Clinical trial results:
A Phase II, Multicenter, Open Label Study of Bintrafusp Alfa (M7824) Monotherapy in Participants With Advanced, Unresectable Cervical Cancer With Disease Progression During or After Platinum-Containing Chemotherapy

Summary

EudraCT number	2019-003583-40
Trial protocol	FR ES HU BE
Global end of trial date	14 December 2022

Results information

Result version number	v1 (current)
This version publication date	03 November 2023
First version publication date	03 November 2023

Trial information

Trial identification

Sponsor protocol code	MS200647_0017

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04246489
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck Healthcare KGaA, Darmstadt, Germany
Sponsor organisation address	Frankfurter Strasse 250, Darmstadt, Germany, 64293
Public contact	Communication Centre, Merck Healthcare KGaA, Darmstadt, Germany, +49 6151725200, service@merckgroup.com
Scientific contact	Communication Centre, Merck Healthcare KGaA, Darmstadt, Germany, +49 6151725200, service@merckgroup.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	14 December 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 December 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main purpose of this study was to evaluate clinical efficacy and safety of bintrafusp alfa in subjects with advanced, unresectable cervical cancer with disease progression during or after platinum-containing chemotherapy.

Protection of trial subjects:

Subject protection was ensured by following high medical and ethical standards in accordance with the principles laid down in the Declaration of Helsinki, and that are consistent with Good Clinical Practice and applicable regulation.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 March 2020
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: 3
Country: Number of subjects enrolled	Australia: 4
Country: Number of subjects enrolled	Belgium: 7
Country: Number of subjects enrolled	Brazil: 6
Country: Number of subjects enrolled	China: 23
Country: Number of subjects enrolled	France: 17
Country: Number of subjects enrolled	Hungary: 4
Country: Number of subjects enrolled	Japan: 42
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 23
Country: Number of subjects enrolled	Russian Federation: 4
Country: Number of subjects enrolled	Spain: 9
Country: Number of subjects enrolled	United States: 4
Worldwide total number of subjects	146
EEA total number of subjects	37

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)	123
From 65 to 84 years	23
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 203 subjects were screened, of which 146 subjects received bintrafusp alfa monotherapy.

Period 1

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

Arms

Arm title	Bintrafusp Alfa

Arm description:

Subjects received an intravenous infusion of 1200 milligrams (mg) bintrafusp alfa once every 2 weeks until confirmed disease progression, unacceptable toxicity, study withdrawal or death.

Arm type	Experimental
Investigational medicinal product name	Bintrafusp alfa
Investigational medicinal product code	
Other name	M7824
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received an intravenous infusion of 1200 milligrams (mg) bintrafusp alfa once every 2 weeks until confirmed disease progression, death, unacceptable toxicity and study withdrawal.

Number of subjects in period 1	Bintrafusp Alfa
Started	146
Completed	146

Baseline characteristics

Reporting groups	
Reporting group title	Bintrafusp Alfa
Reporting group description:	
Subjects received an intravenous infusion of 1200 milligrams (mg) bintrafusp alfa once every 2 weeks until confirmed disease progression, unacceptable toxicity, study withdrawal or death.	

Reporting group values	Bintrafusp Alfa	Total	
Number of subjects	146	146	
Age categorical Units: subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	123	123	
From 65-84 years	23	23	
85 years and over	0	0	
Sex: Female, Male Units: subjects			
Female	146	146	
Male	0	0	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	11	11	
Not Hispanic or Latino	132	132	
Unknown or Not Reported	3	3	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	90	90	
Native Hawaiian or Other Pacific Islander	1	1	
Black or African American	1	1	
White	37	37	
More than one race	0	0	
Unknown or Not Reported	17	17	

End points

End points reporting groups

Reporting group title	Bintrafusp Alfa

Reporting group description:

Subjects received an intravenous infusion of 1200 milligrams (mg) bintrafusp alfa once every 2 weeks until confirmed disease progression, unacceptable toxicity, study withdrawal or death.

Primary: Number of Subjects With Confirmed Objective Response According to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) as Assessed by Independent Review Committee (IRC)

End point title	Number of Subjects With Confirmed Objective Response According to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) as Assessed by Independent Review Committee (IRC)[1]

End point description:

Confirmed objective response was defined as the number of subjects with a confirmed objective response of complete response (CR) or partial response (PR). CR: Disappearance of all evidence of target and non-target lesions. PR: At least 30 percent (%) reduction from baseline in the sum of the longest diameter (SLD) of all lesions. Confirmed CR = at least 2 determinations of CR at least 4 weeks apart and before progression. Confirmed PR = at least 2 determinations of PR at least 4 weeks apart and before progression (and not qualifying for a CR). Confirmed objective response was determined according to RECIST v1.1 and as adjudicated by IRC. Full Analysis Set (FAS) included all subjects who were administered at least one dose of bintrafusp alfa.

End point type	Primary

End point timeframe:

Time from first treatment to up to data cutoff up to 688 days

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical and comparison analysis were performed in single arm for this endpoint.

End point values	Bintrafusp Alfa			
Subject group type	Reporting group			
Number of subjects analysed	146			
Units: subjects	32			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) According to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) as Assessed by Independent Review Committee (IRC)

End point title	Duration of Response (DOR) According to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) as Assessed by Independent Review Committee (IRC)

End point description:

DOR was defined for subjects with confirmed response, as the time from first documentation of confirmed objective response (Complete Response [CR] or Partial Response [PR]) according to RECIST 1.1 to the date of first documentation of progression disease (PD) or death due to any cause, whichever

occurred first. CR: Disappearance of all evidence of target and non-target lesions. PR: At least 30% reduction from baseline in the SLD of all lesions. PD: At least a 20 percent (%) increase in the SLD, taking as reference the smallest SLD recorded from baseline or the appearance of 1 or more new lesions. DOR was determined according to RECIST v1.1 and assessed by IRC. Results were calculated based on Kaplan-Meier estimates. FAS included all subjects who were administered at least one dose of bintrafusp alfa.

End point type	Secondary

End point timeframe:

Time from first documentation of a confirmed objective response up to 688 days

End point values	Bintrafusp Alfa			
Subject group type	Reporting group			
Number of subjects analysed	146[2]			
Units: months				
median (confidence interval 95%)	99999 (7.4 to 99999)			

Notes:

[2] - The median was not reached and the upper limit was not estimated. 99999 represents no observation.

Statistical analyses

No statistical analyses for this end point

Secondary: Durable Response According to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) as Assessed by Independent Review Committee (IRC)

End point title	Durable Response According to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) as Assessed by Independent Review Committee (IRC)

End point description:

Durable Response was defined as the number of subjects with confirmed objective response (CR or PR) according to RECIST 1.1, determined by IRC with duration of at least 6 months. CR: Disappearance of all evidence of target and non-target lesions. PR: At least 30% reduction from baseline in the SLD of all lesions. PD: At least a 20 percent (%) increase in the SLD, taking as reference the smallest SLD recorded from baseline or the appearance of 1 or more new lesions. FAS included all subjects who were administered at least one dose of bintrafusp alfa.

End point type	Secondary

End point timeframe:

Time from first treatment up to 688 days

End point values	Bintrafusp Alfa			
Subject group type	Reporting group			
Number of subjects analysed	146			
Units: subjects	19			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) and Treatment-Related TEAEs, Including Adverse Event of Special Interests (AESIs)

End point title	Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) and Treatment-Related TEAEs, Including Adverse Event of Special Interests (AESIs)

End point description:

Adverse Event (AE) was defined any untoward medical occurrence in a subjects administered with a study drug, which does not necessarily had a causal relationship with this treatment. Serious AE was defined AE that resulted in any of the following outcomes: death; life threatening; persistent/significant disability/incapacity; initial/prolonged inpatient hospitalization; congenital anomaly/birth defect. TEAEs: TEAEs was defined as events with onset date or worsening during the on-treatment period. TEAEs included serious AEs and non-serious AEs. Treatment-related TEAEs: reasonably related to the study intervention. AESIs included Infusion-related reactions, Immune-related AEs, Transforming growth factor- beta (TGF-ß) inhibition mediated skin AE, bleeding and anemia. Safety analysis set included all subjects who were administered at least one dose of bintrafusp alfa.

End point type	Secondary

End point timeframe:

Time from first treatment up to 688 days

End point values	Bintrafusp Alfa			
Subject group type	Reporting group			
Number of subjects analysed	146			
Units: subjects				
TEAE's	145			
Treatment Related TEAEs	106			
AESI: Infusion-related reaction	5			
AESI: Immune-related AE	49			
AESI: TGF-beta inhibition mediated skin AE	7			
AESI: Anemia	82			
AESI: Bleeding events	81			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS) According to Response Evaluation Criteria in Solid Tumors (RECIST Version 1.1) Assessed by Independent Review Committee (IRC)

End point title	Progression-Free Survival (PFS) According to Response Evaluation Criteria in Solid Tumors (RECIST Version 1.1) Assessed by Independent Review Committee (IRC)

End point description:

PFS was defined as the time from first administration of study intervention until date of the first documentation of disease progression (PD) or death due to any cause, whichever occurred first. PD: At least a 20 percent (%) increase in the SLD, taking as reference the smallest SLD recorded from baseline or the appearance of 1 or more new lesions. Kaplan-Meier estimates was used to calculate PFS. FAS included all subjects who were administered at least one dose of bintrafusp alfa.

End point type	Secondary

End point timeframe:

Time from first administration of study drug until the first documentation of PD or death, assessed up to 688 days

End point values	Bintrafusp Alfa			
Subject group type	Reporting group			
Number of subjects analysed	146			
Units: months				
median (confidence interval 95%)	1.9 (1.8 to 2.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as the time from first administration of study intervention to the date of death due to any cause. The OS was analyzed by using the Kaplan-Meier method. FAS included all subjects who were administered at least one dose of bintrafusp alfa.

End point type	Secondary

End point timeframe:

Time from first administration of study drug up to 688 days

End point values	Bintrafusp Alfa			
Subject group type	Reporting group			
Number of subjects analysed	146			
Units: months				
median (confidence interval 95%)	13.7 (10.6 to 17.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Confirmed Objective Response According to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) as Assessed by the Investigator

End point title	Number of Subjects With Confirmed Objective Response According to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) as Assessed by the Investigator

End point description:

Confirmed objective response was defined as the number of subjects with a confirmed objective response of complete response (CR) or partial response (PR). CR: Disappearance of all evidence of target and non-target lesions. PR: At least 30% reduction from baseline in the sum of the longest diameter (SLD) of all lesions. Confirmed CR = at least 2 determinations of CR at least 4 weeks apart and before progression. Confirmed PR = at least 2 determinations of PR at least 4 weeks apart and before progression (and not qualifying for a CR). Confirmed objective response was determined according to RECIST v1.1 and as adjudicated by Investigator. FAS included all subjects who were administered at least one dose of bintrafusp alfa.

End point type	Secondary

End point timeframe:

Time from first treatment up to 688 days

End point values	Bintrafusp Alfa			
Subject group type	Reporting group			
Number of subjects analysed	146			
Units: subjects	25			

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Pre-Dose Concentrations (Ctrough) of Bintrafusp Alfa

End point title	Serum Pre-Dose Concentrations (Ctrough) of Bintrafusp Alfa

End point description:

Ctrough was defined as the concentration observed immediately before next dosing (corresponding to pre-dose or trough concentration for multiple dosing). Pharmacokinetic (PK) analysis set included all subjects who completed at least one dose of bintrafusp alfa and who provided at least one sample with a measurable concentration of bintrafusp alfa. Here, "Overall Number of Subjects Analyzed" signifies those subjects who were evaluable for this endpoint and "number analyzed(n)" signifies those subjects who were evaluable at specified time points for this endpoint.

End point type	Secondary

End point timeframe:

At Day 15, Day 29, Day 43, Day 85, Day 127, Day 169, Day 253, Day 337, Day 421, Day 505 and Day 589

End point values	Bintrafusp Alfa			
Subject group type	Reporting group			
Number of subjects analysed	143			
Units: microgram per milliliter (mcg/mL)				
geometric mean (geometric coefficient of variation)				
Day 15(n=125)	73.7 (± 55.3)			
Day 29(n=103)	107 (± 48.7)			
Day 43(n=84)	108 (± 53)			
Day 85(n=47)	115 (± 44.9)			
Day 127(n=35)	107 (± 69)			

Day 169(n=25)	137 (± 41)			
Day 253(n=12)	101 (± 45.8)			
Day 337(n=11)	120 (± 50.9)			
Day 421(n=5)	103 (± 56.4)			
Day 505(n=4)	220 (± 22.4)			
Day 589(n=3)	154 (± 10.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Confirmed Objective Response According to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) as Assessed by Independent Review Committee (IRC) According to Programmed Death Ligand 1 (PD-L1) Expression

End point title	Percentage of Subjects With Confirmed Objective Response According to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) as Assessed by Independent Review Committee (IRC) According to Programmed Death Ligand 1 (PD-L1) Expression

End point description:

Confirmed objective response was defined as the percentage of subjects with a confirmed objective response of complete response (CR) or partial response (PR). CR: Disappearance of all evidence of target and non-target lesions. PR: At least 30% reduction from baseline in the sum of the longest diameter (SLD) of all lesions. Confirmed CR = at least 2 determinations of CR at least 4 weeks apart and before progression. Confirmed PR = at least 2 determinations of PR at least 4 weeks apart and before progression (and not qualifying for a CR). Subjects with PD-L1 positive tumors (Combined positive score (CPS) >=1) and PD-L1 negative tumors (CPS<1). FAS included all subjects who were administered at least one dose of bintrafusp alfa. Here, "Overall Number of Subjects Analyzed" signifies those subjects who were evaluable for this endpoint and "number analyzed(n)" signifies those subjects who were evaluable at specified categories for this endpoint.

End point type	Secondary

End point timeframe:

Time from first treatment up to 688 days

End point values	Bintrafusp Alfa			
Subject group type	Reporting group			
Number of subjects analysed	141			
Units: percentage of subjects				
number (confidence interval 95%)				
PD-L1 positive tumors (CPS>=1)(n=86)	25.6 (16.8 to 36.1)			
PD-L1 negative tumors (CPS <1)(n=55)	18.2 (9.1 to 30.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Concentration at End of Infusion (CEOI) of Bintrafusp Alfa

End point title	Serum Concentration at End of Infusion (CEOI) of Bintrafusp Alfa

End point description:

Serum Concentration at End of Infusion (CEOI) of bintrafusp alfa is reported. PK analysis set included all subjects who completed at least one dose of Bintrafusp Alfa and who provided at least one sample with a measurable concentration of Bintrafusp Alfa. Here, "Overall Number of Subjects Analyzed" signifies those subjects who were evaluable for this endpoint and "number analyzed(n)" signifies those subjects who were evaluable at specified time points for this endpoint.

End point type	Secondary

End point timeframe:

At Day 1 and Day 29

End point values	Bintrafusp Alfa			
Subject group type	Reporting group			
Number of subjects analysed	143			
Units: mcg/mL				
geometric mean (geometric coefficient of variation)				
Day 1(n=142) Day 29(n=102)	469 (± 21.9) 546 (± 24.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Positive Antidrug Antibodies (ADA)

End point title	Number of Subjects With Positive Antidrug Antibodies (ADA)

End point description:

Serum samples were analyzed by a validated assay method to detect the presence of antidrug antibodies (ADA). Number of subjects with positive ADA were reported. Immunogenicity analysis set included all subjects who received at least one dose of bintrafusp alfa and who had at least one valid result of ADA.

End point type	Secondary

End point timeframe:

Time from first treatment up to 688 days

End point values	Bintrafusp Alfa			
Subject group type	Reporting group			
Number of subjects analysed	142			
Units: subjects	33			

Statistical analyses

No statistical analyses for this end point

Secondary: PFS According to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) as Assessed by Independent Review Committee (IRC) According to Programmed Death Ligand 1 (PD-L1) Expression

End point title	PFS According to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) as Assessed by Independent Review Committee (IRC) According to Programmed Death Ligand 1 (PD-L1) Expression

End point description:

PFS was defined as the time from first administration of study intervention until the first documentation of disease progression (PD) or death due to any cause, whichever occurred first. PD: At least a 20 percent (%) increase in the SLD, taking as reference the smallest SLD recorded from baseline or the appearance of 1 or more new lesions. PFS was determined according to RECIST v1.1 and as adjudicated by IRC through PD-L1 Subgroup. Subjects with PD-L1 positive tumors (Combined positive score (CPS) >=1) and PD-L1 negative tumors (CPS<1). FAS included all subjects who were administered at least one dose of bintrafusp alfa. Here, "Overall Number of Subjects Analyzed" signifies those subjects who were evaluable for this endpoint and "number analyzed(n)" signifies those subjects who were evaluable at specified categories for this endpoint.

End point type	Secondary

End point timeframe:

Time from first administration of study drug until the first documentation of PD or death, assessed up to 688 days

End point values	Bintrafusp Alfa			
Subject group type	Reporting group			
Number of subjects analysed	141			
Units: months				
median (confidence interval 95%)				
PD-L1 positive tumors (CPS>=1)(n=86)	1.9 (1.8 to 4.3)			
PD-L1 negative tumors (CPS<1)(n=55)	1.9 (1.7 to 2.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: OS as Assessed According to Programmed Death Ligand 1 (PD-L1) Expression

End point title	OS as Assessed According to Programmed Death Ligand 1 (PD-L1) Expression

End point description:

OS was defined as the time from first administration of study intervention to the date of death due to any cause. The OS was analyzed by using the Kaplan-Meier method. Participants with PD-L1 positive tumors (Combined positive score (CPS) >=1) and PD-L1 negative tumors (CPS<1). FAS included all subjects who were administered at least one dose of bintrafusp alfa. Here, "Overall Number of Subjects Analyzed" signifies those subjects who were evaluable for this endpoint and "number analyzed(n)" signifies those subjects who were evaluable at specified categories for this endpoint.

End point type	Secondary

End point timeframe:

Time from first administration of study drug up to 688 days

End point values	Bintrafusp Alfa			
Subject group type	Reporting group			
Number of subjects analysed	141[3]			
Units: months				
median (confidence interval 95%)				
PD-L1positive tumors(CPS>=1)(n=86)	17.5 (12.5 to 99999)			
PD-L1negative tumors(CPS<1)(n=55)	8.7 (5.8 to 11.8)			

Notes:

[3] - Due to small number of events Upper limit was not derived. 99999 represents no observation.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Time from first treatment up to 688 days	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups	
Reporting group title	Bintrafusp Alfa

Reporting group description:

Subjects received an intravenous infusion of 1200 milligrams (mg) bintrafusp alfa once every 2 weeks until confirmed disease progression, unacceptable toxicity, study withdrawal or death.

Serious adverse events	Bintrafusp Alfa		
Total subjects affected by serious adverse events			
subjects affected / exposed	94 / 146 (64.38%)		
number of deaths (all causes)	76		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder cancer			
subjects affected / exposed	1 / 146 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cancer pain			
subjects affected / exposed	1 / 146 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Malignant ascites			
subjects affected / exposed	1 / 146 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Malignant pleural effusion			
subjects affected / exposed	1 / 146 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Metastases to spine				
subjects affected / exposed	1 / 146 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Squamous cell carcinoma of skin				
subjects affected / exposed	1 / 146 (0.68%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Tumour haemorrhage				
subjects affected / exposed	1 / 146 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tumour pain				
subjects affected / exposed	1 / 146 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Deep vein thrombosis				
subjects affected / exposed	1 / 146 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypovolaemic shock				
subjects affected / exposed	1 / 146 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haematoma				
subjects affected / exposed	1 / 146 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Venous thrombosis limb				
subjects affected / exposed	1 / 146 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration				

site conditions				
Asthenia				
subjects affected / exposed	2 / 146 (1.37%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Disease progression				
subjects affected / exposed	12 / 146 (8.22%)			
occurrences causally related to treatment / all	0 / 12			
deaths causally related to treatment / all	0 / 0			
Pain				
subjects affected / exposed	1 / 146 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Malaise				
subjects affected / exposed	1 / 146 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General physical health deterioration				
subjects affected / exposed	4 / 146 (2.74%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast disorders				
Female genital tract fistula				
subjects affected / exposed	1 / 146 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Genital haemorrhage				
subjects affected / exposed	1 / 146 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intermenstrual bleeding				
subjects affected / exposed	2 / 146 (1.37%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			

Vaginal haemorrhage				
subjects affected / exposed	1 / 146 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Asphyxia				
subjects affected / exposed	1 / 146 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	2 / 146 (1.37%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	4 / 146 (2.74%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Pulmonary thrombosis				
subjects affected / exposed	1 / 146 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Product issues				
Device dislocation				
subjects affected / exposed	2 / 146 (1.37%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Investigations				
Amylase increased				
subjects affected / exposed	1 / 146 (0.68%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Lipase increased				

subjects affected / exposed	1 / 146 (0.68%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Transaminases increased			
subjects affected / exposed	1 / 146 (0.68%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Cystitis radiation			
subjects affected / exposed	2 / 146 (1.37%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Lumbar vertebral fracture			
subjects affected / exposed	1 / 146 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Stoma obstruction			
subjects affected / exposed	1 / 146 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Spinal compression fracture			
subjects affected / exposed	1 / 146 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Radiation proctitis			
subjects affected / exposed	1 / 146 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	1 / 146 (0.68%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Nervous system disorders			
Altered state of consciousness			
subjects affected / exposed	2 / 146 (1.37%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Brain oedema			
subjects affected / exposed	1 / 146 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Embolic stroke			
subjects affected / exposed	1 / 146 (0.68%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Myasthenia gravis			
subjects affected / exposed	1 / 146 (0.68%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Neuritis			
subjects affected / exposed	1 / 146 (0.68%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Polyneuropathy in malignant disease			
subjects affected / exposed	1 / 146 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	2 / 146 (1.37%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Blood loss anaemia			
subjects affected / exposed	1 / 146 (0.68%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Anaemia				
subjects affected / exposed	14 / 146 (9.59%)			
occurrences causally related to treatment / all	4 / 14			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal pain				
subjects affected / exposed	2 / 146 (1.37%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Anal haemorrhage				
subjects affected / exposed	1 / 146 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Colitis				
subjects affected / exposed	4 / 146 (2.74%)			
occurrences causally related to treatment / all	4 / 4			
deaths causally related to treatment / all	0 / 0			
Dental caries				
subjects affected / exposed	1 / 146 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastric haemorrhage				
subjects affected / exposed	1 / 146 (0.68%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastric ulcer haemorrhage				
subjects affected / exposed	1 / 146 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ileus				
subjects affected / exposed	1 / 146 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Malignant gastrointestinal				

obstruction			
subjects affected / exposed	1 / 146 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mouth ulceration			
subjects affected / exposed	1 / 146 (0.68%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Obstructive defaecation			
subjects affected / exposed	1 / 146 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatitis			
subjects affected / exposed	1 / 146 (0.68%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatitis acute			
subjects affected / exposed	2 / 146 (1.37%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Rectal haemorrhage			
subjects affected / exposed	1 / 146 (0.68%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Subileus			
subjects affected / exposed	1 / 146 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 146 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			

Cholangitis acute				
subjects affected / exposed	1 / 146 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatic function abnormal				
subjects affected / exposed	2 / 146 (1.37%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Hepatic pain				
subjects affected / exposed	1 / 146 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Drug-induced liver injury				
subjects affected / exposed	1 / 146 (0.68%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Immune-mediated dermatitis				
subjects affected / exposed	2 / 146 (1.37%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Erythema multiforme				
subjects affected / exposed	1 / 146 (0.68%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Acute kidney injury				
subjects affected / exposed	3 / 146 (2.05%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Cystitis haemorrhagic				
subjects affected / exposed	2 / 146 (1.37%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			

Haematuria			
subjects affected / exposed	15 / 146 (10.27%)		
occurrences causally related to treatment / all	6 / 15		
deaths causally related to treatment / all	0 / 0		
Haemorrhage urinary tract			
subjects affected / exposed	1 / 146 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hydronephrosis			
subjects affected / exposed	3 / 146 (2.05%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Renal failure			
subjects affected / exposed	2 / 146 (1.37%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Ureteral polyp			
subjects affected / exposed	1 / 146 (0.68%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary bladder haemorrhage			
subjects affected / exposed	1 / 146 (0.68%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary retention			
subjects affected / exposed	2 / 146 (1.37%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Secondary adrenocortical insufficiency			
subjects affected / exposed	1 / 146 (0.68%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Inappropriate antidiuretic hormone secretion				
subjects affected / exposed	1 / 146 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Immune-mediated thyroiditis				
subjects affected / exposed	1 / 146 (0.68%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Adrenal insufficiency				
subjects affected / exposed	2 / 146 (1.37%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Pathological fracture				
subjects affected / exposed	2 / 146 (1.37%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Arthralgia				
subjects affected / exposed	1 / 146 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Back pain				
subjects affected / exposed	1 / 146 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Myositis				
subjects affected / exposed	1 / 146 (0.68%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Abdominal sepsis				

subjects affected / exposed	1 / 146 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Brain abscess				
subjects affected / exposed	1 / 146 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intestinal fistula infection				
subjects affected / exposed	1 / 146 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Kidney infection				
subjects affected / exposed	1 / 146 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lung abscess				
subjects affected / exposed	1 / 146 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis				
subjects affected / exposed	1 / 146 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis acute				
subjects affected / exposed	1 / 146 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	1 / 146 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Septic arthritis streptococcal				

subjects affected / exposed	1 / 146 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	2 / 146 (1.37%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection bacterial			
subjects affected / exposed	1 / 146 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urosepsis			
subjects affected / exposed	1 / 146 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 146 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diabetic ketoacidosis			
subjects affected / exposed	2 / 146 (1.37%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Malnutrition			
subjects affected / exposed	1 / 146 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Type 1 diabetes mellitus			
subjects affected / exposed	1 / 146 (0.68%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Bintrafusp Alfa		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	145 / 146 (99.32%)		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	23 / 146 (15.75%)		
occurrences (all)	23		
Fatigue			
subjects affected / exposed	14 / 146 (9.59%)		
occurrences (all)	14		
Pyrexia			
subjects affected / exposed	25 / 146 (17.12%)		
occurrences (all)	25		
Oedema peripheral			
subjects affected / exposed	12 / 146 (8.22%)		
occurrences (all)	12		
Reproductive system and breast disorders			
Vaginal haemorrhage			
subjects affected / exposed	11 / 146 (7.53%)		
occurrences (all)	11		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	13 / 146 (8.90%)		
occurrences (all)	13		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	11 / 146 (7.53%)		
occurrences (all)	11		
Investigations			
Weight decreased			
subjects affected / exposed	8 / 146 (5.48%)		
occurrences (all)	8		
Lipase increased			

subjects affected / exposed	10 / 146 (6.85%)		
occurrences (all)	10		
Blood creatinine increased			
subjects affected / exposed	9 / 146 (6.16%)		
occurrences (all)	9		
Aspartate aminotransferase increased			
subjects affected / exposed	19 / 146 (13.01%)		
occurrences (all)	19		
Amylase increased			
subjects affected / exposed	8 / 146 (5.48%)		
occurrences (all)	8		
Alanine aminotransferase increased			
subjects affected / exposed	20 / 146 (13.70%)		
occurrences (all)	20		
Blood alkaline phosphatase increased			
subjects affected / exposed	10 / 146 (6.85%)		
occurrences (all)	10		
Nervous system disorders			
Headache			
subjects affected / exposed	11 / 146 (7.53%)		
occurrences (all)	11		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	80 / 146 (54.79%)		
occurrences (all)	80		
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	20 / 146 (13.70%)		
occurrences (all)	20		
Stomatitis			
subjects affected / exposed	10 / 146 (6.85%)		
occurrences (all)	10		
Nausea			
subjects affected / exposed	30 / 146 (20.55%)		
occurrences (all)	30		
Diarrhoea			

subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Gingival bleeding subjects affected / exposed occurrences (all)	12 / 146 (8.22%) 12 22 / 146 (15.07%) 22 12 / 146 (8.22%) 12 17 / 146 (11.64%) 17		
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all)	17 / 146 (11.64%) 17 24 / 146 (16.44%) 24		
Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all)	26 / 146 (17.81%) 26		
Endocrine disorders Hyperthyroidism subjects affected / exposed occurrences (all) Hypothyroidism subjects affected / exposed occurrences (all)	10 / 146 (6.85%) 10 17 / 146 (11.64%) 17		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all)	8 / 146 (5.48%) 8 10 / 146 (6.85%) 10		

Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all)	 14 / 146 (9.59%) 14		
Metabolism and nutrition disorders Hypoalbuminaemia subjects affected / exposed occurrences (all) Hypokalaemia subjects affected / exposed occurrences (all) Hyponatraemia subjects affected / exposed occurrences (all) Decreased appetite subjects affected / exposed occurrences (all)	 15 / 146 (10.27%) 15 12 / 146 (8.22%) 12 8 / 146 (5.48%) 8 24 / 146 (16.44%) 24		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 June 2020	The protocol is being amended to incorporate the main changes to specify and enroll a more homogeneous population (inclusion criterion #2), add contingency plan for the possibility of continued enrollment in China to meet local requirements (if needed), and to reflect the change in patient interview approach to exit interviews only, therewith incorporating regulatory feedback obtained.
22 June 2021	The primary purpose of this amendment is to update the risk classification. In addition, the primary analysis time point has been moved from 8 months to 12 months after the accrual of the last global subject.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported