Clinical trial results:
A Phase II/III, Multicenter, Randomized, Placebo-controlled Study of Gemcitabine Plus Cisplatin With or Without Bintrafusp Alfa (M7824) as First-line Treatment of Biliary Tract Cancer

Summary

EudraCT number	2019-001992-35
Trial protocol	DE FR PL ES IT
Global end of trial date	

Results information

Result version number	v1
This version publication date	20 October 2022
First version publication date	20 October 2022

Trial information

Trial identification

Sponsor protocol code	MS200647_0055

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04066491
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	Interim
Date of interim/final analysis	20 May 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

The aim of the study was to evaluate whether bintrafusp alfa in combination with the current standard of care (SoC) (gemcitabine plus cisplatin) improves overall survival (OS) in chemotherapy and immunotherapy-naïve participants with locally advanced or metastatic Biliary Tract Cancer (BTC) compared to placebo, gemcitabine and cisplatin.

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	20 September 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	China: 15
Country: Number of subjects enrolled	Japan: 53
Country: Number of subjects enrolled	Korea, Republic of: 91
Country: Number of subjects enrolled	Taiwan: 28
Country: Number of subjects enrolled	Australia: 10
Country: Number of subjects enrolled	France: 10
Country: Number of subjects enrolled	Germany: 7
Country: Number of subjects enrolled	Poland: 12
Country: Number of subjects enrolled	Spain: 20
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Argentina: 16
Country: Number of subjects enrolled	Brazil: 1
Country: Number of subjects enrolled	Chile: 24
Country: Number of subjects enrolled	United States: 21
Worldwide total number of subjects	309
EEA total number of subjects	49

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)	152
From 65 to 84 years	157
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

First subject signed informed consent: 20-Sep-2019, Primary Analysis cutoff date: 20-May-2021.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Safety Run-In Part: M7824 + Gemcitabine + Cisplatin

Arm description:

Subjects received intravenous infusion of M7824 at a dose of 2400 milligrams (mg), once every 3 weeks (Q3W) 2 years (in case of Complete Response), otherwise until criterion pre-specified in protocol for discontinuation is met, in combination with intravenous infusion of Gemcitabine and Cisplatin at a dose of 1000 milligram per meter square (mg/m^2) and 25 mg/m^2 respectively on Day 1 and Day 8 of 21-day cycle, for 8 cycles every 3 weeks.

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

Dosage and administration details:

Subjects received intravenous infusion of M7824 at a dose of 2400 mg Q3W 2 years (in case of Complete Response), otherwise until criterion pre-specified in protocol for discontinuation is met.

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received Cisplatin intravenously at a dose of 25 mg/m^2 on Day 1 and Day 8 of 21-day cycle, for 8 cycles Q3W.

Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received Gemcitabine intravenously at a dose of 1000 mg/m^2 on Day 1 and Day 8 of 21-day cycle, for 8 cycles Q3W.

Arm title	Double-blinded Part: Placebo + Gemcitabine + Cisplatin

Arm description:

Subjects received intravenous infusion of M7824 matched placebo, once every 3 weeks (Q3W) until 2 years (in case of CR), otherwise until criterion pre-specified in protocol for discontinuation is met, in

combination with intravenous infusion of Gemcitabine and Cisplatin at a dose of 1000 mg/m^2 and 25 mg/m^2 respectively on Day 1 and Day 8 of 21- day cycle, for 8 cycles every 3 weeks. In case of any missed dose for chemotherapy, gemcitabine and cisplatin combination administered on Day 15 of that cycle or at the end of the scheduled 8 cycles (up to 16 administrations of gemcitabine and cisplatin combination). The administration of the missed dose on Day 15 or at the end of 8 cycles is Investigator's clinical decision.

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

Dosage and administration details:

Subjects received intravenous infusion of M7824 matched placebo, Q3W until 2 years (in case of complete response), otherwise until criterion pre-specified in protocol for discontinuation is met.

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received Cisplatin intravenously at a dose of 25 mg/m^2 on Day 1 and Day 8 of 21-day cycle, for 8 cycles Q3W.

Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received Gemcitabine intravenously at a dose of 1000 mg/m^2 on Day 1 and Day 8 of 21-day cycle, for 8 cycles Q3W.

Arm title	Double-blinded Part: M7824 + Gemcitabine + Cisplatin

Arm description:

Subjects received intravenous infusion of M7824 at a dose of 2400 milligrams (mg), once every 3 weeks (Q3W) 2 years (in case of CR), otherwise until criterion pre-specified in protocol for discontinuation is met, in combination with intravenous infusion of Gemcitabine and Cisplatin at a dose of 1000 mg/m^2 and 25 mg/m^2 respectively on Day 1 and Day 8 of 21- day cycle, for 8 cycles every 3 weeks. In case of any missed dose for chemotherapy, gemcitabine and cisplatin combination administered on Day 15 of that cycle or at the end of the scheduled 8 cycles (up to 16 administrations of gemcitabine and cisplatin combination). The administration of the missed dose on Day 15 or at the end of 8 cycles is Investigator's clinical decision.

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

Dosage and administration details:

Subjects received intravenous infusion of M7824 at a dose of 2400 mg Q3W 2 years (in case of Complete Response), otherwise until criterion pre-specified in protocol for discontinuation is met.

Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received Gemcitabine intravenously at a dose of 1000 mg/m^2 on Day 1 and Day 8 of 21-day cycle, for 8 cycles Q3W.

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received Cisplatin intravenously at a dose of 25 mg/m^2 on Day 1 and Day 8 of 21-day cycle, for 8 cycles Q3W.

Number of subjects in period 1	Safety Run-In Part: M7824 + Gemcitabine + Cisplatin	Double-blinded Part: Placebo + Gemcitabine + Cisplatin	Double-blinded Part: M7824 + Gemcitabine + Cisplatin
Started	12	149	148
Treated	12	149	146
Completed	8	38	39
Not completed	4	111	109
Treatment ongoing	2	72	66
Treatment completed/discontinued and in follow-up,	2	39	41
Randomized, not treated	-	-	2

Baseline characteristics

Reporting groups

Reporting group title	Safety Run-In Part: M7824 + Gemcitabine + Cisplatin

Reporting group description:

Subjects received intravenous infusion of M7824 at a dose of 2400 milligrams (mg), once every 3 weeks (Q3W) 2 years (in case of Complete Response), otherwise until criterion pre-specified in protocol for discontinuation is met, in combination with intravenous infusion of Gemcitabine and Cisplatin at a dose of 1000 milligram per meter square (mg/m^2) and 25 mg/m^2 respectively on Day 1 and Day 8 of 21-day cycle, for 8 cycles every 3 weeks.

Reporting group title	Double-blinded Part: Placebo + Gemcitabine + Cisplatin

Reporting group description:

Subjects received intravenous infusion of M7824 matched placebo, once every 3 weeks (Q3W) until 2 years (in case of CR), otherwise until criterion pre-specified in protocol for discontinuation is met, in combination with intravenous infusion of Gemcitabine and Cisplatin at a dose of 1000 mg/m^2 and 25 mg/m^2 respectively on Day 1 and Day 8 of 21- day cycle, for 8 cycles every 3 weeks. In case of any missed dose for chemotherapy, gemcitabine and cisplatin combination administered on Day 15 of that cycle or at the end of the scheduled 8 cycles (up to 16 administrations of gemcitabine and cisplatin combination). The administration of the missed dose on Day 15 or at the end of 8 cycles is Investigator's clinical decision.

Reporting group title	Double-blinded Part: M7824 + Gemcitabine + Cisplatin

Reporting group description:

Subjects received intravenous infusion of M7824 at a dose of 2400 milligrams (mg), once every 3 weeks (Q3W) 2 years (in case of CR), otherwise until criterion pre-specified in protocol for discontinuation is met, in combination with intravenous infusion of Gemcitabine and Cisplatin at a dose of 1000 mg/m^2 and 25 mg/m^2 respectively on Day 1 and Day 8 of 21- day cycle, for 8 cycles every 3 weeks. In case of any missed dose for chemotherapy, gemcitabine and cisplatin combination administered on Day 15 of that cycle or at the end of the scheduled 8 cycles (up to 16 administrations of gemcitabine and cisplatin combination). The administration of the missed dose on Day 15 or at the end of 8 cycles is Investigator's clinical decision.

Reporting group values	Safety Run-In Part: M7824 + Gemcitabine + Cisplatin	Double-blinded Part: Placebo + Gemcitabine + Cisplatin	Double-blinded Part: M7824 + Gemcitabine + Cisplatin
Number of subjects	12	149	148
Age categorical Units:			
Age Continuous Units: Years			
arithmetic mean	66	64	63
standard deviation	± 11.9	± 10.6	± 10.8
Sex: Female, Male Units: Subjects			
Female	5	78	68
Male	7	71	80
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	1	21	22
Not Hispanic or Latino	11	128	126
Unknown or Not Reported	0	0	0
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	1	0

Asian	6	93	90
Native Hawaiian or Other Pacific Islander	0	1	0
Black or African American	0	0	1
White	6	51	51
More than one race	0	0	1
Unknown or Not Reported	0	3	5

Reporting group values	Total		
Number of subjects	309		
Age categorical Units:			

Age Continuous Units: Years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male Units: Subjects			
Female	151		
Male	158		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	44		
Not Hispanic or Latino	265		
Unknown or Not Reported	0		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	1		
Asian	189		
Native Hawaiian or Other Pacific Islander	1		
Black or African American	1		
White	108		
More than one race	1		
Unknown or Not Reported	8		

End points

End points reporting groups

Reporting group title	Safety Run-In Part: M7824 + Gemcitabine + Cisplatin

Reporting group description:

Subjects received intravenous infusion of M7824 at a dose of 2400 milligrams (mg), once every 3 weeks (Q3W) 2 years (in case of Complete Response), otherwise until criterion pre-specified in protocol for discontinuation is met, in combination with intravenous infusion of Gemcitabine and Cisplatin at a dose of 1000 milligram per meter square (mg/m^2) and 25 mg/m^2 respectively on Day 1 and Day 8 of 21-day cycle, for 8 cycles every 3 weeks.

Reporting group title	Double-blinded Part: Placebo + Gemcitabine + Cisplatin

Reporting group description:

Subjects received intravenous infusion of M7824 matched placebo, once every 3 weeks (Q3W) until 2 years (in case of CR), otherwise until criterion pre-specified in protocol for discontinuation is met, in combination with intravenous infusion of Gemcitabine and Cisplatin at a dose of 1000 mg/m^2 and 25 mg/m^2 respectively on Day 1 and Day 8 of 21- day cycle, for 8 cycles every 3 weeks. In case of any missed dose for chemotherapy, gemcitabine and cisplatin combination administered on Day 15 of that cycle or at the end of the scheduled 8 cycles (up to 16 administrations of gemcitabine and cisplatin combination). The administration of the missed dose on Day 15 or at the end of 8 cycles is Investigator's clinical decision.

Reporting group title	Double-blinded Part: M7824 + Gemcitabine + Cisplatin

Reporting group description:

Subjects received intravenous infusion of M7824 at a dose of 2400 milligrams (mg), once every 3 weeks (Q3W) 2 years (in case of CR), otherwise until criterion pre-specified in protocol for discontinuation is met, in combination with intravenous infusion of Gemcitabine and Cisplatin at a dose of 1000 mg/m^2 and 25 mg/m^2 respectively on Day 1 and Day 8 of 21- day cycle, for 8 cycles every 3 weeks. In case of any missed dose for chemotherapy, gemcitabine and cisplatin combination administered on Day 15 of that cycle or at the end of the scheduled 8 cycles (up to 16 administrations of gemcitabine and cisplatin combination). The administration of the missed dose on Day 15 or at the end of 8 cycles is Investigator's clinical decision.

Primary: Double-blind Part: Overall Survival

End point title	Double-blind Part: Overall Survival[1][2]

End point description:

Overall Survival was defined as the time from study day 1 to the date of death due to any cause. The overall survival was analyzed by using the Kaplan-Meier method. Intent-to-Treat analysis set included all randomized subjects. Here, "Number of Subjects Analyzed" signifies those subjects who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

Time from study day 1 up to data cutoff (assessed up to 609 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: Only descriptive statistics was planned to be reported for this endpoint.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: It was planned to report data for only double -blind part. Therefore, other arms has not been selected.

End point values	Double-blinded Part: Placebo + Gemcitabine + Cisplatin	Double-blinded Part: M7824 + Gemcitabine + Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	23		
Units: Months				
median (full range (min-max))	11.5 (0.9 to 15.2)	11.5 (0.2 to 13.9)		

Statistical analyses

No statistical analyses for this end point

Primary: Safety Run-in Part: Number of Subjects Who Experienced Dose Limiting Toxicities (DLTs)

End point title	Safety Run-in Part: Number of Subjects Who Experienced Dose Limiting Toxicities (DLTs)[3][4]

End point description:

DLT: toxicity related to study intervention that meets, following criteria as evaluated in open-label, safety run-in: Grade (Gr) 3/4 Immune-related adverse event (irAE) that needs permanent discontinuation of M7824 treatment; a malignant skin lesion induced by M7824 that is local and can be resected with a negative resection margin is not a DLT; Gr 3/4 nonhematologic toxicity other than irAE, A life threatening hematological toxicity (unless clearly attributable to chemotherapy alone), which is hardly medically manageable, including a bleeding event resulting in urgent intervention and admission to an intensive care unit and Gr5 toxicity. DLT analysis set: all subjects who experienced at least 1 DLT (either by Investigator/by Safety Monitoring Committee (SMC)/who completed safety run-in, receiving at least 1 infusion of M7824 and of both gemcitabine and cisplatin and not being withdrawn during the DLT evaluation period for reasons other than toxicity.

End point type	Primary

End point timeframe:

Day 1 up to Day 21 of Cycle 1 (each Cycle is of 21 days)

Notes:

[3] - 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: Only descriptive statistics was planned to be reported for this endpoint.

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: It was planned to report data for only safety run-in part. Therefore, other arms has not been selected.

End point values	Safety Run-In Part: M7824 + Gemcitabine + Cisplatin			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: Subjects	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Safety Run-in Part: Number of Subjects With Treatment-Emergent Adverse Events (TEAEs), Serious TEAEs (SAEs) and Treatment Related TEAEs According to National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.0

End point title	Safety Run-in Part: Number of Subjects With Treatment-Emergent Adverse Events (TEAEs), Serious TEAEs (SAEs) and Treatment Related TEAEs According to National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.0[5]

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. TEAE was defined as events with onset date or worsening during the on treatment period. TEAEs included serious TEAEs and non-serious TEAEs. Safety run-in (SRI) analysis set included all subjects from the safety run-in part who were administered any dose of any study intervention.

End point type	Secondary

End point timeframe:

Time from first treatment to up to data cutoff (assessed up to 609 days)

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: It was planned to report data for only safety run-in part. Therefore, other arms has not been selected.

End point values	Safety Run-In Part: M7824 + Gemcitabine + Cisplatin			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: Subjects				
Subjects with TEAEs	12			
Subjects with Serious TEAEs	5			
Subjects with Treatment-related TEAEs	11			

Statistical analyses

No statistical analyses for this end point

Secondary: Safety Run-in Part: Number of Subjects With Grade Greater than or Equal (>=) 3 Laboratory Abnormalities

End point title	Safety Run-in Part: Number of Subjects With Grade Greater than or Equal (>=) 3 Laboratory Abnormalities[6]

End point description:

Laboratory investigation included hematology and biochemistry. The number of subjects with Grade >=3 laboratory abnormalities were reported. Severity of grade 3 or higher TEAEs were graded using NCI-CTCAE v5.0 toxicity grades, as follows: Grade 3 = Severe; Grade 4 = Life-threatening and Grade 5 = Death. The safety run-in (SRI) analysis set includes all subjects from the safety run-in part who were administered any dose of any study intervention.

End point type	Secondary

End point timeframe:

Time from first treatment to up to data cutoff (assessed up to 609 days)

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: It was planned to report data for only safety run-in part. Therefore, other arms has not been selected.

End point values	Safety Run-In Part: M7824 + Gemcitabine + Cisplatin			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: Subjects				
Hemoglobin low	6			
Leukocytes low	4			
Neutrophils low	6			
Platelets low	3			
Alanine Aminotransferase high	2			
Bilirubin high	1			
Creatinine high	1			
Lipase high	1			
Potassium low	1			
Lymphocytes low	2			
Corrected Calcium high	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Double-blind Part: 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	Double-blind Part: Progression-Free Survival (PFS) According to Response Evaluation Criteria in Solid Tumors (RECIST Version 1.1) Assessed by Independent Review Committee (IRC)[7]

End point description:

Progression free survival was defined as the time from randomization of study intervention until the first documentation of disease progression (PD) or death due to any cause in the absence of documented PD, whichever occurred first. PD: At least a 20 percent (%) increase in the sum of the longest diameter (SLD) taking as reference the smallest SLD recorded from baseline or the appearance of 1 or more new lesions. Intent-to-Treat analysis set included all randomized subjects. Here, "Number of Subjects Analyzed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Time from randomization of study drug until the first documentation of PD or death, assessed approximately up to 609 days

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: It was planned to report data for only double-blind part. Therefore, other arms has not been selected.

End point values	Double-blinded Part: Placebo + Gemcitabine + Cisplatin	Double-blinded Part: M7824 + Gemcitabine + Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	49		
Units: Months				
median (confidence interval 95%)	5.6 (4.2 to 6.9)	5.5 (2.8 to 6.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Double-blind Part: 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	Double-blind Part: 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)[8]

End point description:

Percentage of subjects with confirmed objective response that is at least one overall assessment of complete response (CR) or partial response (PR) reported here. 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. Intent-to-Treat analysis set included all randomized subjects. Here, "Number of Subjects Analyzed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Time from randomization of study drug up to data cut off (assessed up to 609 days)

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: It was planned to report data for only double -blind part. Therefore, other arms has not been selected.

End point values	Double-blinded Part: Placebo + Gemcitabine + Cisplatin	Double-blinded Part: M7824 + Gemcitabine + Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	73		
Units: Percentage of subjects				
number (confidence interval 95%)	19.5 (11.3 to 30.1)	31.5 (21.1 to 43.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Double-blind Part: 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	Double-blind Part: 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)[9]

End point description:

DOR was defined for subjects with objective response, as the time from first documentation of objective response (confirmed 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. Intent-to-Treat analysis set included all randomized subjects. Here, "Number of Subjects Analyzed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From first documented objective response to PD or death due to any cause, assessed approximately up to 609 days

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: It was planned to report data for only double -blind part. Therefore, other arms has not been selected.

End point values	Double-blinded Part: Placebo + Gemcitabine + Cisplatin	Double-blinded Part: M7824 + Gemcitabine + Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	9		
Units: Months				
median (full range (min-max))	12.5 (2.7 to 12.5)	7.0 (1.4 to 8.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Double-blind Part: Number of Subjects With Treatment-Emergent Adverse Events (TEAEs), Serious TEAEs (SAEs), Treatment Related TEAEs and Adverse Events of Special Interest (AESIs) According to NCI-CTCAE version 5.0

End point title	Double-blind Part: Number of Subjects With Treatment-Emergent Adverse Events (TEAEs), Serious TEAEs (SAEs), Treatment Related TEAEs and Adverse Events of Special Interest (AESIs) According to NCI-CTCAE version 5.0[10]

End point description:

AE: 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: AE that resulted in any of following outcomes: death; life threatening; persistent/significant disability/incapacity; initial/prolonged inpatient hospitalization; congenital anomaly/birth defect. TEAE: events with onset date/worsening during the on-treatment period. TEAEs included serious TEAEs and non-serious TEAEs. Adverse events of special interest (AESI) are serious/non-serious AEs that are of clinical interest and should be closely followed. AESIs include following: Infusion-related reactions including immediate hypersensitivity; Immune-related AEs; Transforming growth factor beta (TGFβ) inhibition mediated skin reactions; Anemia; Bleeding AEs. Safety analysis set: all subjects who were administered at least 1 dose of any study treatment (M7824, placebo, gemcitabine or cisplatin).

End point type	Secondary

End point timeframe:

Time from first treatment to up to data cutoff (assessed up to 609 days)

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: It was planned to report data for only double -blind part. Therefore, other arms has not been selected.

End point values	Double-blinded Part: Placebo + Gemcitabine + Cisplatin	Double-blinded Part: M7824 + Gemcitabine + Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	149	146		
Units: Subjects				
Subjects with TEAEs	145	140		
Subjects with Serious TEAEs	36	58		
Subjects with Treatment-related TEAEs	136	133		
Subjects with AESIs	8	16		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Time from first treatment to up to data cutoff (assessed up to 609 days)

Adverse event reporting additional description:

Safety Run-In Part: The safety run-in (SRI) analysis set includes all subjects from the safety run-in part who were administered any dose of any study intervention and double-blinded part safety analysis set included all randomized subjects who were administered at least one dose of study treatment (M7824, Placebo, Gemcitabine or Cisplatin).

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Safety Run-In Part: M7824 + Gemcitabine + Cisplatin

Reporting group description:

Subjects received intravenous infusion of M7824 at a dose of 2400 milligrams (mg), once every 3 weeks (Q3W) 2 years (in case of Complete Response), otherwise until criterion pre-specified in protocol for discontinuation is met, in combination with intravenous infusion of Gemcitabine and Cisplatin at a dose of 1000 milligram per meter square (mg/m^2) and 25 mg/m^2 respectively on Day 1 and Day 8 of 21-day cycle, for 8 cycles every 3 weeks.

Reporting group title	Double-blinded Part: Placebo + Gemcitabine + Cisplatin

Reporting group description:

Subjects received intravenous infusion of M7824 matched placebo, once every 3 weeks (Q3W) until 2 years (in case of CR), otherwise until criterion pre-specified in protocol for discontinuation is met, in combination with intravenous infusion of Gemcitabine and Cisplatin at a dose of 1000 mg/m^2 and 25 mg/m^2 respectively on Day 1 and Day 8 of 21- day cycle, for 8 cycles every 3 weeks. In case of any missed dose for chemotherapy, gemcitabine and cisplatin combination administered on Day 15 of that cycle or at the end of the scheduled 8 cycles (up to 16 administrations of gemcitabine and cisplatin combination). The administration of the missed dose on Day 15 or at the end of 8 cycles is Investigator's clinical decision.

Reporting group title	Double-blinded Part: M7824 + Gemcitabine + Cisplatin

Reporting group description:

Subjects received intravenous infusion of M7824 at a dose of 2400 milligrams (mg), once every 3 weeks (Q3W) 2 years (in case of CR), otherwise until criterion pre-specified in protocol for discontinuation is met, in combination with intravenous infusion of Gemcitabine and Cisplatin at a dose of 1000 mg/m^2 and 25 mg/m^2 respectively on Day 1 and Day 8 of 21- day cycle, for 8 cycles every 3 weeks. In case of any missed dose for chemotherapy, gemcitabine and cisplatin combination administered on Day 15 of that cycle or at the end of the scheduled 8 cycles (up to 16 administrations of gemcitabine and cisplatin combination). The administration of the missed dose on Day 15 or at the end of 8 cycles is Investigator's clinical decision.

Serious adverse events	Safety Run-In Part: M7824 + Gemcitabine + Cisplatin	Double-blinded Part: Placebo + Gemcitabine + Cisplatin	Double-blinded Part: M7824 + Gemcitabine + Cisplatin
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 12 (41.67%)	36 / 149 (24.16%)	58 / 146 (39.73%)
number of deaths (all causes)	7	26	31
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Cancer pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 149 (0.67%)	0 / 146 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to bone			
subjects affected / exposed	0 / 12 (0.00%)	2 / 149 (1.34%)	0 / 146 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 12 (0.00%)	0 / 149 (0.00%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma			
subjects affected / exposed	0 / 12 (0.00%)	0 / 149 (0.00%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour associated fever			
subjects affected / exposed	0 / 12 (0.00%)	1 / 149 (0.67%)	0 / 146 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 12 (0.00%)	0 / 149 (0.00%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Embolism			
subjects affected / exposed	0 / 12 (0.00%)	0 / 149 (0.00%)	2 / 146 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic venous thrombosis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 149 (0.67%)	0 / 146 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration			

site conditions			
Asthenia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 149 (0.00%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chills			
subjects affected / exposed	0 / 12 (0.00%)	1 / 149 (0.67%)	0 / 146 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	0 / 12 (0.00%)	0 / 149 (0.00%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Disease progression			
subjects affected / exposed	0 / 12 (0.00%)	1 / 149 (0.67%)	0 / 146 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Fatigue			
subjects affected / exposed	0 / 12 (0.00%)	0 / 149 (0.00%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hernia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 149 (0.00%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaise			
subjects affected / exposed	0 / 12 (0.00%)	0 / 149 (0.00%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	0 / 12 (0.00%)	0 / 149 (0.00%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			

subjects affected / exposed	1 / 12 (8.33%)	2 / 149 (1.34%)	4 / 146 (2.74%)
occurrences causally related to treatment / all	0 / 1	1 / 2	3 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic shock			
subjects affected / exposed	0 / 12 (0.00%)	0 / 149 (0.00%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 149 (0.00%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 12 (0.00%)	1 / 149 (0.67%)	0 / 146 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory distress			
subjects affected / exposed	0 / 12 (0.00%)	0 / 149 (0.00%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Respiratory failure			
subjects affected / exposed	0 / 12 (0.00%)	0 / 149 (0.00%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device occlusion			
subjects affected / exposed	0 / 12 (0.00%)	0 / 149 (0.00%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			

subjects affected / exposed	0 / 12 (0.00%)	0 / 149 (0.00%)	2 / 146 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood albumin decreased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 149 (0.00%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood bilirubin increased			
subjects affected / exposed	0 / 12 (0.00%)	3 / 149 (2.01%)	2 / 146 (1.37%)
occurrences causally related to treatment / all	0 / 0	1 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood sodium decreased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 149 (0.67%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lipase increased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 149 (0.67%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphocyte count decreased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 149 (0.67%)	0 / 146 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutrophil count decreased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 149 (0.67%)	0 / 146 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelet count decreased			
subjects affected / exposed	0 / 12 (0.00%)	2 / 149 (1.34%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases increased			

subjects affected / exposed	1 / 12 (8.33%)	0 / 149 (0.00%)	0 / 146 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Incisional hernia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 149 (0.00%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infusion related reaction			
subjects affected / exposed	0 / 12 (0.00%)	0 / 149 (0.00%)	3 / 146 (2.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic intracranial haemorrhage			
subjects affected / exposed	0 / 12 (0.00%)	1 / 149 (0.67%)	0 / 146 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	0 / 12 (0.00%)	0 / 149 (0.00%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Nervous system disorders			
Cerebral ischaemia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 149 (0.67%)	0 / 146 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral infarction			
subjects affected / exposed	0 / 12 (0.00%)	0 / 149 (0.00%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalopathy			
subjects affected / exposed	0 / 12 (0.00%)	0 / 149 (0.00%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Facial paralysis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 149 (0.00%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage intracranial			
subjects affected / exposed	0 / 12 (0.00%)	0 / 149 (0.00%)	2 / 146 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Ischaemic cerebral infarction			
subjects affected / exposed	0 / 12 (0.00%)	1 / 149 (0.67%)	0 / 146 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 12 (0.00%)	2 / 149 (1.34%)	7 / 146 (4.79%)
occurrences causally related to treatment / all	0 / 0	1 / 2	7 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 149 (0.00%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 149 (0.67%)	0 / 146 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 149 (0.67%)	0 / 146 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	1 / 12 (8.33%)	2 / 149 (1.34%)	0 / 146 (0.00%)
occurrences causally related to treatment / all	1 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			

Ulcerative keratitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 149 (0.00%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 149 (0.67%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	0 / 12 (0.00%)	0 / 149 (0.00%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	0 / 12 (0.00%)	1 / 149 (0.67%)	0 / 146 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer haemorrhage			
subjects affected / exposed	1 / 12 (8.33%)	0 / 149 (0.00%)	0 / 146 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 149 (0.00%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric haemorrhage			
subjects affected / exposed	0 / 12 (0.00%)	0 / 149 (0.00%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer			
subjects affected / exposed	0 / 12 (0.00%)	0 / 149 (0.00%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric stenosis			

subjects affected / exposed	0 / 12 (0.00%)	0 / 149 (0.00%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 12 (8.33%)	1 / 149 (0.67%)	2 / 146 (1.37%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal vascular malformation haemorrhagic			
subjects affected / exposed	0 / 12 (0.00%)	0 / 149 (0.00%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematochezia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 149 (0.67%)	0 / 146 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 12 (0.00%)	0 / 149 (0.00%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 12 (0.00%)	0 / 149 (0.00%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 12 (0.00%)	0 / 149 (0.00%)	3 / 146 (2.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstruction gastric			
subjects affected / exposed	0 / 12 (0.00%)	1 / 149 (0.67%)	0 / 146 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			

subjects affected / exposed	0 / 12 (0.00%)	0 / 149 (0.00%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	0 / 12 (0.00%)	0 / 149 (0.00%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 12 (0.00%)	0 / 149 (0.00%)	3 / 146 (2.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 12 (0.00%)	0 / 149 (0.00%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Hepatobiliary disorders			
Bile duct stenosis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 149 (0.00%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bile duct stone			
subjects affected / exposed	0 / 12 (0.00%)	1 / 149 (0.67%)	0 / 146 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis			
subjects affected / exposed	0 / 12 (0.00%)	5 / 149 (3.36%)	6 / 146 (4.11%)
occurrences causally related to treatment / all	0 / 0	0 / 5	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Biliary obstruction			
subjects affected / exposed	1 / 12 (8.33%)	3 / 149 (2.01%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			

subjects affected / exposed	1 / 12 (8.33%)	1 / 149 (0.67%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic failure			
subjects affected / exposed	0 / 12 (0.00%)	0 / 149 (0.00%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cholestasis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 149 (0.00%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune-mediated hepatitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 149 (0.00%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice cholestatic			
subjects affected / exposed	0 / 12 (0.00%)	0 / 149 (0.00%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 149 (0.00%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erythema multiforme			
subjects affected / exposed	0 / 12 (0.00%)	0 / 149 (0.00%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urticaria			
subjects affected / exposed	0 / 12 (0.00%)	1 / 149 (0.67%)	0 / 146 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	1 / 12 (8.33%)	0 / 149 (0.00%)	2 / 146 (1.37%)
occurrences causally related to treatment / all	1 / 1	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysuria			
subjects affected / exposed	0 / 12 (0.00%)	0 / 149 (0.00%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	0 / 12 (0.00%)	1 / 149 (0.67%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tubulointerstitial nephritis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 149 (0.00%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	0 / 12 (0.00%)	0 / 149 (0.00%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 12 (0.00%)	0 / 149 (0.00%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypophysitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 149 (0.00%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypopituitarism			
subjects affected / exposed	0 / 12 (0.00%)	0 / 149 (0.00%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypothyroidism			

subjects affected / exposed	0 / 12 (0.00%)	0 / 149 (0.00%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 149 (0.67%)	0 / 146 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abdominal infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 149 (0.00%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 149 (0.00%)	2 / 146 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Biliary sepsis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 149 (0.00%)	2 / 146 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Biliary tract infection			
subjects affected / exposed	0 / 12 (0.00%)	3 / 149 (2.01%)	2 / 146 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
COVID-19			
subjects affected / exposed	0 / 12 (0.00%)	1 / 149 (0.67%)	0 / 146 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Diarrhoea infectious			
subjects affected / exposed	0 / 12 (0.00%)	0 / 149 (0.00%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Herpes simplex encephalitis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 149 (0.67%)	0 / 146 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Klebsiella infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 149 (0.00%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver abscess			
subjects affected / exposed	0 / 12 (0.00%)	2 / 149 (1.34%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pseudomonas infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 149 (0.00%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 149 (0.67%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 149 (0.00%)	2 / 146 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Soft tissue infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 149 (0.00%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 12 (0.00%)	1 / 149 (0.67%)	0 / 146 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular device infection			

subjects affected / exposed	0 / 12 (0.00%)	0 / 149 (0.00%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 12 (0.00%)	0 / 149 (0.00%)	2 / 146 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	0 / 12 (0.00%)	0 / 149 (0.00%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypomagnesaemia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 149 (0.00%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 149 (0.00%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Safety Run-In Part: M7824 + Gemcitabine + Cisplatin	Double-blinded Part: Placebo + Gemcitabine + Cisplatin	Double-blinded Part: M7824 + Gemcitabine + Cisplatin
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 12 (100.00%)	142 / 149 (95.30%)	134 / 146 (91.78%)
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 12 (8.33%)	11 / 149 (7.38%)	6 / 146 (4.11%)
occurrences (all)	1	11	6
General disorders and administration site conditions			
Asthenia			

subjects affected / exposed	2 / 12 (16.67%)	18 / 149 (12.08%)	23 / 146 (15.75%)
occurrences (all)	2	18	23
Fatigue			
subjects affected / exposed	4 / 12 (33.33%)	35 / 149 (23.49%)	29 / 146 (19.86%)
occurrences (all)	4	35	29
Generalised oedema			
subjects affected / exposed	1 / 12 (8.33%)	0 / 149 (0.00%)	0 / 146 (0.00%)
occurrences (all)	1	0	0
Malaise			
subjects affected / exposed	0 / 12 (0.00%)	11 / 149 (7.38%)	5 / 146 (3.42%)
occurrences (all)	0	11	5
Oedema peripheral			
subjects affected / exposed	1 / 12 (8.33%)	10 / 149 (6.71%)	9 / 146 (6.16%)
occurrences (all)	1	10	9
Mucosal inflammation			
subjects affected / exposed	1 / 12 (8.33%)	4 / 149 (2.68%)	1 / 146 (0.68%)
occurrences (all)	1	4	1
Pyrexia			
subjects affected / exposed	3 / 12 (25.00%)	19 / 149 (12.75%)	33 / 146 (22.60%)
occurrences (all)	3	19	33
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 12 (25.00%)	9 / 149 (6.04%)	3 / 146 (2.05%)
occurrences (all)	3	9	3
Dyspnoea exertional			
subjects affected / exposed	1 / 12 (8.33%)	0 / 149 (0.00%)	3 / 146 (2.05%)
occurrences (all)	1	0	3
Epistaxis			
subjects affected / exposed	2 / 12 (16.67%)	3 / 149 (2.01%)	19 / 146 (13.01%)
occurrences (all)	2	3	19
Pulmonary embolism			
subjects affected / exposed	1 / 12 (8.33%)	1 / 149 (0.67%)	2 / 146 (1.37%)
occurrences (all)	1	1	2
Psychiatric disorders			

Adjustment disorder			
subjects affected / exposed	1 / 12 (8.33%)	1 / 149 (0.67%)	0 / 146 (0.00%)
occurrences (all)	1	1	0
Anxiety			
subjects affected / exposed	1 / 12 (8.33%)	6 / 149 (4.03%)	3 / 146 (2.05%)
occurrences (all)	1	6	3
Insomnia			
subjects affected / exposed	1 / 12 (8.33%)	2 / 149 (1.34%)	12 / 146 (8.22%)
occurrences (all)	1	2	12
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 12 (16.67%)	20 / 149 (13.42%)	13 / 146 (8.90%)
occurrences (all)	2	20	13
Amylase increased			
subjects affected / exposed	2 / 12 (16.67%)	8 / 149 (5.37%)	4 / 146 (2.74%)
occurrences (all)	2	8	4
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 12 (16.67%)	22 / 149 (14.77%)	13 / 146 (8.90%)
occurrences (all)	2	22	13
Blood albumin decreased			
subjects affected / exposed	1 / 12 (8.33%)	4 / 149 (2.68%)	1 / 146 (0.68%)
occurrences (all)	1	4	1
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 12 (8.33%)	8 / 149 (5.37%)	7 / 146 (4.79%)
occurrences (all)	1	8	7
Blood creatinine increased			
subjects affected / exposed	1 / 12 (8.33%)	7 / 149 (4.70%)	6 / 146 (4.11%)
occurrences (all)	1	7	6
Blood bilirubin increased			
subjects affected / exposed	0 / 12 (0.00%)	14 / 149 (9.40%)	9 / 146 (6.16%)
occurrences (all)	0	14	9
Blood magnesium decreased			
subjects affected / exposed	1 / 12 (8.33%)	3 / 149 (2.01%)	2 / 146 (1.37%)
occurrences (all)	1	3	2
Haemoglobin decreased			

subjects affected / exposed	1 / 12 (8.33%)	0 / 149 (0.00%)	3 / 146 (2.05%)
occurrences (all)	1	0	3
Creatinine renal clearance decreased			
subjects affected / exposed	1 / 12 (8.33%)	9 / 149 (6.04%)	4 / 146 (2.74%)
occurrences (all)	1	9	4
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 12 (8.33%)	10 / 149 (6.71%)	4 / 146 (2.74%)
occurrences (all)	1	10	4
Neutrophil count decreased			
subjects affected / exposed	5 / 12 (41.67%)	59 / 149 (39.60%)	28 / 146 (19.18%)
occurrences (all)	5	59	28
White blood cell count decreased			
subjects affected / exposed	3 / 12 (25.00%)	36 / 149 (24.16%)	19 / 146 (13.01%)
occurrences (all)	3	36	19
Platelet count decreased			
subjects affected / exposed	3 / 12 (25.00%)	38 / 149 (25.50%)	34 / 146 (23.29%)
occurrences (all)	3	38	34
Lipase increased			
subjects affected / exposed	2 / 12 (16.67%)	9 / 149 (6.04%)	5 / 146 (3.42%)
occurrences (all)	2	9	5
Iron binding capacity total decreased			
subjects affected / exposed	1 / 12 (8.33%)	0 / 149 (0.00%)	0 / 146 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	1 / 12 (8.33%)	3 / 149 (2.01%)	6 / 146 (4.11%)
occurrences (all)	1	3	6
Cardiac disorders			
Bradycardia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 149 (0.00%)	0 / 146 (0.00%)
occurrences (all)	1	0	0
Tachycardia			
subjects affected / exposed	1 / 12 (8.33%)	1 / 149 (0.67%)	0 / 146 (0.00%)
occurrences (all)	1	1	0
Nervous system disorders			

Dysgeusia			
subjects affected / exposed	2 / 12 (16.67%)	3 / 149 (2.01%)	6 / 146 (4.11%)
occurrences (all)	2	3	6
Dizziness			
subjects affected / exposed	0 / 12 (0.00%)	13 / 149 (8.72%)	8 / 146 (5.48%)
occurrences (all)	0	13	8
Headache			
subjects affected / exposed	0 / 12 (0.00%)	13 / 149 (8.72%)	12 / 146 (8.22%)
occurrences (all)	0	13	12
Taste disorder			
subjects affected / exposed	1 / 12 (8.33%)	0 / 149 (0.00%)	0 / 146 (0.00%)
occurrences (all)	1	0	0
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 12 (8.33%)	1 / 149 (0.67%)	5 / 146 (3.42%)
occurrences (all)	1	1	5
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	1 / 12 (8.33%)	7 / 149 (4.70%)	4 / 146 (2.74%)
occurrences (all)	1	7	4
Anaemia			
subjects affected / exposed	6 / 12 (50.00%)	79 / 149 (53.02%)	78 / 146 (53.42%)
occurrences (all)	6	79	78
Lymphopenia			
subjects affected / exposed	1 / 12 (8.33%)	1 / 149 (0.67%)	1 / 146 (0.68%)
occurrences (all)	1	1	1
Thrombocytopenia			
subjects affected / exposed	1 / 12 (8.33%)	12 / 149 (8.05%)	14 / 146 (9.59%)
occurrences (all)	1	12	14
Neutropenia			
subjects affected / exposed	1 / 12 (8.33%)	40 / 149 (26.85%)	25 / 146 (17.12%)
occurrences (all)	1	40	25
Ear and labyrinth disorders			
Ear discomfort			
subjects affected / exposed	1 / 12 (8.33%)	0 / 149 (0.00%)	0 / 146 (0.00%)
occurrences (all)	1	0	0
Ear congestion			

subjects affected / exposed	1 / 12 (8.33%)	0 / 149 (0.00%)	0 / 146 (0.00%)
occurrences (all)	1	0	0
Tinnitus			
subjects affected / exposed	1 / 12 (8.33%)	0 / 149 (0.00%)	3 / 146 (2.05%)
occurrences (all)	1	0	3
Eye disorders			
Vision blurred			
subjects affected / exposed	1 / 12 (8.33%)	1 / 149 (0.67%)	0 / 146 (0.00%)
occurrences (all)	1	1	0
Eye pain			
subjects affected / exposed	1 / 12 (8.33%)	1 / 149 (0.67%)	0 / 146 (0.00%)
occurrences (all)	1	1	0
Retinal haemorrhage			
subjects affected / exposed	1 / 12 (8.33%)	0 / 149 (0.00%)	0 / 146 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal pain lower			
subjects affected / exposed	1 / 12 (8.33%)	0 / 149 (0.00%)	0 / 146 (0.00%)
occurrences (all)	1	0	0
Abdominal pain upper			
subjects affected / exposed	2 / 12 (16.67%)	6 / 149 (4.03%)	5 / 146 (3.42%)
occurrences (all)	2	6	5
Abdominal pain			
subjects affected / exposed	2 / 12 (16.67%)	11 / 149 (7.38%)	13 / 146 (8.90%)
occurrences (all)	2	11	13
Abdominal distension			
subjects affected / exposed	1 / 12 (8.33%)	3 / 149 (2.01%)	5 / 146 (3.42%)
occurrences (all)	1	3	5
Aphthous ulcer			
subjects affected / exposed	1 / 12 (8.33%)	0 / 149 (0.00%)	0 / 146 (0.00%)
occurrences (all)	1	0	0
Constipation			
subjects affected / exposed	4 / 12 (33.33%)	51 / 149 (34.23%)	40 / 146 (27.40%)
occurrences (all)	4	51	40
Ascites			

subjects affected / exposed	0 / 12 (0.00%)	9 / 149 (6.04%)	1 / 146 (0.68%)
occurrences (all)	0	9	1
Gingival bleeding			
subjects affected / exposed	1 / 12 (8.33%)	0 / 149 (0.00%)	13 / 146 (8.90%)
occurrences (all)	1	0	13
Dyspepsia			
subjects affected / exposed	1 / 12 (8.33%)	10 / 149 (6.71%)	6 / 146 (4.11%)
occurrences (all)	1	10	6
Diarrhoea			
subjects affected / exposed	3 / 12 (25.00%)	15 / 149 (10.07%)	20 / 146 (13.70%)
occurrences (all)	3	15	20
Rectal haemorrhage			
subjects affected / exposed	1 / 12 (8.33%)	1 / 149 (0.67%)	1 / 146 (0.68%)
occurrences (all)	1	1	1
Nausea			
subjects affected / exposed	6 / 12 (50.00%)	72 / 149 (48.32%)	64 / 146 (43.84%)
occurrences (all)	6	72	64
Stomatitis			
subjects affected / exposed	0 / 12 (0.00%)	6 / 149 (4.03%)	16 / 146 (10.96%)
occurrences (all)	0	6	16
Vomiting			
subjects affected / exposed	1 / 12 (8.33%)	32 / 149 (21.48%)	31 / 146 (21.23%)
occurrences (all)	1	32	31
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 149 (0.00%)	0 / 146 (0.00%)
occurrences (all)	1	0	0
Cholangitis			
subjects affected / exposed	1 / 12 (8.33%)	3 / 149 (2.01%)	2 / 146 (1.37%)
occurrences (all)	1	3	2
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 12 (0.00%)	16 / 149 (10.74%)	5 / 146 (3.42%)
occurrences (all)	0	16	5
Blister			

subjects affected / exposed	1 / 12 (8.33%)	0 / 149 (0.00%)	0 / 146 (0.00%)
occurrences (all)	1	0	0
Dermatitis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 149 (0.00%)	3 / 146 (2.05%)
occurrences (all)	1	0	3
Erythema multiforme			
subjects affected / exposed	1 / 12 (8.33%)	1 / 149 (0.67%)	2 / 146 (1.37%)
occurrences (all)	1	1	2
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 12 (8.33%)	0 / 149 (0.00%)	1 / 146 (0.68%)
occurrences (all)	1	0	1
Pigmentation disorder			
subjects affected / exposed	1 / 12 (8.33%)	0 / 149 (0.00%)	0 / 146 (0.00%)
occurrences (all)	1	0	0
Pruritus			
subjects affected / exposed	4 / 12 (33.33%)	14 / 149 (9.40%)	35 / 146 (23.97%)
occurrences (all)	4	14	35
Rash			
subjects affected / exposed	6 / 12 (50.00%)	21 / 149 (14.09%)	36 / 146 (24.66%)
occurrences (all)	6	21	36
Skin lesion			
subjects affected / exposed	1 / 12 (8.33%)	0 / 149 (0.00%)	1 / 146 (0.68%)
occurrences (all)	1	0	1
Rash maculo-papular			
subjects affected / exposed	0 / 12 (0.00%)	4 / 149 (2.68%)	10 / 146 (6.85%)
occurrences (all)	0	4	10
Rash papular			
subjects affected / exposed	1 / 12 (8.33%)	0 / 149 (0.00%)	1 / 146 (0.68%)
occurrences (all)	1	0	1
Urticaria			
subjects affected / exposed	1 / 12 (8.33%)	6 / 149 (4.03%)	3 / 146 (2.05%)
occurrences (all)	1	6	3
Renal and urinary disorders			
Pollakiuria			

subjects affected / exposed	1 / 12 (8.33%)	2 / 149 (1.34%)	0 / 146 (0.00%)
occurrences (all)	1	2	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 12 (8.33%)	6 / 149 (4.03%)	8 / 146 (5.48%)
occurrences (all)	1	6	8
Myalgia			
subjects affected / exposed	0 / 12 (0.00%)	10 / 149 (6.71%)	0 / 146 (0.00%)
occurrences (all)	0	10	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 149 (0.00%)	0 / 146 (0.00%)
occurrences (all)	1	0	0
Herpes zoster			
subjects affected / exposed	1 / 12 (8.33%)	0 / 149 (0.00%)	0 / 146 (0.00%)
occurrences (all)	1	0	0
Cystitis			
subjects affected / exposed	1 / 12 (8.33%)	1 / 149 (0.67%)	4 / 146 (2.74%)
occurrences (all)	1	1	4
Clostridium difficile infection			
subjects affected / exposed	1 / 12 (8.33%)	0 / 149 (0.00%)	0 / 146 (0.00%)
occurrences (all)	1	0	0
Systemic candida			
subjects affected / exposed	1 / 12 (8.33%)	0 / 149 (0.00%)	0 / 146 (0.00%)
occurrences (all)	1	0	0
Urinary tract infection			
subjects affected / exposed	0 / 12 (0.00%)	4 / 149 (2.68%)	9 / 146 (6.16%)
occurrences (all)	0	4	9
Pneumonia			
subjects affected / exposed	1 / 12 (8.33%)	1 / 149 (0.67%)	0 / 146 (0.00%)
occurrences (all)	1	1	0
Oral candidiasis			
subjects affected / exposed	1 / 12 (8.33%)	1 / 149 (0.67%)	0 / 146 (0.00%)
occurrences (all)	1	1	0
Metabolism and nutrition disorders			

Hypocalcaemia			
subjects affected / exposed	1 / 12 (8.33%)	4 / 149 (2.68%)	1 / 146 (0.68%)
occurrences (all)	1	4	1
Hypercalcaemia			
subjects affected / exposed	1 / 12 (8.33%)	4 / 149 (2.68%)	3 / 146 (2.05%)
occurrences (all)	1	4	3
Diabetes mellitus			
subjects affected / exposed	1 / 12 (8.33%)	1 / 149 (0.67%)	0 / 146 (0.00%)
occurrences (all)	1	1	0
Decreased appetite			
subjects affected / exposed	3 / 12 (25.00%)	36 / 149 (24.16%)	30 / 146 (20.55%)
occurrences (all)	3	36	30
Hypokalaemia			
subjects affected / exposed	1 / 12 (8.33%)	10 / 149 (6.71%)	7 / 146 (4.79%)
occurrences (all)	1	10	7
Hypophosphataemia			
subjects affected / exposed	1 / 12 (8.33%)	3 / 149 (2.01%)	1 / 146 (0.68%)
occurrences (all)	1	3	1
Hyponatraemia			
subjects affected / exposed	0 / 12 (0.00%)	8 / 149 (5.37%)	10 / 146 (6.85%)
occurrences (all)	0	8	10
Hypomagnesaemia			
subjects affected / exposed	0 / 12 (0.00%)	13 / 149 (8.72%)	8 / 146 (5.48%)
occurrences (all)	0	13	8

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 October 2019	• To describe a single primary endpoint (overall survival) in the randomized, double-blind part of the study rather than dual primary endpoints. • To remove the requirement for initial progressive disease as determined by the Investigator to be verified by an Independent Review Committee (IRC). • The analysis of progression-free survival (PFS) and other tumor-based efficacy endpoints was based on Investigator assessment; analysis based on IRC assessment was only performed if the study is not expanded to Phase III. • To acknowledge that, for the purposes of marketing authorization in Japan, if the study was not expanded into Phase III, it will not be acceptable as a confirmatory study. • To provide additional information on the power to detect differences in efficacy among the different biliary tract cancer anatomical subgroups. • To exclude subjects with history of bleeding diathesis and provide further guidance on dose modifications for bleeding events according to National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) severity grade and site of bleeding. • To include additional patient-reported outcome measures to enable subjects experience of the study intervention to be further characterized. • To allow chemotherapy to be given on Day 15 of a given cycle if administration on Day 1 or Day 8 was not possible.
27 July 2020	• Updated maximal number of subjects for Phase II. • Updated text to clarify that initial 150 subjects recruited in Phase II were analyzed for an expansion decision into Phase III. • Updated a minimum follow-up period at least 19 weeks for the first 150 subjects randomized were included. • Updated assumptions of sample size calculation (i.e., number of subjects and time periods). • Added the information about the Independent Data Monitoring Committee (IDMC) and Independent Review Committee (IRC) responsibility for Phase II and Phase III study. • Added clarification that Independent Review Committee (IRC) used in Phase II only. • Updated exclusion criteria 2, 5 and 16. • Clarified administration of chemotherapy and dose modification for neutropenia and thrombocytopenia in the case of gemcitabine and/or cisplatin-related adverse drug reactions. • Clarified the magnetic resonance imaging (MRI) areas. • Removed the information for central imaging read and interpretation for all scans. • Added Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1). • Clarified that radiological images collected from the remaining 350 subjects must be submitted.

20 April 2021	• An additional criterion has been added to the definition of the efficacy analysis set was used for the analysis for decision on the expansion to Phase III sample size. • Futility criterion was introduced for expansion decision and Overall Survival (OS) analysis. • A description was added to provide clarity on the type of study population to be analyzed for efficacy and safety analysis for expansion into Phase III. This clarification would also help IDMC's assessment of efficacy and safety data and to provide their recommendation for expansion into the Phase III. • A note has been added to guide in checking enrollment of the study population. • Further information was added to explain the rationale for selecting antibiotics-naïve subjects for expansion decision. • Edits are done to highlight dose modification of the study intervention in a specific condition. • Inclusion criterion number 2 has been updated. • Exclusion criterion number 5 and 13 has been updated. • Details were added on study treatment administration. Edits were done in this section to indicate dose modification of M7824/placebo to 1200 mg was allowed in the study.
14 July 2021	• Text was revised to include a summary of the additional criterion for expansion into Phase III. • Exclusion criterion 10 was split into 2 separate bullets without change in content. • Text related to local requirements for dosing of gemcitabine and cisplatin was revised. Links to Sections 6.6.3 and 6.6.4 referring to dose modification instructions for gemcitabine and cisplatin were added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Data collection and analysis of Pharmacokinetics and Immunogenicity were omitted and not conducted due to business reason.

Notes: