0				

subjects affected / exposed	2 / 122 (1.64%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sinusitis			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 122 (0.82%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 122 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 122 (0.82%)	3 / 123 (2.44%)	
occurrences causally related to treatment / all	1 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 122 (0.82%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 122 (0.82%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 122 (0.82%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Metabolism and nutrition disorders			
Dehydration			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 122 (0.00%)	2 / 123 (1.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gout			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 122 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	2 / 122 (1.64%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 122 (0.82%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 122 (0.82%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemia			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 122 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Steroid Diabetes			

subjects affected / exposed	0 / 122 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Pembrolizumab+Pomalidomide+Dexamethasone	Standard of Care (SOC) Pomalidomide+Dexamethasone	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	115 / 122 (94.26%)	114 / 123 (92.68%)	
Investigations			
Alanine aminotransferase increased alternative dictionary used: MedDRA 21.0 subjects affected / exposed occurrences (all)	10 / 122 (8.20%) 11	4 / 123 (3.25%) 4	
Blood creatinine increased alternative dictionary used: MedDRA 21.0 subjects affected / exposed occurrences (all)	7 / 122 (5.74%) 10	4 / 123 (3.25%) 4	
Neutrophil count decreased alternative dictionary used: MedDRA 21.0 subjects affected / exposed occurrences (all)	16 / 122 (13.11%) 28	17 / 123 (13.82%) 26	
Platelet count decreased alternative dictionary used: MedDRA 21.0 subjects affected / exposed occurrences (all)	7 / 122 (5.74%) 11	10 / 123 (8.13%) 12	
Weight decreased alternative dictionary used: MedDRA 21.0 subjects affected / exposed occurrences (all)	7 / 122 (5.74%) 7	5 / 123 (4.07%) 5	
White blood cell count decreased alternative dictionary used: MedDRA 21.0			

subjects affected / exposed occurrences (all)	13 / 122 (10.66%) 19	11 / 123 (8.94%) 21	
Nervous system disorders			
Dizziness alternative dictionary used: MedDRA 21.0 subjects affected / exposed occurrences (all)	16 / 122 (13.11%) 19	14 / 123 (11.38%) 15	
Headache alternative dictionary used: MedDRA 21.0 subjects affected / exposed occurrences (all)	16 / 122 (13.11%) 20	5 / 123 (4.07%) 7	
Neuropathy peripheral alternative dictionary used: MedDRA 21.0 subjects affected / exposed occurrences (all)	8 / 122 (6.56%) 8	5 / 123 (4.07%) 5	
Tremor alternative dictionary used: MedDRA 21.0 subjects affected / exposed occurrences (all)	10 / 122 (8.20%) 11	10 / 123 (8.13%) 10	
Blood and lymphatic system disorders			
Anaemia alternative dictionary used: MedDRA 21.0 subjects affected / exposed occurrences (all)	34 / 122 (27.87%) 53	40 / 123 (32.52%) 57	
Leukopenia alternative dictionary used: MedDRA 21.0 subjects affected / exposed occurrences (all)	10 / 122 (8.20%) 21	9 / 123 (7.32%) 16	
Neutropenia alternative dictionary used: MedDRA 21.0 subjects affected / exposed occurrences (all)	49 / 122 (40.16%) 120	33 / 123 (26.83%) 63	
Thrombocytopenia alternative dictionary used: MedDRA 21.0			

subjects affected / exposed occurrences (all)	26 / 122 (21.31%) 49	19 / 123 (15.45%) 27	
General disorders and administration site conditions			
Asthenia alternative dictionary used: MedDRA 21.0 subjects affected / exposed occurrences (all)	15 / 122 (12.30%) 21	14 / 123 (11.38%) 17	
Chest pain alternative dictionary used: MedDRA 21.0 subjects affected / exposed occurrences (all)	9 / 122 (7.38%) 11	5 / 123 (4.07%) 6	
Fatigue alternative dictionary used: MedDRA 21.0 subjects affected / exposed occurrences (all)	33 / 122 (27.05%) 36	37 / 123 (30.08%) 44	
Oedema peripheral alternative dictionary used: MedDRA 21.0 subjects affected / exposed occurrences (all)	22 / 122 (18.03%) 26	20 / 123 (16.26%) 23	
Pyrexia alternative dictionary used: MedDRA 21.0 subjects affected / exposed occurrences (all)	26 / 122 (21.31%) 35	19 / 123 (15.45%) 23	
Gastrointestinal disorders			
Constipation alternative dictionary used: MedDRA 21.0 subjects affected / exposed occurrences (all)	30 / 122 (24.59%) 37	26 / 123 (21.14%) 27	
Diarrhoea alternative dictionary used: MedDRA 21.0 subjects affected / exposed occurrences (all)	21 / 122 (17.21%) 30	27 / 123 (21.95%) 35	
Gastrooesophageal reflux disease alternative dictionary used: MedDRA 21.0			

subjects affected / exposed occurrences (all) 4 / 122 (3.28%) 4	7 / 123 (5.69%) 7	
Nausea alternative dictionary used: MedDRA 21.0 subjects affected / exposed occurrences (all) 23 / 122 (18.85%) 26	16 / 123 (13.01%) 19	
Vomiting alternative dictionary used: MedDRA 21.0 subjects affected / exposed occurrences (all) 10 / 122 (8.20%) 17	13 / 123 (10.57%) 14	
Respiratory, thoracic and mediastinal disorders Cough alternative dictionary used: MedDRA 21.0 subjects affected / exposed occurrences (all) 19 / 122 (15.57%) 23	18 / 123 (14.63%) 21	
Dyspnoea alternative dictionary used: MedDRA 21.0 subjects affected / exposed occurrences (all) 21 / 122 (17.21%) 26	19 / 123 (15.45%) 25	
Epistaxis alternative dictionary used: MedDRA 21.0 subjects affected / exposed occurrences (all) 9 / 122 (7.38%) 9	3 / 123 (2.44%) 5	
Skin and subcutaneous tissue disorders Pruritus alternative dictionary used: MedDRA 21.0 subjects affected / exposed occurrences (all) 6 / 122 (4.92%) 6	10 / 123 (8.13%) 10	
Rash alternative dictionary used: MedDRA 21.0 subjects affected / exposed occurrences (all) 12 / 122 (9.84%) 13	10 / 123 (8.13%) 12	
Psychiatric disorders		

Depression alternative dictionary used: MedDRA 21.0 subjects affected / exposed occurrences (all)	7 / 122 (5.74%) 7	3 / 123 (2.44%) 3	
Insomnia alternative dictionary used: MedDRA 21.0 subjects affected / exposed occurrences (all)	10 / 122 (8.20%) 11	17 / 123 (13.82%) 18	
Musculoskeletal and connective tissue disorders Arthralgia alternative dictionary used: MedDRA 21.0 subjects affected / exposed occurrences (all) Back pain alternative dictionary used: MedDRA 21.0 subjects affected / exposed occurrences (all) Muscle spasms alternative dictionary used: MedDRA 21.0 subjects affected / exposed occurrences (all) Muscular weakness alternative dictionary used: MedDRA 21.0 subjects affected / exposed occurrences (all) Musculoskeletal chest pain alternative dictionary used: MedDRA 21.0 subjects affected / exposed occurrences (all) Pain in extremity alternative dictionary used: MedDRA 21.0 subjects affected / exposed occurrences (all)	10 / 122 (8.20%) 11 14 / 122 (11.48%) 15 15 / 122 (12.30%) 16 6 / 122 (4.92%) 10 12 / 122 (9.84%) 14 6 / 122 (4.92%) 8	16 / 123 (13.01%) 17 21 / 123 (17.07%) 23 14 / 123 (11.38%) 15 11 / 123 (8.94%) 13 6 / 123 (4.88%) 6 7 / 123 (5.69%) 7	
Infections and infestations			

Nasopharyngitis alternative dictionary used: MedDRA 21.0 subjects affected / exposed occurrences (all)	7 / 122 (5.74%) 7	6 / 123 (4.88%) 8	
Upper respiratory tract infection alternative dictionary used: MedDRA 21.0 subjects affected / exposed occurrences (all)	21 / 122 (17.21%) 27	25 / 123 (20.33%) 33	
Urinary tract infection alternative dictionary used: MedDRA 21.0 subjects affected / exposed occurrences (all)	1 / 122 (0.82%) 1	8 / 123 (6.50%) 9	
Pneumonia subjects affected / exposed occurrences (all)	7 / 122 (5.74%) 7	2 / 123 (1.63%) 2	
Metabolism and nutrition disorders Decreased appetite alternative dictionary used: MedDRA 21.0 subjects affected / exposed occurrences (all) Hyperglycaemia alternative dictionary used: MedDRA 21.0 subjects affected / exposed occurrences (all) Hypokalaemia alternative dictionary used: MedDRA 21.0 subjects affected / exposed occurrences (all) Hypomagnesaemia alternative dictionary used: MedDRA 21.0 subjects affected / exposed occurrences (all)	9 / 122 (7.38%) 9 7 / 122 (5.74%) 7 11 / 122 (9.02%) 16 3 / 122 (2.46%) 6	8 / 123 (6.50%) 8 5 / 123 (4.07%) 5 8 / 123 (6.50%) 9 8 / 123 (6.50%) 8	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 April 2016	a. Sections 5.7.3, 5.7.4, 6.1, 7.1.5.2 - Addition of Pomalidomide pregnancy prevention plan for subjects in clinical trials. Added row to flowchart for Pomalidomide education and counseling. b. Section 12.9. 12.10, 12.11 - Supplemental information/sheets from the Pomalidomide Adult Pregnancy Risk Minimization Plan for Clinical Trials added as Appendices. c. Section 5.7.5.1 - Removed section
22 August 2016	Section 5.3 - Clarified the exclusion criteria related to pneumonitis.
07 February 2017	a. Section 5.2.1.2.1 - Updated Table 4 to permanently discontinue for any recurrent grade 2 pneumonitis. b. Sections 7.1.5.4.1; 7.1.5.5.2; 7.2.3.2.1 - Clarification of follow-up for allogeneic SCT with collect additional information regarding allogeneic Stem Cell Transplants and complications following treatment with pembrolizumab.
05 October 2017	Sections 1.0, 2.1, 5.2.3, 6.1, 6.1.1, 7.1.5.3, 8.0 - Added treatment discontinuation statement with defined population. The FDA determined that the risks of pembrolizumab plus pomalidomide or lenalidomide outweighed any potential benefit for patients with multiple myeloma. Based on this decision, the treatment phase of KN183 and KN185 is closed effective immediately. All subjects must stop study treatment, complete the Discontinuation Visit and move into the long-term safety and survival follow-up per protocol.
10 May 2018	a. Section 4.2.3.4 - Added in the second paragraph: Samples obtained for PK may be used to conduct additional safety analysis, if needed. b. Section 6.1 - Added in footnote #6: Pharmacokinetic/anti-drug antibody (PK/ADA) samples may be used to conduct additional safety analysis, if needed. c. Section 7.1.3.2.1 - Added in the second paragraph: Samples obtained for PK or ADA may be used to conduct additional safety analysis, if needed.
16 July 2020	a. Section 1.0 - Updated duration of survival follow-up to 12 months following discontinuation visit. b. Section 2.1 - Updated follow-up after stem cell transplant (SCT) to provide for completion of follow-up at the end of the trial. c. Section 5.10 - Updated criteria for end of the trial to include Sponsor decision to close.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
05 October 2017	The FDA determined that the risks of pembrolizumab plus pomalidomide or lenalidomide outweighed any potential benefit for patients with multiple myeloma. Based on this decision, the treatment phase of KN183 and KN185 is closed effective immediately.	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The MK-3475-183 study was stopped/terminated early. Endpoint statistics may be biased due to the incomplete treatment and follow-up of subjects after study termination

Notes: