Clinical trial results:
A Phase II, Multicenter, Open-label Study to Investigate the Clinical Efficacy of M7824 Monotherapy in Participants With Locally Advanced or Metastatic Biliary Tract Cancer Who Fail or Are Intolerant to First-line Platinum-Based Chemotherapy

Summary

EudraCT number	2018-003707-19
Trial protocol	FR DE GB ES IT
Global end of trial date	30 September 2022

Results information

Result version number	v1 (current)
This version publication date	01 October 2023
First version publication date	01 October 2023

Trial information

Trial identification

Sponsor protocol code	MS200647_0047

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03833661
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	30 September 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 September 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to evaluate M7824 monotherapy in subjects with advanced or metastatic biliary tract cancer (BTC) who failed or were intolerant to first-line (1L) 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 regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 March 2019
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	United States: 23
Country: Number of subjects enrolled	France: 15
Country: Number of subjects enrolled	Spain: 17
Country: Number of subjects enrolled	Italy: 19
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Germany: 9
Country: Number of subjects enrolled	Japan: 21
Country: Number of subjects enrolled	Korea, Republic of: 34
Country: Number of subjects enrolled	China: 11
Country: Number of subjects enrolled	Taiwan: 9
Worldwide total number of subjects	159
EEA total number of subjects	60

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)	76
From 65 to 84 years	83
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

First subject signed informed consent: 26 Mar 2019, Clinical cutoff date: 30 March 2021.

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	M7824

Arm description:

Subjects received intravenous infusion of M7824 at a dose of 1200 milligrams (mg) once every 2 weeks until confirmed progression of disease, death, unacceptable toxicity, or study withdrawal.

Arm type	Experimental
Investigational medicinal product name	M7824
Investigational medicinal product code	
Other name	Bintrafusp alfa
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

M7824 administered to subjects at a dose of 1200 mg once every 2 weeks until confirmed progression of disease, death, unacceptable toxicity, or study withdrawal.

Number of subjects in period 1	M7824
Started	159
Completed	159

Baseline characteristics

Reporting groups	
Reporting group title	M7824
Reporting group description:	
Subjects received intravenous infusion of M7824 at a dose of 1200 milligrams (mg) once every 2 weeks until confirmed progression of disease, death, unacceptable toxicity, or study withdrawal.	

Reporting group values	M7824	Total	
Number of subjects	159	159	
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	64		
standard deviation	± 8.9	-	
Sex: Female, Male Units: subjects			
Female	65	65	
Male	94	94	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	77	77	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	0	0	
White	64	64	
More than one race	0	0	
Unknown or Not Reported	18	18	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	4	4	
Not Hispanic or Latino	155	155	
Unknown or Not Reported	0	0	

End points

End points reporting groups

Reporting group title	M7824

Reporting group description:

Subjects received intravenous infusion of M7824 at a dose of 1200 milligrams (mg) once every 2 weeks until confirmed progression of disease, death, unacceptable toxicity, or study withdrawal.

Primary: 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)

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)[1]

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). Confirmed objective response was determined according to RECIST v1.1 and as adjudicated by IRC. Intention-To-Treat (ITT) analysis set included all subjects who were administered at least one dose of M7824.

End point type	Primary

End point timeframe:

Time from first treatment to data cutoff (assessed up to 736 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	M7824			
Subject group type	Reporting group			
Number of subjects analysed	159			
Units: percentage of subjects				
number (confidence interval 95%)	10.7 (6.4 to 16.6)			

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

objective response (Complete Response [CR] or Partial Response [PR]) 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. ITT analysis set was used. "Number of Subjects Analyzed" = subjects who were evaluable for this endpoint. "99.9" = The upper limit could not be estimated due to insufficient number of events by the date of data cutoff.

End point type	Secondary

End point timeframe:

Time from first documentation of objective response to data cutoff (assessed up to 736 days)

End point values	M7824			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: months				
median (confidence interval 95%)	10.0 (3.9 to 99.9)			

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 subject 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-β) inhibition mediated skin AE and anemia. Safety analysis set included all subjects who were administered at least one dose of M7824.

End point type	Secondary

End point timeframe:

Time from first treatment to data cutoff (assessed up to 736 days)

End point values	M7824			
Subject group type	Reporting group			
Number of subjects analysed	159			
Units: subjects				
TEAEs	152			
Treatment Related TEAEs	99			
AESI: Infusion-related reaction	10			
AESI: Immune-related AE	46			
AESI: TGF-β inhibition mediated skin AE	13			
AESI: Anemia	44			

Statistical analyses

No statistical analyses for this end point

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

End point description:

DRR was defined as the percentage of subjects with confirmed objective response (CR or PR) 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. DRR was determined according to RECIST v1.1 and assessed by IRC. ITT analysis set included all subjects who were administered at least one dose of M7824. Here, "Overall Number of Subjects Analyzed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Time from first treatment to data cutoff (assessed up to 736 days)

End point values	M7824			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: percentage of subjects				
number (confidence interval 95%)	6.3 (3.1 to 11.3)			

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 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. ITT analysis set included all subjects who were administered at least one dose of M7824.

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 data-cutoff (736 days)

End point values	M7824			
Subject group type	Reporting group			
Number of subjects analysed	159			
Units: months				
median (confidence interval 95%)	1.8 (1.7 to 1.8)			

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 the Investigator

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 the Investigator

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). Confirmed objective response was determined according to RECIST v1.1 and as adjudicated by Investigator. ITT analysis set included all subjects who were administered at least one dose of M7824.

End point type	Secondary

End point timeframe:

Time from first treatment to data cutoff (assessed up to 736 days)

End point values	M7824			
Subject group type	Reporting group			
Number of subjects analysed	159			
Units: percentage of subjects				
number (confidence interval 95%)	10.7 (6.4 to 16.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Durable Response Rate (DRR) Acoording to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) as Assessed by the Investigator

End point title	Durable Response Rate (DRR) Acoording to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) as Assessed by the Investigator

End point description:

DRR was defined as the percentage of subjects with confirmed objective response (CR or PR) 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. DRR was determined according to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) and assessed by Investigator. ITT analysis set included all subjects who were administered at least one dose of M7824. Here, "Number of Subjects Analyzed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Time from first treatment to data cutoff (assessed up to 736 days)

End point values	M7824			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: percentage of subjects				
number (confidence interval 95%)	5.7 (2.6 to 10.5)			

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 the Investigator

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

End point description:

DOR was defined for subjects with confirmed response, as the time from first documentation of objective response (Complete Response [CR] or Partial Response [PR]) 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 Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) and assessed by Investigator. Results were calculated based on Kaplan-Meier estimates. ITT analysis set included all subjects who were administered at least one dose of M7824. Here, "Number of Subjects Analyzed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Time from first documentation of objective response to data cutoff (assessed up to 736 days)

End point values	M7824			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: months				
median (confidence interval 95%)	8.2 (3.9 to 12.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS) According to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) as Assessed by the Investigator

End point title	Progression-Free Survival (PFS) According to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) as Assessed by the Investigator

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. ITT analysis set included all subjects who were administered at least one dose of M7824.

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 data-cutoff (736 days)

End point values	M7824			
Subject group type	Reporting group			
Number of subjects analysed	159			
Units: months				
median (confidence interval 95%)	1.8 (1.7 to 1.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Pre-Dose Concentrations (Ctrough) of M7824

End point title	Serum Pre-Dose Concentrations (Ctrough) of M7824

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 M7824 and who provided at least one sample with a measurable concentration of M7824. Here, "Number of subjects Analyzed" signifies those subjects who were evaluable for this endpoint and "n" signifies those participants who were evaluable at specified time points for this endpoint. Here, "9999"=Geometric Mean and Geometric Coefficient of Variation were not calculated if fewer than 3 subjects have reportable parameter values.

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 and Day 505

End point values	M7824			
Subject group type	Reporting group			
Number of subjects analysed	138			
Units: microgram per milliliter (mcg/mL)				
geometric mean (geometric coefficient of variation)				
Day 15: n = 138	70.7 (± 40.7)			
Day 29: n = 105	84.2 (± 58.0)			
Day 43: n = 89	93.4 (± 52.6)			
Day 85: n = 40	105 (± 42.6)			
Day 127: n = 26	117 (± 41.5)			
Day 169: n = 12	101 (± 55.6)			
Day 253: n =13	115 (± 46.8)			
Day 337: n = 6	91.3 (± 41.5)			
Day 421: n = 5	114 (± 36.7)			
Day 505: n = 2	9999 (± 9999)			

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. ITT analysis set included all subjects who were administered at least one dose of M7824.

End point type	Secondary

End point timeframe:

Time from first administration of study drug to data cutoff (assessed up to 736 days)

End point values	M7824			
Subject group type	Reporting group			
Number of subjects analysed	159			
Units: months				
median (confidence interval 95%)	7.6 (5.8 to 9.5)			

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: percentage of subjects with a confirmed objective response of CR or 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 IRC through PD-L1 Subgroup: PD-L1 expression on tumor cells (TC) and on immune cells (IC) at baseline and in the following categories: <1%, >=1%, <5%, >=5%, <25%, >=25%, <50%, >=50% were reported. ITT analysis set was used. "Number of Subjects Analyzed" = subjects who were evaluable for this endpoint and "n" = subjects who were evaluable for the specified categories for this endpoint.

End point type	Secondary

End point timeframe:

Time from first treatment to data cutoff (assessed up to 736 days)

End point values	M7824			
Subject group type	Reporting group			
Number of subjects analysed	141			
Units: percentage of subjects				
number (confidence interval 95%)				
PD-L1 expression on TC: < 1%; n = 98	10.2 (5.0 to 18.0)			
PD-L1 expression on TC: >= 1%; n = 43	7.0 (1.5 to 19.1)			
PD-L1 expression on TC: < 5%; n = 113	9.7 (5.0 to 16.8)			
PD-L1 expression on TC: >= 5%; n = 28	7.1 (0.9 to 23.5)			

PD-L1 expression on TC: < 25%; n = 126	8.7 (4.4 to 15.1)			
PD-L1 expression on TC: >= 25%; n = 15	13.3 (1.7 to 40.5)			
PD-L1 expression on TC: < 50%; n = 130	9.2 (4.9 to 15.6)			
PD-L1 expression on TC: >= 50%; n = 11	9.1 (0.2 to 41.3)			
PD-L1 expression on IC: < 1%; n = 22	13.6 (2.9 to 34.9)			
PD-L1 expression on IC: >= 1%; n = 108	7.4 (3.3 to 14.1)			
PD-L1 expression on IC: < 5%; n = 46	8.7 (2.4 to 20.8)			
PD-L1 expression on IC: >= 5%; n = 84	8.3 (3.4 to 16.4)			
PD-L1 expression on IC: < 25%; n = 120	7.5 (3.5 to 13.8)			
PD-L1 expression on IC: >= 25%; n = 10	20.0 (2.5 to 55.6)			
PD-L1 expression on IC: < 50%; n = 129	8.5 (4.3 to 14.7)			
PD-L1 expression on IC: >= 50%; n = 1	0.0 (0.0 to 97.5)			

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 M7824 and who had at least one valid result of ADA.

End point type	Secondary

End point timeframe:

Time from first treatment to data cutoff (assessed up to 736 days)

End point values	M7824			
Subject group type	Reporting group			
Number of subjects analysed	157			
Units: subjects	45			

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Concentration at End of Infusion (CEOI) of M7824

End point title	Serum Concentration at End of Infusion (CEOI) of M7824

End point description:

Serum Concentration at End of Infusion (CEOI) of M7824 is reported. Pharmacokinetic (PK) analysis set included all subjects who completed at least one dose of M7824 and who provided at least one sample with a measurable concentration of M7824. Here, "Number of subjects Analyzed" signifies those subjects who were evaluable for this endpoint and "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	M7824			
Subject group type	Reporting group			
Number of subjects analysed	152			
Units: mcg/mL				
geometric mean (geometric coefficient of variation)				
Day 1: n = 152 Day 29: n = 104	399 (± 31.5) 434 (± 48.5)			

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

DOR: subjects with confirmed response, as time from first documentation of objective response (CR/PR) to date of first documentation of PD/death due to any cause, whichever occurred first. PD: At least a 20% increase in SLD, taking as reference smallest SLD recorded from baseline or the appearance of 1 or more new lesions. DOR was adjudicated by IRC through PD-L1 Subgroup: PD-L1 expression on tumor cells (TC) and on immune cells (IC) at baseline and in following categories: <1%, >=1%, <5%, >=5%, <25%, >=25%, <50%, >=50% was reported. ITT analysis set was used. "Number of Subjects Analyzed" =subjects who were evaluable for this endpoint; "n"=subjects who were evaluable for the specified categories for this endpoint. "999" = Due to small number of events, Median and Upper limit of 95% Confidence Interval could not derive and "99999" = None of the subjects were evaluable for the specified category.

End point type	Secondary

End point timeframe:

Time from first documentation of objective response to data cutoff (assessed up to 736 days)

End point values	M7824			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: months				
median (confidence interval 95%)				
PD-L1 expression on TC: < 1%; n = 10	999 (3.4 to 999)			
PD-L1 expression on TC: >= 1%; n = 3	5.8 (3.9 to 999)			
PD-L1 expression on TC: < 5%; n = 11	999 (3.4 to 999)			
PD-L1 expression on TC: >= 5%; n = 2	999 (3.9 to 999)			
PD-L1 expression on TC: < 25%; n = 11	999 (3.4 to 999)			
PD-L1 expression on TC: >= 25%; n = 2	999 (3.9 to 999)			
PD-L1 expression on TC: < 50%; n = 12	999 (3.7 to 999)			
PD-L1 expression on TC: >= 50%; n = 1	999 (999 to 999)			
PD-L1 expression on IC: < 1%; n = 3	999 (3.4 to 999)			
PD-L1 expression on IC: >= 1%; n = 8	999 (3.7 to 999)			
PD-L1 expression on IC: < 5%; n = 4	999 (3.4 to 999)			
PD-L1 expression on IC: >= 5%; n = 7	999 (3.9 to 999)			
PD-L1 expression on IC: < 25%; n = 9	999 (3.4 to 999)			
PD-L1 expression on IC: >= 25%; n = 2	999 (999 to 999)			
PD-L1 expression on IC: < 50%; n = 11	999 (3.4 to 999)			
PD-L1 expression on IC: >= 50%; n = 0	99999 (99999 to 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Confirmed Objective Response (OR) as per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) Assessed by Independent Review Committee (IRC) According to Microsatellite instability (MSI) Status

End point title	Percentage of Subjects With Confirmed Objective Response (OR) as per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) Assessed by Independent Review Committee (IRC) According to Microsatellite instability (MSI) Status

End point description:

Confirmed OR: percentage of subjects with a confirmed OR of CR or PR.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 OR was adjudicated by IRC through MSI Status subgroups as:- MSI High = if subject is MSI High for any (at least one) test;- Microsatellite stable (MSS) or MSI Low = if subject is not MSI High for

any test;- Unknown (missing) = no MSI tests available at baseline was reported. MSI high: if 2 or more unstable markers were detected in sample; MSI low: if 1 marker was unstable and remaining markers were stable and MSS if all markers were stable. ITT analysis set was used. "Number of Subjects Analyzed"=subjects who were evaluable for this endpoint and "n"=subjects who were evaluable for the specified categories for this endpoint. "99999" = None of subjects were evaluable for specified category.

End point type	Secondary

End point timeframe:

Time from first treatment to data cutoff (assessed up to 736 days)

End point values	M7824			
Subject group type	Reporting group			
Number of subjects analysed	153			
Units: percentage of subjects				
number (confidence interval 95%)				
High: n = 3	0.0 (0.0 to 70.8)			
Low or Microsatellite stable: n = 150	10.0 (5.7 to 16.0)			
Unknown (missing): n = 0	99999 (99999 to 99999)			

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

DOR: participants with confirmed response, as the time from first documentation of objective response (CR/PR) to the date of first documentation of PD or death due to any cause, whichever occurred first.PD: At least a 20% increase in the SLD, taking as reference the smallest SLD recorded from baseline or the appearance of 1 or more new lesions. DOR was by IRC through MSI Status subgroups as:- MSI High = if subject is MSI High for any (at least one) test;- MSS or MSI Low = if subject is not MSI High for any test;- Unknown (missing) = no MSI tests available at baseline was reported. ITT analysis set was used. "Number of Subjects Analyzed" =subjects who were evaluable for this endpoint and "n"= subjects who were evaluable for the specified categories for this endpoint. "999" = Due to small number of events, Median and Upper limit of 95% Confidence Interval could not derive and "99999" = None of the subjects were evaluable for the specified category.

End point type	Secondary

End point timeframe:

Time from first documentation of objective response to data cutoff (assessed up to 736 days)

End point values	M7824			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: months				
median (confidence interval 95%)				
High: n = 0	99999 (99999 to 99999)			
Low or Microsatellite stable: n = 15	999 (3.7 to 999)			
Unknown (missing): n = 0	99999 (99999 to 99999)			

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

DRR was defined as the percentage of subjects with confirmed objective response (CR or PR) 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. DRR was determined according to RECIST v1.1 and adjudicated by IRC through PD-L1 Subgroup: PD-L1 expression on tumor cells (TC) and on immune cells (IC) at baseline and in the following categories: <1%, >=1%, <5%, >=5%, <25%, >=25%, <50%, >=50% was reported. ITT analysis set was used. "Number of Subjects Analyzed" =subjects who were evaluable for this endpoint and "n" signifies those subjects who were evaluable for the specified categories for this endpoint.

End point type	Secondary

End point timeframe:

Time from first treatment to data cutoff (assessed up to 736 days)

End point values	M7824			
Subject group type	Reporting group			
Number of subjects analysed	141			
Units: percentage of subjects				
number (confidence interval 95%)				
PD-L1 expression on TC: < 1%; n = 98	6.1 (2.3 to 12.9)			
PD-L1 expression on TC: >= 1%; n = 43	2.3 (0.1 to 12.3)			
PD-L1 expression on TC: < 5%; n = 113	5.3 (2.0 to 11.2)			
PD-L1 expression on TC: >= 5%; n = 28	3.6 (0.1 to 18.3)			
PD-L1 expression on TC: < 25%; n = 126	4.8 (1.8 to 10.1)			

PD-L1 expression on TC at >= 25%; n = 15	6.7 (0.2 to 31.9)			
PD-L1 expression on TC: < 50%; n = 130	4.6 (1.7 to 9.8)			
PD-L1 expression on TC: >= 50%; n = 11	9.1 (0.2 to 41.3)			
PD-L1 expression on IC: < 1%; n = 22	9.1 (1.1 to 29.2)			
PD-L1 expression on IC: >= 1%; n = 108	3.7 (1.0 to 9.2)			
PD-L1 expression on IC: < 5%; n = 46	4.3 (0.5 to 14.8)			
PD-L1 expression on IC: >= 5%; n = 84	4.8 (1.3 to 11.7)			
PD-L1 expression on IC: < 25%; n = 120	3.3 (0.9 to 8.3)			
PD-L1 expression on IC: >= 25%; n = 10	20.0 (2.5 to 55.6)			
PD-L1 expression on IC: < 50%; n = 129	4.7 (1.7 to 9.8)			
PD-L1 expression on IC: >= 50%; n = 1	0.0 (0.0 to 97.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Durable Response Rate (DRR) as per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) Assessed by an Independent Review Committee (IRC) According to According to Microsatellite instability (MSI) Status

End point title	Durable Response Rate (DRR) as per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) Assessed by an Independent Review Committee (IRC) According to According to Microsatellite instability (MSI) Status

End point description:

DRR: percentage of subjects with confirmed OR (CR/PR) with duration of at least 6 months. PD: At least a 20% increase in the SLD, taking as reference the smallest SLD recorded from baseline or the appearance of 1 or more new lesions. DRR was determined according to RECIST v1.1 and adjudicated by IRC through MSI Status subgroups as:- MSI High = if subject is MSI High for any (at least one) test;- MSS or MSI Low = if subject is not MSI High for any test;- Unknown (missing) = no MSI tests available at baseline was reported. ITT analysis set included all subjects who were administered at least one dose of M7824. Here, "Number of Subjects Analyzed" signifies those subjects who were evaluable for this endpoint and "n" signifies those subjects who were evaluable for the specified categories for this endpoint. Here, "99999" = None of subjects were evaluable for specified category.

End point type	Secondary

End point timeframe:

Time from first treatment to data cutoff (assessed up to 736 days)

End point values	M7824			
Subject group type	Reporting group			
Number of subjects analysed	153			
Units: percentage of subjects				
number (confidence interval 95%)				
High: n = 3	0.0 (0.0 to 70.8)			
Low or Microsatellite stable: n = 150	4.0 (1.5 to 8.5)			
Unknown (missing): n = 0	99999 (99999 to 99999)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Time from first treatment to data cutoff (assessed up to 736 days)	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups	
Reporting group title	M7824

Reporting group description:

Subjects received intravenous infusion of M7824 at a dose of 1200 milligrams (mg) once every 2 weeks until confirmed progression of disease, death, unacceptable toxicity, or study withdrawal.

Serious adverse events	M7824		
Total subjects affected by serious adverse events			
subjects affected / exposed	86 / 159 (54.09%)		
number of deaths (all causes)	108		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatocellular carcinoma			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Keratoacanthoma			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Malignant ascites			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tumour hyperprogression			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Tumour pain				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tumour necrosis				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Vascular disorders				
Hypertension				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Surgical and medical procedures				
Biliary stent placement				
subjects affected / exposed	1 / 159 (0.63%)			
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	1 / 159 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Disease progression				
subjects affected / exposed	16 / 159 (10.06%)			
occurrences causally related to treatment / all	0 / 16			
deaths causally related to treatment / all	0 / 14			
Fatigue				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General physical health deterioration				

subjects affected / exposed	2 / 159 (1.26%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Multiple organ dysfunction syndrome				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Pyrexia				
subjects affected / exposed	2 / 159 (1.26%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast disorders				
Prostatitis				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Pneumonitis				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haemoptysis				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Interstitial lung disease				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Pulmonary embolism			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Dyspnoea			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Delirium			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Myocarditis			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ventricular fibrillation			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Immune-mediated encephalitis			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 159 (3.14%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Haemolytic anaemia			

subjects affected / exposed	1 / 159 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 159 (1.26%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Abdominal pain upper			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ascites			
subjects affected / exposed	2 / 159 (1.26%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Colitis			
subjects affected / exposed	2 / 159 (1.26%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Duodenal stenosis			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dysphagia			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastric stenosis			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastritis erosive			

subjects affected / exposed	1 / 159 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhage				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal vascular malformation haemorrhagic				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haemorrhoidal haemorrhage				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ileus				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Mechanical ileus				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Small intestinal obstruction				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Upper gastrointestinal haemorrhage				

subjects affected / exposed	1 / 159 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	2 / 159 (1.26%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Bile duct stenosis				
subjects affected / exposed	3 / 159 (1.89%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Bile duct obstruction				
subjects affected / exposed	3 / 159 (1.89%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Cholangitis				
subjects affected / exposed	8 / 159 (5.03%)			
occurrences causally related to treatment / all	0 / 8			
deaths causally related to treatment / all	0 / 1			
Cholangitis acute				
subjects affected / exposed	2 / 159 (1.26%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cholestasis				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatic failure				
subjects affected / exposed	4 / 159 (2.52%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	1 / 3			
Hepatitis				

subjects affected / exposed	1 / 159 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatocellular injury				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Jaundice				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Jaundice cholestatic				
subjects affected / exposed	3 / 159 (1.89%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Liver injury				
subjects affected / exposed	2 / 159 (1.26%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Lichenoid keratosis				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pemphigoid				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rash				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rash maculo-papular				

subjects affected / exposed	2 / 159 (1.26%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Toxic skin eruption				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Acute kidney injury				
subjects affected / exposed	3 / 159 (1.89%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Nephritis				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Back pain				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Myositis				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pain in extremity				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Abdominal infection				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Bacterial sepsis			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Biliary tract infection			
subjects affected / exposed	6 / 159 (3.77%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Bursitis infective			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
COVID-19			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infective spondylitis			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Osteomyelitis			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	2 / 159 (1.26%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis acute			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			

subjects affected / exposed	3 / 159 (1.89%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 1			
Staphylococcal infection				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Subcutaneous abscess				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urosepsis				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Varicella zoster pneumonia				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Varicella zoster virus infection				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular device infection				
subjects affected / exposed	1 / 159 (0.63%)			
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	3 / 159 (1.89%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Hyponatraemia				

subjects affected / exposed	2 / 159 (1.26%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Latent autoimmune diabetes in adults			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	M7824		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	144 / 159 (90.57%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Anogenital warts			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Cancer pain			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Infected neoplasm			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Keratoacanthoma			
subjects affected / exposed	8 / 159 (5.03%)		
occurrences (all)	8		
Lip squamous cell carcinoma			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Melanocytic naevus			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Seborrhoeic keratosis			

subjects affected / exposed	2 / 159 (1.26%)		
occurrences (all)	2		
Squamous cell carcinoma of skin			
subjects affected / exposed	3 / 159 (1.89%)		
occurrences (all)	3		
Tumour pain			
subjects affected / exposed	2 / 159 (1.26%)		
occurrences (all)	2		
Basal cell carcinoma			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Vascular disorders			
Embolism			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Flushing			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Haematoma			
subjects affected / exposed	2 / 159 (1.26%)		
occurrences (all)	2		
Hot flush			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Hypertension			
subjects affected / exposed	8 / 159 (5.03%)		
occurrences (all)	8		
Hypotension			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Phlebitis			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Orthostatic hypotension			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		

General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	23 / 159 (14.47%)		
occurrences (all)	23		
Fatigue			
subjects affected / exposed	23 / 159 (14.47%)		
occurrences (all)	23		
Oedema peripheral			
subjects affected / exposed	11 / 159 (6.92%)		
occurrences (all)	11		
Pyrexia			
subjects affected / exposed	25 / 159 (15.72%)		
occurrences (all)	25		
Chest discomfort			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Chest pain			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Chills			
subjects affected / exposed	4 / 159 (2.52%)		
occurrences (all)	4		
Disease progression			
subjects affected / exposed	2 / 159 (1.26%)		
occurrences (all)	2		
Generalised oedema			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Influenza like illness			
subjects affected / exposed	2 / 159 (1.26%)		
occurrences (all)	2		
Malaise			
subjects affected / exposed	5 / 159 (3.14%)		
occurrences (all)	2		
Mucosal inflammation			

subjects affected / exposed	4 / 159 (2.52%)		
occurrences (all)	4		
Non-cardiac chest pain			
subjects affected / exposed	2 / 159 (1.26%)		
occurrences (all)	2		
Oedema			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Pain			
subjects affected / exposed	4 / 159 (2.52%)		
occurrences (all)	4		
Mucosal haemorrhage			
subjects affected / exposed	2 / 159 (1.26%)		
occurrences (all)	2		
Immune system disorders			
Contrast media allergy			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Hypersensitivity			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Infusion related hypersensitivity reaction			
subjects affected / exposed	3 / 159 (1.89%)		
occurrences (all)	3		
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Nipple pain			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Prostatitis			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Pruritus genital			

subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Scrotal oedema			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	8 / 159 (5.03%)		
occurrences (all)	8		
Epistaxis			
subjects affected / exposed	8 / 159 (5.03%)		
occurrences (all)	8		
Hypoxia			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Cough			
subjects affected / exposed	7 / 159 (4.40%)		
occurrences (all)	7		
Dysphonia			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Dyspnoea exertional			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Haemoptysis			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Pleural effusion			
subjects affected / exposed	3 / 159 (1.89%)		
occurrences (all)	3		
Productive cough			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Pulmonary artery thrombosis			

subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Pulmonary embolism			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Rhinorrhoea			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Sputum increased			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Pneumonitis			
subjects affected / exposed	2 / 159 (1.26%)		
occurrences (all)	2		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Delirium			
subjects affected / exposed	3 / 159 (1.89%)		
occurrences (all)	3		
Depression			
subjects affected / exposed	4 / 159 (2.52%)		
occurrences (all)	4		
Insomnia			
subjects affected / exposed	8 / 159 (5.03%)		
occurrences (all)	8		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	24 / 159 (15.09%)		
occurrences (all)	24		
Aspartate aminotransferase increased			
subjects affected / exposed	26 / 159 (16.35%)		
occurrences (all)	26		
Blood alkaline phosphatase increased			

subjects affected / exposed	17 / 159 (10.69%)			
occurrences (all)	17			
Blood bilirubin increased				
subjects affected / exposed	16 / 159 (10.06%)			
occurrences (all)	16			
Activated partial thromboplastin time prolonged				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences (all)	1			
Amylase increased				
subjects affected / exposed	5 / 159 (3.14%)			
occurrences (all)	5			
Bilirubin conjugated increased				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences (all)	1			
Blood albumin decreased				
subjects affected / exposed	4 / 159 (2.52%)			
occurrences (all)	4			
Blood albumin increased				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences (all)	1			
Blood glucose increased				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences (all)	1			
Blood lactate dehydrogenase increased				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences (all)	1			
Blood potassium decreased				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences (all)	1			
Blood sodium decreased				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences (all)	1			
Blood thyroid stimulating hormone increased				

subjects affected / exposed	1 / 159 (0.63%)			
occurrences (all)	1			
Blood urea increased				
subjects affected / exposed	2 / 159 (1.26%)			
occurrences (all)	2			
C-reactive protein increased				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences (all)	1			
Blood creatinine increased				
subjects affected / exposed	7 / 159 (4.40%)			
occurrences (all)	7			
cell marker increased				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences (all)	1			
Gamma-glutamyltransferase increased				
subjects affected / exposed	5 / 159 (3.14%)			
occurrences (all)	5			
Heart rate increased				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences (all)	1			
International normalised ratio increased				
subjects affected / exposed	2 / 159 (1.26%)			
occurrences (all)	2			
Lipase increased				
subjects affected / exposed	6 / 159 (3.77%)			
occurrences (all)	6			
Liver function test increased				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences (all)	1			
Lymphocyte count decreased				
subjects affected / exposed	2 / 159 (1.26%)			
occurrences (all)	2			
Platelet count decreased				

subjects affected / exposed	6 / 159 (3.77%)		
occurrences (all)	6		
Weight decreased			
subjects affected / exposed	7 / 159 (4.40%)		
occurrences (all)	7		
Blood cholesterol increased			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	8 / 159 (5.03%)		
occurrences (all)	8		
Contusion			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Fal			
subjects affected / exposed	2 / 159 (1.26%)		
occurrences (all)	2		
Limb traumatic amputation			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Rib fracture			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Toxicity to various agents			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Upper limb fracture			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	2 / 159 (1.26%)		
occurrences (all)	2		
Pericardial effusion			

subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	11 / 159 (6.92%)		
occurrences (all)	11		
Amnesia			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Dizziness			
subjects affected / exposed	5 / 159 (3.14%)		
occurrences (all)	5		
Hypoaesthesia			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Neuropathy peripheral			
subjects affected / exposed	2 / 159 (1.26%)		
occurrences (all)	2		
Peripheral sensory neuropathy			
subjects affected / exposed	2 / 159 (1.26%)		
occurrences (all)	2		
Seizure			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Syncope			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Visual field defect			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	42 / 159 (26.42%)		
occurrences (all)	42		
Anaemia of malignant disease			

subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Increased tendency to bruise			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Leukocytosis			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Myelosuppression			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Neutropenia			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Thrombocytopenia			
subjects affected / exposed	2 / 159 (1.26%)		
occurrences (all)	2		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Eye disorders			
Dry eye			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Diplopia			
subjects affected / exposed	2 / 159 (1.26%)		
occurrences (all)	2		
Lacrimation increased			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Uveitis			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Vision blurred			

subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	8 / 159 (5.03%)		
occurrences (all)	8		
Constipation			
subjects affected / exposed	24 / 159 (15.09%)		
occurrences (all)	24		
Diarrhoea			
subjects affected / exposed	13 / 159 (8.18%)		
occurrences (all)	13		
Nausea			
subjects affected / exposed	23 / 159 (14.47%)		
occurrences (all)	23		
Vomiting			
subjects affected / exposed	12 / 159 (7.55%)		
occurrences (all)	12		
Abdominal pain			
subjects affected / exposed	21 / 159 (13.21%)		
occurrences (all)	21		
Hiatus hernia			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Large intestine polyp			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Melaena			
subjects affected / exposed	2 / 159 (1.26%)		
occurrences (all)	2		
Mouth haemorrhage			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Portal hypertensive gastropathy			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		

Proctalgia				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences (all)	1			
Stomatitis				
subjects affected / exposed	3 / 159 (1.89%)			
occurrences (all)	3			
Toothache				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences (all)	1			
Upper gastrointestinal haemorrhage				
subjects affected / exposed	2 / 159 (1.26%)			
occurrences (all)	2			
Abdominal discomfort				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences (all)	1			
Abdominal distension				
subjects affected / exposed	6 / 159 (3.77%)			
occurrences (all)	6			
Abdominal pain upper				
subjects affected / exposed	4 / 159 (2.52%)			
occurrences (all)	4			
Anal haemorrhage				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences (all)	1			
Angular cheilitis				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences (all)	1			
Colitis				
subjects affected / exposed	2 / 159 (1.26%)			
occurrences (all)	2			
Dry mouth				
subjects affected / exposed	3 / 159 (1.89%)			
occurrences (all)	3			
Duodenal ulcer				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences (all)	1			

Duodenitis				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences (all)	1			
Dyspepsia				
subjects affected / exposed	7 / 159 (4.40%)			
occurrences (all)	7			
Enterocolitis				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences (all)	1			
Eructation				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences (all)	1			
Flatulence				
subjects affected / exposed	3 / 159 (1.89%)			
occurrences (all)	3			
Gastritis				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences (all)	1			
Gastrointestinal haemorrhage				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences (all)	1			
Gastrooesophageal reflux disease				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences (all)	1			
Gingival bleeding				
subjects affected / exposed	7 / 159 (4.40%)			
occurrences (all)	7			
Haematochezia				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences (all)	1			
Haemorrhoidal haemorrhage				
subjects affected / exposed	2 / 159 (1.26%)			
occurrences (all)	2			
Haemorrhoids				
subjects affected / exposed	2 / 159 (1.26%)			
occurrences (all)	2			

Hepatobiliary disorders			
Biliary obstruction			
subjects affected / exposed	2 / 159 (1.26%)		
occurrences (all)	2		
Cholangitis			
subjects affected / exposed	3 / 159 (1.89%)		
occurrences (all)	3		
Cholelithiasis			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Hepatitis			
subjects affected / exposed	2 / 159 (1.26%)		
occurrences (all)	2		
Hyperbilirubinaemia			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Jaundice			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Jaundice cholestatic			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Liver disorder			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Liver injury			
subjects affected / exposed	3 / 159 (1.89%)		
occurrences (all)	3		
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	29 / 159 (18.24%)		
occurrences (all)	29		
Rash			
subjects affected / exposed	20 / 159 (12.58%)		
occurrences (all)	20		
Rash macular			

subjects affected / exposed	1 / 159 (0.63%)			
occurrences (all)	1			
Acanthosis nigricans				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences (all)	1			
Actinic keratosis				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences (all)	1			
Decubitus ulcer				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences (all)	1			
Dermatitis				
subjects affected / exposed	2 / 159 (1.26%)			
occurrences (all)	2			
Dermatitis acneiform				
subjects affected / exposed	5 / 159 (3.14%)			
occurrences (all)	5			
Dermatitis allergic				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences (all)	1			
Dermatitis bullous				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences (all)	1			
Dry skin				
subjects affected / exposed	2 / 159 (1.26%)			
occurrences (all)	2			
Eczema				
subjects affected / exposed	2 / 159 (1.26%)			
occurrences (all)	2			
Eczema asteatotic				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences (all)	1			
Rash pruritic				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences (all)	1			
Scab				

subjects affected / exposed	1 / 159 (0.63%)			
occurrences (all)	1			
Seborrhoeic dermatitis				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences (all)	1			
Skin exfoliation				
subjects affected / exposed	2 / 159 (1.26%)			
occurrences (all)	2			
Skin mass				
subjects affected / exposed	2 / 159 (1.26%)			
occurrences (all)	2			
Skin ulcer				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences (all)	1			
Toxic skin eruption				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences (all)	1			
Urticaria				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences (all)	1			
Erythema				
subjects affected / exposed	4 / 159 (2.52%)			
occurrences (all)	4			
Erythema nodosum				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences (all)	1			
Hyperhidrosis				
subjects affected / exposed	2 / 159 (1.26%)			
occurrences (all)	1			
Hyperkeratosis				
subjects affected / exposed	3 / 159 (1.89%)			
occurrences (all)	3			
Intertrigo				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences (all)	1			
Keratosis pilaris				

subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Lichenoid keratosis			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Milia			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Rash maculo-papular			
subjects affected / exposed	5 / 159 (3.14%)		
occurrences (all)	5		
Night sweats			
subjects affected / exposed	2 / 159 (1.26%)		
occurrences (all)	2		
Pigmentation disorder			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Psoriasis			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Azotaemia			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Chromaturia			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Haematuria			
subjects affected / exposed	2 / 159 (1.26%)		
occurrences (all)	2		
Nephritis			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		

Nocturia subjects affected / exposed occurrences (all)	1 / 159 (0.63%) 1			
Renal failure subjects affected / exposed occurrences (all)	1 / 159 (0.63%) 1			
Renal injury subjects affected / exposed occurrences (all)	1 / 159 (0.63%) 1			
Tubulointerstitial nephritis subjects affected / exposed occurrences (all)	1 / 159 (0.63%) 1			
Urinary incontinence subjects affected / exposed occurrences (all)	1 / 159 (0.63%) 1			
Urinary retention subjects affected / exposed occurrences (all)	1 / 159 (0.63%) 1			
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)	9 / 159 (5.66%) 9			
Adrenal insufficiency subjects affected / exposed occurrences (all)	4 / 159 (2.52%) 4			
Hypercalcaemia of malignancy subjects affected / exposed occurrences (all)	1 / 159 (0.63%) 1			
Hyperthyroidism subjects affected / exposed occurrences (all)	7 / 159 (4.40%) 7			
Hypophysitis subjects affected / exposed occurrences (all)	1 / 159 (0.63%) 1			
Hypopituitarism				

subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	11 / 159 (6.92%)		
occurrences (all)	11		
Spinal pain			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Arthralgia			
subjects affected / exposed	10 / 159 (6.29%)		
occurrences (all)	10		
Bone pain			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Muscle discomfort			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Muscle spasms			
subjects affected / exposed	3 / 159 (1.89%)		
occurrences (all)	3		
Musculoskeletal chest pain			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Musculoskeletal stiffness			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	3 / 159 (1.89%)		
occurrences (all)	3		
Myositis			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Neck pain			

subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	5 / 159 (3.14%)		
occurrences (all)	5		
Sarcopenia			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Infections and infestations			
Bacteraemia			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Bacterial vaginosis			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Biliary tract infection			
subjects affected / exposed	2 / 159 (1.26%)		
occurrences (all)	2		
Bronchitis			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Candida infections			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Conjunctivitis			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Device related infection			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Gingivitis			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Herpes oesophagitis			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		

Herpes zoster				
subjects affected / exposed	2 / 159 (1.26%)			
occurrences (all)	2			
Infection				
subjects affected / exposed	2 / 159 (1.26%)			
occurrences (all)	2			
Nasopharyngitis				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences (all)	1			
Osteomyelitis				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences (all)	1			
Periodontitis				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences (all)	1			
Pneumonia				
subjects affected / exposed	5 / 159 (3.14%)			
occurrences (all)	5			
Pyuria				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences (all)	1			
Rhinitis				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences (all)	1			
Skin infection				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences (all)	1			
Staphylococcal skin infection				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences (all)	1			
Upper respiratory tract infection				
subjects affected / exposed	1 / 159 (0.63%)			
occurrences (all)	1			
Urinary tract infection				
subjects affected / exposed	4 / 159 (2.52%)			
occurrences (all)	4			

Vulvovaginal candidiasis			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	34 / 159 (21.38%)		
occurrences (all)	34		
Hypoalbuminaemia			
subjects affected / exposed	16 / 159 (10.06%)		
occurrences (all)	16		
Hyponatraemia			
subjects affected / exposed	11 / 159 (6.92%)		
occurrences (all)	11		
Electrolyte imbalance			
subjects affected / exposed	2 / 159 (1.26%)		
occurrences (all)	2		
Hyperammonaemia			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Hypercalcaemia			
subjects affected / exposed	5 / 159 (3.14%)		
occurrences (all)	5		
Hyperglycaemia			
subjects affected / exposed	5 / 159 (3.14%)		
occurrences (all)	5		
Hyperkalaemia			
subjects affected / exposed	4 / 159 (2.52%)		
occurrences (all)	4		
Hypernatraemia			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Hypocalcaemia			
subjects affected / exposed	3 / 159 (1.89%)		
occurrences (all)	3		
Hypokalaemia			

subjects affected / exposed	5 / 159 (3.14%)		
occurrences (all)	5		
Hypomagnesaemia			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Hypophosphataemia			
subjects affected / exposed	3 / 159 (1.89%)		
occurrences (all)	3		
Hypoproteinaemia			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Steroid diabetes			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		
Type 1 diabetes mellitus			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 August 2019	• To clarify eligibility criteria of the study population. • To modify non-serious adverse event of special interest (AESI) reporting. • To include separate consent forms for treatment after initial and confirmed progressive disease. • To revise the laboratory assessments. • To include exploratory analysis of tumor shrinkage per biliary tract cancer (BTC) subtype.
10 October 2019	To clarify exclusion criteria of the study population and the management of immune-related adverse event and bleeding events during study intervention.
20 October 2020	• Provide sufficient survival follow up data collection for participants with long-term benefit. • Minor text revisions are made for clarity, readability, consistency of language across the development program, and compliance with current Sponsor guidelines.
22 June 2021	• The risk reclassification was based on in-depth analysis of a pooled safety dataset of N = 765 subjects who received M7824 monotherapy at 1200 mg Q2W. The information on the number of subjects treated with M7824 is provided in the IB. • Infusion-related reactions are reclassified from “important identified risk” to “identified risk” for M7824. • Skin Adverse Events have been renamed to TGF-β Inhibition Mediated Skin Reactions. • Term “treatment-related anemia events” has been revised to “anemia” and reclassified from “important potential risk” to “important identified risk” for M7824. • Bleeding events are reclassified from “potential risk” to “important identified risk” for M7824.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported