



Clinical trial results:

RESILIENT: A Randomized, Open Label Phase 3 Study of Irinotecan Liposome Injection (ONIVYDE®) versus Topotecan in Patients with Small Cell Lung Cancer Who Have Progressed on or After Platinum-based First-Line Therapy

Summary

EudraCT number	2017-004261-26
Trial protocol	DE FR ES HU BE IT RO
Global end of trial date	27 July 2023

Results information

Result version number	v1 (current)
This version publication date	06 July 2024
First version publication date	06 July 2024

Trial information

Trial identification

Sponsor protocol code	MM-398-01-03-04
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03088813
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ipsen Bioscience Inc.
Sponsor organisation address	One Main Street, Cambridge, Massachusetts, United States, 02142
Public contact	Medical Director, Ipsen Bioscience, Inc, clinical.trials@ipsen.com
Scientific contact	Medical Director, Ipsen Bioscience, Inc, clinical.trials@ipsen.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	14 September 2023
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	27 July 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Part 1:

- To describe the safety and tolerability of irinotecan liposome injection monotherapy administered every 2 weeks
- To determine the irinotecan liposome injection monotherapy dose (85 milligrams/meter square [mg/m²] or 70 mg/m² administered every 2 weeks) for Part 2 of this study.

Part 2:

- To compare overall survival (OS) following treatment with irinotecan liposome injection with OS following treatment with intravenous (i.v.) topotecan.

Protection of trial subjects:

The study was conducted under the provisions of the Declaration of Helsinki, in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice and in compliance with independent ethics committee or institutional review board, and informed consent regulations. This study adhered to the United States of America Food and Drug Administration regulations and all applicable local regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 April 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 7
Country: Number of subjects enrolled	Belgium: 10
Country: Number of subjects enrolled	Brazil: 14
Country: Number of subjects enrolled	China: 34
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	Germany: 8
Country: Number of subjects enrolled	Hungary: 20
Country: Number of subjects enrolled	Italy: 3
Country: Number of subjects enrolled	Korea, Republic of: 22
Country: Number of subjects enrolled	Poland: 16
Country: Number of subjects enrolled	Romania: 21
Country: Number of subjects enrolled	Russian Federation: 62
Country: Number of subjects enrolled	Serbia: 39
Country: Number of subjects enrolled	Spain: 82

Country: Number of subjects enrolled	Taiwan: 17
Country: Number of subjects enrolled	Türkiye: 20
Country: Number of subjects enrolled	Ukraine: 47
Country: Number of subjects enrolled	United States: 62
Worldwide total number of subjects	491
EEA total number of subjects	167

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)	301
From 65 to 84 years	190
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This Phase III, 2-part (Part 1: Dose Evaluation [open-label, single-arm dose evaluation period] and Part 2: Randomized Study [randomized, open-label period]) study was conducted in participants with small cell lung cancer (SCLC) who progressed on or after platinum-based first-line therapy.

Pre-assignment

Screening details:

Each part consisted of screening stage (up to 28 days), treatment/active follow-up stage, and a long-term monthly follow-up stage. A total of 30 participants in Part 1 received study treatment and 461 participants in Part 2 were randomized to receive study treatment in this study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Part 1: Irinotecan Liposome Injection 85 mg/m ²

Arm description:

Participants received irinotecan liposome injection 85 mg/m² i.v. over 90 minutes every 2 weeks in a 6-week cycle until disease progression (PD), death, unacceptable study treatment-related toxicity or withdrawal of consent.

Arm type	Experimental
Investigational medicinal product name	Irinotecan liposome
Investigational medicinal product code	
Other name	ONIVYDE
Pharmaceutical forms	Concentrate for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Irinotecan liposome injection was administered at a dose of 85 mg/m² i.v. over 90 minutes, every 2 weeks in a 6-week cycle until protocol-defined discontinuation criteria was met.

Arm title	Part 1: Irinotecan Liposome Injection 70 mg/m ²
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Arm description:

Participants received irinotecan liposome injection 70 mg/m² i.v. over 90 minutes every 2 weeks in a 6-week cycle until PD, death, unacceptable study treatment-related toxicity or withdrawal of consent.

Arm type	Experimental
Investigational medicinal product name	Irinotecan liposome
Investigational medicinal product code	
Other name	ONIVYDE
Pharmaceutical forms	Concentrate for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Irinotecan liposome injection was administered at a dose of 70 mg/m² i.v. over 90 minutes, every 2 weeks in a 6-week cycle until protocol-defined discontinuation criteria was met.

Arm title	Part 2: Irinotecan Liposome Injection 70 mg/m ²
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Arm description:

Eligible participants received irinotecan liposome injection 70 mg/m² i.v. over 90 minutes, every 2 weeks in a 6-week cycle until PD, death, unacceptable study treatment-related toxicity or withdrawal of consent.

Arm type	Experimental
Investigational medicinal product name	Irinotecan liposome
Investigational medicinal product code	
Other name	ONIVYDE
Pharmaceutical forms	Concentrate for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Irinotecan liposome injection was administered at a dose of 70 mg/m² i.v. over 90 minutes, every 2 weeks in a 6-week cycle until protocol-defined discontinuation criteria was met.

Arm title	Part 2: Topotecan 1.5 mg/m ²
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Arm description:

Eligible participants received topotecan 1.5 mg/m² i.v. over 30 minutes daily for 5 consecutive days, every 3 weeks in a 6-week cycle until PD, death, unacceptable study treatment-related toxicity or withdrawal of consent.

Arm type	Active comparator
Investigational medicinal product name	Topotecan
Investigational medicinal product code	
Other name	HYCAMTIN
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Topotecan was administered at an initial dose of 1.5 mg/m² i.v. over 30 minutes daily for 5 consecutive days, every 3 weeks in a 6-week cycle until protocol-defined discontinuation criteria was met.

Number of subjects in period 1	Part 1: Irinotecan Liposome Injection 85 mg/m ²	Part 1: Irinotecan Liposome Injection 70 mg/m ²	Part 2: Irinotecan Liposome Injection 70 mg/m ²
Started	5	25	229
Completed	5	24	202
Not completed	0	1	27
Consent withdrawn by subject	-	1	18
Investigator decision	-	-	2
Screen failure	-	-	-
Unspecified	-	-	3
Lost to follow-up	-	-	3
Protocol deviation	-	-	1

Number of subjects in period 1	Part 2: Topotecan 1.5 mg/m ²
Started	232
Completed	211
Not completed	21
Consent withdrawn by subject	14
Investigator decision	2
Screen failure	1
Unspecified	-

Lost to follow-up	4
Protocol deviation	-

Baseline characteristics

Reporting groups

Reporting group title	Part 1: Irinotecan Liposome Injection 85 mg/m ²
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Reporting group description:

Participants received irinotecan liposome injection 85 mg/m² i.v. over 90 minutes every 2 weeks in a 6-week cycle until disease progression (PD), death, unacceptable study treatment-related toxicity or withdrawal of consent.

Reporting group title	Part 1: Irinotecan Liposome Injection 70 mg/m ²
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Reporting group description:

Participants received irinotecan liposome injection 70 mg/m² i.v. over 90 minutes every 2 weeks in a 6-week cycle until PD, death, unacceptable study treatment-related toxicity or withdrawal of consent.

Reporting group title	Part 2: Irinotecan Liposome Injection 70 mg/m ²
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Reporting group description:

Eligible participants received irinotecan liposome injection 70 mg/m² i.v. over 90 minutes, every 2 weeks in a 6-week cycle until PD, death, unacceptable study treatment-related toxicity or withdrawal of consent.

Reporting group title	Part 2: Topotecan 1.5 mg/m ²
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Reporting group description:

Eligible participants received topotecan 1.5 mg/m² i.v. over 30 minutes daily for 5 consecutive days, every 3 weeks in a 6-week cycle until PD, death, unacceptable study treatment-related toxicity or withdrawal of consent.

Reporting group values	Part 1: Irinotecan Liposome Injection 85 mg/m ²	Part 1: Irinotecan Liposome Injection 70 mg/m ²	Part 2: Irinotecan Liposome Injection 70 mg/m ²
Number of subjects	5	25	229
Age categorical Units: Subjects			

Age continuous Units: years			
arithmetic mean	63.4	59.8	62.9
standard deviation	± 5.03	± 7.22	± 8.13
Gender categorical Units: Subjects			
Female	2	16	79
Male	3	9	150
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	37
Black or African American	0	0	4
White	5	25	184
Not Reported	0	0	4
Ethnicity Units: Subjects			
Hispanic or Latino	0	2	6
Not Hispanic or Latino	5	20	214
Not Reported/ Unknown	0	3	9

Reporting group values	Part 2: Topotecan 1.5 mg/m ²	Total	
Number of subjects	232	491	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	61.7 ± 7.46	-	
Gender categorical Units: Subjects			
Female	69	166	
Male	163	325	
Race Units: Subjects			
American Indian or Alaska Native	1	1	
Asian	36	73	
Black or African American	4	8	
White	182	396	
Not Reported	9	13	
Ethnicity Units: Subjects			
Hispanic or Latino	9	17	
Not Hispanic or Latino	218	457	
Not Reported/ Unknown	5	17	

End points

End points reporting groups

Reporting group title	Part 1: Irinotecan Liposome Injection 85 mg/m ²
Reporting group description: Participants received irinotecan liposome injection 85 mg/m ² i.v. over 90 minutes every 2 weeks in a 6-week cycle until disease progression (PD), death, unacceptable study treatment-related toxicity or withdrawal of consent.	
Reporting group title	Part 1: Irinotecan Liposome Injection 70 mg/m ²
Reporting group description: Participants received irinotecan liposome injection 70 mg/m ² i.v. over 90 minutes every 2 weeks in a 6-week cycle until PD, death, unacceptable study treatment-related toxicity or withdrawal of consent.	
Reporting group title	Part 2: Irinotecan Liposome Injection 70 mg/m ²
Reporting group description: Eligible participants received irinotecan liposome injection 70 mg/m ² i.v. over 90 minutes, every 2 weeks in a 6-week cycle until PD, death, unacceptable study treatment-related toxicity or withdrawal of consent.	
Reporting group title	Part 2: Topotecan 1.5 mg/m ²
Reporting group description: Eligible participants received topotecan 1.5 mg/m ² i.v. over 30 minutes daily for 5 consecutive days, every 3 weeks in a 6-week cycle until PD, death, unacceptable study treatment-related toxicity or withdrawal of consent.	

Primary: Part 1: Number of Participants With Treatment-Emergent Adverse Events (TEAEs) and Treatment-Emergent Serious Adverse Events (SAEs)

End point title	Part 1: Number of Participants With Treatment-Emergent Adverse Events (TEAEs) and Treatment-Emergent Serious Adverse Events (SAEs) ^{[1][2]}
End point description: An adverse event (AE) was any untoward medical occurrence in a participant following or during exposure to a study treatment, whether or not causally related to the study treatment. An undesirable medical condition could be symptoms, signs or abnormal results of an investigation. An SAE was any AE that: resulted in death; was life-threatening; required hospitalization or prolongation of existing hospitalization; resulted in persistent or significant disability or incapacity; resulted in congenital anomaly or birth defect; or was medically important. A TEAE was any AE that occurred or worsened on or after the day of first dose of study treatment and within 30 days after discontinuation of study treatment. Part 1: Safety population included all enrolled participants who were treated with at least 1 dose of irinotecan liposome injection.	
End point type	Primary
End point timeframe: The TEAEs were reported from the time of first study treatment administration (Day 1) up to 30 days after the date of last study treatment administration, approximately 680 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: As the endpoint is descriptive in nature, no statistical analysis is presented. [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: Only participants in Part 1 were analyzed for this endpoint.	

End point values	Part 1: Irinotecan Liposome Injection 85 mg/m ²	Part 1: Irinotecan Liposome Injection 70 mg/m ²		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	25		
Units: participants				
Any TEAE	5	25		
Serious TEAEs	4	9		

Statistical analyses

No statistical analyses for this end point

Primary: Part 1: Number of Participants With Dose-Limiting Toxicities (DLT)

End point title	Part 1: Number of Participants With Dose-Limiting Toxicities (DLT) ^{[3][4]}
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End point description:

A TEAE was considered as DLT if it occurred during the safety evaluation period (i.e. first 28 days of treatment or 14 days after the second dose of study treatment if there was a treatment delay due to non-DLT related reasons) and were deemed related to the study treatment by the investigator. The determination of whether an AE was considered a Dose Limiting Toxicity was made by the Safety Review Committee (SRC) comprising the Part 1 Investigators and the Medical Monitor(s) of the Sponsor. Part 1: Safety population included all enrolled participants who were treated with at least 1 dose of irinotecan liposome injection.

End point type	Primary
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End point timeframe:

From the start of the first study treatment administration (Day 1) up to 14 days after the second dose of study treatment administration, a maximum of 42 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: As the endpoint is descriptive in nature, no statistical analysis is presented.

[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: Only participants in Part 1 were analyzed for this endpoint.

End point values	Part 1: Irinotecan Liposome Injection 85 mg/m ²	Part 1: Irinotecan Liposome Injection 70 mg/m ²		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	25		
Units: participants	4	2		

Statistical analyses

No statistical analyses for this end point

Primary: Part 2: Overall Survival (OS)

End point title	Part 2: Overall Survival (OS) ^[5]
End point description: The OS was defined as the time from randomization date to the date of death from any cause. In the absence of confirmation of death, survival time was censored at the last date the participant was known to be alive. The OS was calculated using Kaplan-Meier technique. Following end of treatment participant and/or family was contacted by telephone every month to assess vital status. Part 2: The ITT population included all randomized participants.	
End point type	Primary
End point timeframe: From date of randomization (within 7 days before start of study treatment) until death. Assessed up to Part 2 primary analysis data cut-off (DCO) date of 08 February 2022 (approximately 900 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: Only participants in Part 2 were analyzed for this endpoint.	

End point values	Part 2: Irinotecan Liposome Injection 70 mg/m ²	Part 2: Topotecan 1.5 mg/m ²		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	229	232		
Units: months				
median (confidence interval 95%)	7.92 (6.87 to 9.23)	8.31 (7.33 to 9.13)		

Statistical analyses

Statistical analysis title	Statistical analysis for OS
Comparison groups	Part 2: Irinotecan Liposome Injection 70 mg/m ² v Part 2: Topotecan 1.5 mg/m ²
Number of subjects included in analysis	461
Analysis specification	Pre-specified
Analysis type	other ^[6]
P-value	= 0.3094 ^[7]
Method	Stratified log-rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	1.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	1.37

Notes:

[6] - The associated HR and two-sided 95% Confidence Interval (CI) were estimated using stratified Cox proportional hazards model, stratified by corrected region and corrected platinum sensitivity.

[7] - From stratified log-rank test, stratified by corrected region and corrected platinum sensitivity.

Secondary: Part 1: Objective Response Rate (ORR)

End point title	Part 1: Objective Response Rate (ORR) ^[8]
End point description: The ORR was defined as the percentage of participants with a best overall response (BOR) characterized as either a complete response (CR) or partial response (PR) recorded from date of first dose of study	

treatment until documented PD or death. ORR analysis was based on BOR using RECIST v1.1 per investigator assessment. Per RECIST v1.1, CR is disappearance of all target lesions; PR is $\geq 30\%$ decrease in the sum of the longest diameter of target lesions; and overall response = CR + PR. Per protocol, participants had computed tomography (CT)-scans and brain magnetic resonance imaging (MRI) every 6 weeks to measure tumor lesion size. This was continued throughout treatment until progressive disease (PD) or commencement of new anti-neoplastic therapy. Part 1: Safety population included all enrolled participants who were treated with at least 1 dose of irinotecan liposome injection.

End point type	Secondary
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End point timeframe:

RECIST assessments performed at Baseline (within 28 days before start of study treatment), every 6 weeks post first dose and treatment pause, 30 days after discontinuation of study treatment, then every month thereafter, approximately maximum of 1177 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: Only participants in Part 1 were analyzed for this endpoint.

End point values	Part 1: Irinotecan Liposome Injection 85 mg/m ²	Part 1: Irinotecan Liposome Injection 70 mg/m ²		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	25		
Units: percentage of participants				
number (confidence interval 95%)	40 (5.27 to 85.34)	44 (24.40 to 65.07)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1: Progression-Free Survival (PFS)

End point title	Part 1: Progression-Free Survival (PFS) ^[9]
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End point description:

The PFS was defined as time from first dose of study treatment to the first documented objective PD using RECIST v1.1 or death due to any cause, whichever occurs first. Per RECIST 1.1, progression is defined as at least 20% increase in the sum of the longest diameter of target lesions, or a measurable increase in a non-target lesion, or the appearance of new lesions. The PFS was calculated using Kaplan-Meier technique. Per protocol, participants had CT-scans and brain MRI every 6 weeks to measure tumor lesion size. This was continued throughout treatment until PD or commencement of new anti-neoplastic therapy. Part 1: Safety population included all enrolled participants who were treated with at least 1 dose of irinotecan liposome injection. 99999=Upper limit of CI was not estimable due to insufficient number of participants with events at study closure.

End point type	Secondary
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End point timeframe:

RECIST assessments performed at Baseline (within 28 days before start of study treatment), every 6 weeks post first dose and treatment pause, 30 days after discontinuation of study treatment, then every month thereafter, approximately maximum of 1177 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: Only participants in Part 1 were analyzed for this endpoint.

End point values	Part 1: Irinotecan Liposome Injection 85 mg/m ²	Part 1: Irinotecan Liposome Injection 70 mg/m ²		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	25		
Units: months				
median (confidence interval 95%)	4.19 (1.58 to 99999)	3.98 (2.69 to 4.24)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1: OS

End point title	Part 1: OS ^[10]
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End point description:

The OS was defined as the time from first dose of study treatment to the date of death from any cause. In the absence of confirmation of death, survival time was censored at the last date the participant was known to be alive. The OS was calculated using Kaplan-Meier technique. Following end of treatment participant and/or family was contacted by telephone every month to assess vital status. Part 1: Safety population included all enrolled participants who were treated with at least 1 dose of irinotecan liposome injection. 99999=Upper limit of CI was not estimable due to insufficient number of participants with events at study closure.

End point type	Secondary
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End point timeframe:

From Baseline (Day 1) until death. Assessed up to Part 1 DCO date of 11 August 2021 (approximately 1177 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: Only participants in Part 1 were analyzed for this endpoint.

End point values	Part 1: Irinotecan Liposome Injection 85 mg/m ²	Part 1: Irinotecan Liposome Injection 70 mg/m ²		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	25		
Units: months				
median (confidence interval 95%)	10.84 (0.99 to 99999)	8.08 (5.16 to 9.82)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: PFS

End point title	Part 2: PFS ^[11]
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End point description:

The PFS was defined as time from randomization to first documented objective PD using RECIST 1.1 (or response assessment in neuro-oncology brain metastases [RANO-BM] criteria for central nervous system [CNS] lesions) as assessed by blinded independent central review (BICR) or death due to any cause, whichever occurred first. Per RECIST 1.1, progression is defined as a 20% increase in the sum of the longest diameter of target lesions, or a measurable increase in a non-target lesion, or the appearance of new lesions. The PFS was calculated using Kaplan-Meier technique. Per protocol, participants had CT-scans and brain MRI every 6 weeks to measure tumor lesion size. This was continued throughout treatment until PD or commencement of new anti-neoplastic therapy. Part 2: The ITT population included all randomized participants.

End point type	Secondary
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End point timeframe:

RECIST assessments performed at Baseline (within 28 days before start of study treatment), every 6 weeks post first dose and treatment pause, 30 days after discontinuation of study treatment, then every month thereafter, approximately maximum of 900 days

Notes:

[11] - 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: Only participants in Part 2 were analyzed for this endpoint.

End point values	Part 2: Irinotecan Liposome Injection 70 mg/m ²	Part 2: Topotecan 1.5 mg/m ²		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	229	232		
Units: months				
median (confidence interval 95%)	4.01 (2.96 to 4.17)	3.25 (2.79 to 4.14)		

Statistical analyses

Statistical analysis title	Statistical analysis for Part 2: PFS
Comparison groups	Part 2: Irinotecan Liposome Injection 70 mg/m ² v Part 2: Topotecan 1.5 mg/m ²
Number of subjects included in analysis	461
Analysis specification	Pre-specified
Analysis type	other ^[12]
P-value	= 0.7053 ^[13]
Method	Stratified log-rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	1.2

Notes:

[12] - The associated HR and two-sided 95% CI were estimated using stratified Cox proportional hazards model, stratified by corrected region and corrected platinum sensitivity.

Secondary: Part 2: ORR

End point title	Part 2: ORR ^[14]
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End point description:

The ORR was defined as percentage of participants with a BOR characterized as either a CR or PR, recorded from randomization until documented PD or death relative to the total number of participants. ORR analysis was based on BOR assessed by BICR using Response evaluation criteria in solid tumors (RECIST) v1.1. Per RECIST v1.1, CR is disappearance of all target lesions; PR is $\geq 30\%$ decrease in the sum of the longest diameter of target lesions; and overall response = CR + PR. Per protocol, participants had CT-scans and brain MRI every 6 weeks to measure tumor lesion size. This was continued throughout treatment until PD or commencement of new anti-neoplastic therapy. Part 2: The ITT population included all randomized participants.

End point type	Secondary
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End point timeframe:

RECIST assessments performed at Baseline (within 28 days before start of study treatment), every 6 weeks post first dose and treatment pause, 30 days after discontinuation of study treatment, then every month thereafter, approximately maximum of 900 days

Notes:

[14] - 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: Only participants in Part 2 were analyzed for this endpoint.

End point values	Part 2: Irinotecan Liposome Injection 70 mg/m ²	Part 2: Topotecan 1.5 mg/m ²		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	229	232		
Units: percentage of participants				
number (confidence interval 95%)	44.1 (37.57 to 50.79)	21.6 (16.44 to 27.41)		

Statistical analyses

Statistical analysis title	Statistical analysis for Part 2: ORR
Comparison groups	Part 2: Irinotecan Liposome Injection 70 mg/m ² v Part 2: Topotecan 1.5 mg/m ²
Number of subjects included in analysis	461
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001 ^[15]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in ORR
Point estimate	22.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	13.97
upper limit	30.61

Notes:

[15] - ORR difference, 95% CI and P-value are obtained from the Cochran-Mantel-Haenszel test stratified by corrected region and corrected platinum sensitivity.

Secondary: Part 2: Median Duration of Response (DoR)

End point title	Part 2: Median Duration of Response (DoR) ^[16]
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End point description:

The DoR was defined as time from the first documented objective response (CR or PR, whichever was earlier) to the date of first documented PD or death due to any cause. The DoR analysis was based on BOR assessed by BICR using RECIST v1.1. Per RECIST v1.1, CR is disappearance of all target lesions and PR is $\geq 30\%$ decrease in the sum of the longest diameter of target lesions. The DoR was calculated using Kaplan-Meier technique. Per protocol, participants had CT-scans and brain MRI every 6 weeks to measure tumor lesion size. This was continued throughout treatment until PD or commencement of new anti-neoplastic therapy. Part 2: The ITT population included all randomized participants. Only participants with objective response were analyzed.

End point type	Secondary
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End point timeframe:

RECIST assessments performed at Baseline (within 28 days before start of study treatment), every 6 weeks post first dose and treatment pause, 30 days after discontinuation of study treatment, then every month thereafter, approximately maximum of 900 days

Notes:

[16] - 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: Only participants in Part 2 were analyzed for this endpoint.

End point values	Part 2: Irinotecan Liposome Injection 70 mg/m ²	Part 2: Topotecan 1.5 mg/m ²		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	101	50		
Units: months				
median (confidence interval 95%)	4.14 (3.06 to 4.34)	4.17 (2.86 to 4.76)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Median Time to Objective Response (OR)

End point title	Part 2: Median Time to Objective Response (OR) ^[17]
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End point description:

Time to OR as per RECIST v1.1 Criteria according to BICR was defined as time from the date of randomization to the date of first documented objective tumor response (CR or PR, whichever was first). Per RECIST v1.1, CR is disappearance of all target lesions; PR is $\geq 30\%$ decrease in the sum of the longest diameter of target lesion. Participants with a new anti-cancer therapy prior to OR were censored at the last tumor assessment prior to new anti-cancer therapy. Per protocol, participants had CT-scans and brain MRI every 6 weeks to measure tumor lesion size. This was continued throughout treatment until PD or commencement of new anti-neoplastic therapy. Part 2: The ITT population included all randomized participants. Only participants with objective response were analyzed. 99999=Upper limit of CI was not estimable due to insufficient number of participants with events at study closure.

End point type	Secondary
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End point timeframe:

RECIST assessments performed at Baseline (within 28 days before start of study treatment), every 6 weeks post first dose and treatment pause, 30 days after discontinuation of study treatment, then every month thereafter, approximately maximum of 900 days

Notes:

[17] - 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: Only participants in Part 2 were analyzed for this endpoint.

End point values	Part 2: Irinotecan Liposome Injection 70 mg/m ²	Part 2: Topotecan 1.5 mg/m ²		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	101	50		
Units: months				
median (confidence interval 95%)	1.68 (1.51 to 4.11)	12.65 (8.41 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Change From Baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 (EORTC QLQ-C30)/Lung Cancer Supplement (LC13) Dyspnea Scale at Week 12

End point title	Part 2: Change From Baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 (EORTC QLQ-C30)/Lung Cancer Supplement (LC13) Dyspnea Scale at Week 12 ^[18]
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End point description:

The EORTC QLQ-LC13 is a lung cancer specific module used in conjunction with EORTC QLQ-C30 and covers typical symptoms of lung cancer (cough, pain, dyspnea, sore mouth, peripheral neuropathy, hair loss). Scores range from 0-100 and a high score represents a high level of symptomatology/problems/worse QoL. Baseline was defined as the last non-missing measurement taken prior to reference start date. Change from baseline in dyspnea scale was calculated regardless of premature study treatment discontinuation. Participants completed these questionnaires on an electronic tablet every 6 weeks during treatment and it was continued until PD or commencement of new anti-neoplastic therapy. Part 2: The ITT population included all randomized participants. Only participants analyzed at Week 12 are reported.

End point type	Secondary
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End point timeframe:

Baseline (Day 1) and Week 12

Notes:

[18] - 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: Only participants in Part 2 were analyzed for this endpoint.

End point values	Part 2: Irinotecan Liposome Injection 70 mg/m ²	Part 2: Topotecan 1.5 mg/m ²		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106	114		
Units: scores on a scale				
arithmetic mean (standard deviation)	4.6 (± 20.74)	1.9 (± 19.17)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Change From Baseline in EORTC QLQ-LC13 Cough Scale at Week 12

End point title	Part 2: Change From Baseline in EORTC QLQ-LC13 Cough Scale at Week 12 ^[19]
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End point description:

The EORTC QLQ-LC13 is a lung cancer specific module used in conjunction with EORTC QLQ-C30 and covers typical symptoms of lung cancer (cough, pain, dyspnea, sore mouth, peripheral neuropathy, hair loss). Score ranges from 0-100 scale and a high score represents a high level of symptomatology/problems/worse QoL. Baseline was defined as the last non-missing measurement taken prior to reference start date. Change from baseline in cough scale was calculated regardless of premature study treatment discontinuation. Participants completed these questionnaires on an electronic tablet every 6 weeks during treatment and it was continued until PD or commencement of new anti-neoplastic therapy. Part 2: The ITT population included all randomized participants. Only participants analyzed at Week 12 are reported.

End point type	Secondary
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End point timeframe:

Baseline (Day 1) and Week 12

Notes:

[19] - 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: Only participants in Part 2 were analyzed for this endpoint.

End point values	Part 2: Irinotecan Liposome Injection 70 mg/m ²	Part 2: Topotecan 1.5 mg/m ²		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106	114		
Units: scores on a scale				
arithmetic mean (standard deviation)	1.6 (± 25.77)	-1.2 (± 27.31)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

TEAEs: From the time of first study treatment administration (Day 1) up to 30 days after the date of last study treatment administration, approximately 680 days for Part 1 and 1452 days for Part 2. All-Cause Mortality: approximately 1919 days

Adverse event reporting additional description:

Part 1: Safety population: All enrolled participants treated with at least 1 dose of irinotecan liposome injection. Part 2: Safety population: All randomized participants treated with at least 1 dose of study treatment. AEs are coded using MedDRA version 26.0. During all study visits, participants were asked to report any AE since prior study visit.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	Part 1: Irinotecan Liposome Injection 85 mg/m ²
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Reporting group description:

Participants received irinotecan liposome injection 85 mg/m² i.v. over 90 minutes every 2 weeks in a 6-week cycle until disease progression (PD), death, unacceptable study treatment-related toxicity or withdrawal of consent.

Reporting group title	Part 1: Irinotecan Liposome Injection 70 mg/m ²
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Reporting group description:

Participants received irinotecan liposome injection 70 mg/m² i.v. over 90 minutes every 2 weeks in a 6-week cycle until PD, death, unacceptable study treatment-related toxicity or withdrawal of consent.

Reporting group title	Part 2: Irinotecan Liposome Injection 70 mg/m ²
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Reporting group description:

Eligible participants received irinotecan liposome injection 70 mg/m² i.v. over 90 minutes, every 2 weeks in a 6-week cycle until PD, death, unacceptable study treatment-related toxicity or withdrawal of consent.

Reporting group title	Part 2: Topotecan 1.5 mg/m ²
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Reporting group description:

Eligible participants received topotecan 1.5 mg/m² i.v. over 30 minutes daily for 5 consecutive days, every 3 weeks in a 6-week cycle until PD, death, unacceptable study treatment-related toxicity or withdrawal of consent.

Serious adverse events	Part 1: Irinotecan Liposome Injection 85 mg/m ²	Part 1: Irinotecan Liposome Injection 70 mg/m ²	Part 2: Irinotecan Liposome Injection 70 mg/m ²
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 5 (80.00%)	9 / 25 (36.00%)	106 / 226 (46.90%)
number of deaths (all causes)	5	23	201
number of deaths resulting from adverse events	1	2	19
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 25 (4.00%)	0 / 226 (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

Embolism arterial			
subjects affected / exposed	0 / 5 (0.00%)	1 / 25 (4.00%)	0 / 226 (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
Superior vena cava syndrome			
subjects affected / exposed	1 / 5 (20.00%)	0 / 25 (0.00%)	0 / 226 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic thrombosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	1 / 226 (0.44%)
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 / 5 (0.00%)	0 / 25 (0.00%)	0 / 226 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	1 / 226 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Subclavian vein thrombosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	1 / 226 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	1 / 226 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	1 / 226 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Death			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	1 / 226 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	2 / 226 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Pyrexia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	2 / 226 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Complication associated with device			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	1 / 226 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related thrombosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	1 / 226 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	1 / 226 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	1 / 226 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	1 / 226 (0.44%)
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 system disorders			

Anaphylactic reaction			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	0 / 226 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypersensitivity			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	1 / 226 (0.44%)
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			
Pulmonary embolism			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	7 / 226 (3.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Dyspnoea			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	2 / 226 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	0 / 226 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	1 / 226 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	1 / 226 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	1 / 226 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

Acute respiratory failure			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	0 / 226 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	1 / 226 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	0 / 226 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	0 / 226 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	1 / 226 (0.44%)
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			
Liver function test abnormal			
subjects affected / exposed	1 / 5 (20.00%)	0 / 25 (0.00%)	0 / 226 (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
Platelet count decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	1 / 226 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutrophil count decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	1 / 226 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Alanine aminotransferase increased subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	1 / 226 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatinine increased subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	0 / 226 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases increased subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	1 / 226 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
White blood cell count decreased subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	0 / 226 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Overdose			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	5 / 226 (2.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radiation pneumonitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	1 / 226 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Exposure to SARS-CoV-2			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	1 / 226 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procedural pneumothorax			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	1 / 226 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	1 / 5 (20.00%)	0 / 25 (0.00%)	0 / 226 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiac tamponade			
subjects affected / exposed	0 / 5 (0.00%)	1 / 25 (4.00%)	0 / 226 (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
Pericardial effusion			
subjects affected / exposed	0 / 5 (0.00%)	1 / 25 (4.00%)	0 / 226 (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
Acute myocardial infarction			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	1 / 226 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	1 / 226 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	1 / 226 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage intracranial			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	1 / 226 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	1 / 226 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cerebral ischaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	1 / 226 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	0 / 226 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myoclonus			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	1 / 226 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	0 / 226 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertebrobasilar stroke			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	0 / 226 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	2 / 226 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Febrile neutropenia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	5 / 226 (2.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	1 / 226 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Anaemia			

subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	2 / 226 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	1 / 226 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myelosuppression			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	0 / 226 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 5 (20.00%)	1 / 25 (4.00%)	19 / 226 (8.41%)
occurrences causally related to treatment / all	1 / 2	1 / 1	19 / 25
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Constipation			
subjects affected / exposed	0 / 5 (0.00%)	1 / 25 (4.00%)	0 / 226 (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
Nausea			
subjects affected / exposed	1 / 5 (20.00%)	0 / 25 (0.00%)	2 / 226 (0.88%)
occurrences causally related to treatment / all	1 / 1	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal stenosis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 25 (4.00%)	1 / 226 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 5 (20.00%)	0 / 25 (0.00%)	3 / 226 (1.33%)
occurrences causally related to treatment / all	1 / 2	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis			

subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	4 / 226 (1.77%)
occurrences causally related to treatment / all	0 / 0	0 / 0	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	3 / 226 (1.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	3 / 226 (1.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer perforation			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	0 / 226 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enteritis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	1 / 226 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	1 / 226 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Narcotic bowel syndrome			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	0 / 226 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	0 / 226 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			

subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	1 / 226 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	0 / 226 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatotoxicity			
subjects affected / exposed	1 / 5 (20.00%)	0 / 25 (0.00%)	0 / 226 (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
Liver disorder			
subjects affected / exposed	0 / 5 (0.00%)	1 / 25 (4.00%)	0 / 226 (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
Hepatitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	1 / 226 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Biliary obstruction			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	0 / 226 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperbilirubinaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	1 / 226 (0.44%)
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 and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	2 / 226 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis haemorrhagic			

subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	1 / 226 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	1 / 226 (0.44%)
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 impairment			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	1 / 226 (0.44%)
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			
Ectopic antidiuretic hormone secretion			
subjects affected / exposed	1 / 5 (20.00%)	0 / 25 (0.00%)	0 / 226 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	2 / 226 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neck pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	1 / 226 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	0 / 226 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myopathy			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	0 / 226 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pain in extremity			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	0 / 226 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pathological fracture			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	1 / 226 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	2 / 5 (40.00%)	2 / 25 (8.00%)	16 / 226 (7.08%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 18
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 6
Abdominal sepsis			
subjects affected / exposed	0 / 5 (0.00%)	2 / 25 (8.00%)	0 / 226 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	2 / 2	0 / 0
COVID-19			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	13 / 226 (5.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 16
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 5
Suspected COVID-19			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	6 / 226 (2.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	5 / 226 (2.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 2
Bronchitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	3 / 226 (1.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19 pneumonia			

subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	3 / 226 (1.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atypical pneumonia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	1 / 226 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Clostridium difficile infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	1 / 226 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	0 / 226 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infectious pleural effusion			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	0 / 226 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia viral			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	0 / 226 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	0 / 226 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 25 (0.00%)	1 / 226 (0.44%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Decreased appetite			

subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	3 / 226 (1.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	1 / 226 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	0 / 226 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	1 / 226 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Part 2: Topotecan 1.5 mg/m ²		
Total subjects affected by serious adverse events			
subjects affected / exposed	88 / 223 (39.46%)		
number of deaths (all causes)	205		
number of deaths resulting from adverse events	9		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 223 (0.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Embolism arterial			
subjects affected / exposed	0 / 223 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Superior vena cava syndrome			
subjects affected / exposed	1 / 223 (0.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Aortic thrombosis			
subjects affected / exposed	0 / 223 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Embolism			
subjects affected / exposed	1 / 223 (0.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemorrhage			
subjects affected / exposed	0 / 223 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Subclavian vein thrombosis			
subjects affected / exposed	0 / 223 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Thrombosis			
subjects affected / exposed	0 / 223 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 223 (0.90%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Death			
subjects affected / exposed	2 / 223 (0.90%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 223 (0.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		

Pyrexia			
subjects affected / exposed	1 / 223 (0.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Complication associated with device			
subjects affected / exposed	0 / 223 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Device related thrombosis			
subjects affected / exposed	0 / 223 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Fatigue			
subjects affected / exposed	0 / 223 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General physical health deterioration			
subjects affected / exposed	0 / 223 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pain			
subjects affected / exposed	0 / 223 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 223 (0.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypersensitivity			
subjects affected / exposed	0 / 223 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal			

disorders				
Pulmonary embolism				
subjects affected / exposed	3 / 223 (1.35%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	0 / 223 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemoptysis				
subjects affected / exposed	2 / 223 (0.90%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Pneumonitis				
subjects affected / exposed	1 / 223 (0.45%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	1 / 223 (0.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Acute respiratory distress syndrome				
subjects affected / exposed	0 / 223 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Acute respiratory failure				
subjects affected / exposed	1 / 223 (0.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	0 / 223 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumothorax				

subjects affected / exposed	1 / 223 (0.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 223 (0.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Depression			
subjects affected / exposed	0 / 223 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Investigations			
Liver function test abnormal			
subjects affected / exposed	0 / 223 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Platelet count decreased			
subjects affected / exposed	8 / 223 (3.59%)		
occurrences causally related to treatment / all	8 / 16		
deaths causally related to treatment / all	0 / 0		
Neutrophil count decreased			
subjects affected / exposed	2 / 223 (0.90%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Alanine aminotransferase increased			
subjects affected / exposed	0 / 223 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood creatinine increased			
subjects affected / exposed	1 / 223 (0.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Transaminases increased			

subjects affected / exposed	0 / 223 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
White blood cell count decreased			
subjects affected / exposed	1 / 223 (0.45%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Overdose			
subjects affected / exposed	0 / 223 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Radiation pneumonitis			
subjects affected / exposed	1 / 223 (0.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Exposure to SARS-CoV-2			
subjects affected / exposed	0 / 223 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Procedural pneumothorax			
subjects affected / exposed	0 / 223 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	0 / 223 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac tamponade			
subjects affected / exposed	0 / 223 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Pericardial effusion				
subjects affected / exposed	0 / 223 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Acute myocardial infarction				
subjects affected / exposed	0 / 223 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Coronary artery disease				
subjects affected / exposed	0 / 223 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Cerebral infarction				
subjects affected / exposed	1 / 223 (0.45%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Haemorrhage intracranial				
subjects affected / exposed	1 / 223 (0.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Seizure				
subjects affected / exposed	1 / 223 (0.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebral ischaemia				
subjects affected / exposed	0 / 223 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ischaemic stroke				
subjects affected / exposed	1 / 223 (0.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Myoclonus				

subjects affected / exposed	0 / 223 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	1 / 223 (0.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vertebrobasilar stroke			
subjects affected / exposed	1 / 223 (0.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	19 / 223 (8.52%)		
occurrences causally related to treatment / all	19 / 24		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	13 / 223 (5.83%)		
occurrences causally related to treatment / all	13 / 13		
deaths causally related to treatment / all	1 / 1		
Thrombocytopenia			
subjects affected / exposed	13 / 223 (5.83%)		
occurrences causally related to treatment / all	13 / 21		
deaths causally related to treatment / all	0 / 0		
Anaemia			
subjects affected / exposed	9 / 223 (4.04%)		
occurrences causally related to treatment / all	9 / 10		
deaths causally related to treatment / all	0 / 0		
Leukopenia			
subjects affected / exposed	6 / 223 (2.69%)		
occurrences causally related to treatment / all	5 / 7		
deaths causally related to treatment / all	0 / 0		
Myelosuppression			

subjects affected / exposed	2 / 223 (0.90%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 223 (0.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	0 / 223 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	3 / 223 (1.35%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Oesophageal stenosis			
subjects affected / exposed	0 / 223 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	3 / 223 (1.35%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Enterocolitis			
subjects affected / exposed	0 / 223 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	0 / 223 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Colitis			

subjects affected / exposed	0 / 223 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Duodenal ulcer perforation			
subjects affected / exposed	1 / 223 (0.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Enteritis			
subjects affected / exposed	0 / 223 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ileus			
subjects affected / exposed	0 / 223 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Narcotic bowel syndrome			
subjects affected / exposed	1 / 223 (0.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatitis acute			
subjects affected / exposed	1 / 223 (0.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Small intestinal obstruction			
subjects affected / exposed	0 / 223 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 223 (0.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatotoxicity			

subjects affected / exposed	0 / 223 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Liver disorder			
subjects affected / exposed	0 / 223 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatitis			
subjects affected / exposed	1 / 223 (0.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Biliary obstruction			
subjects affected / exposed	1 / 223 (0.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperbilirubinaemia			
subjects affected / exposed	0 / 223 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 223 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cystitis haemorrhagic			
subjects affected / exposed	0 / 223 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal failure			
subjects affected / exposed	0 / 223 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal impairment			

subjects affected / exposed	0 / 223 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Ectopic antidiuretic hormone secretion			
subjects affected / exposed	0 / 223 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 223 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neck pain			
subjects affected / exposed	1 / 223 (0.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bone pain			
subjects affected / exposed	1 / 223 (0.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myopathy			
subjects affected / exposed	1 / 223 (0.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pain in extremity			
subjects affected / exposed	1 / 223 (0.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pathological fracture			
subjects affected / exposed	0 / 223 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Infections and infestations Pneumonia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	7 / 223 (3.14%) 1 / 8 0 / 2		
Abdominal sepsis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 223 (0.00%) 0 / 0 0 / 0		
COVID-19 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	8 / 223 (3.59%) 0 / 9 0 / 1		
Suspected COVID-19 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	2 / 223 (0.90%) 0 / 2 0 / 0		
Sepsis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	2 / 223 (0.90%) 2 / 2 0 / 0		
Bronchitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 223 (0.00%) 0 / 0 0 / 0		
COVID-19 pneumonia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 223 (0.00%) 0 / 0 0 / 0		
Atypical pneumonia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 223 (0.00%) 0 / 0 0 / 0		
Clostridium difficile infection			

subjects affected / exposed	0 / 223 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Erysipelas			
subjects affected / exposed	1 / 223 (0.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infectious pleural effusion			
subjects affected / exposed	1 / 223 (0.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia viral			
subjects affected / exposed	1 / 223 (0.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory tract infection			
subjects affected / exposed	1 / 223 (0.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	5 / 223 (2.24%)		
occurrences causally related to treatment / all	0 / 11		
deaths causally related to treatment / all	0 / 0		
Decreased appetite			
subjects affected / exposed	0 / 223 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dehydration			
subjects affected / exposed	0 / 223 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyperglycaemia			

subjects affected / exposed	1 / 223 (0.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	0 / 223 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Part 1: Irinotecan Liposome Injection 85 mg/m ²	Part 1: Irinotecan Liposome Injection 70 mg/m ²	Part 2: Irinotecan Liposome Injection 70 mg/m ²
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 5 (100.00%)	25 / 25 (100.00%)	212 / 226 (93.81%)
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 5 (20.00%)	3 / 25 (12.00%)	10 / 226 (4.42%)
occurrences (all)	1	3	10
Deep vein thrombosis			
subjects affected / exposed	0 / 5 (0.00%)	2 / 25 (8.00%)	0 / 226 (0.00%)
occurrences (all)	0	2	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 5 (20.00%)	10 / 25 (40.00%)	60 / 226 (26.55%)
occurrences (all)	4	22	111
Fatigue			
subjects affected / exposed	1 / 5 (20.00%)	4 / 25 (16.00%)	48 / 226 (21.24%)
occurrences (all)	3	10	83
Oedema peripheral			
subjects affected / exposed	1 / 5 (20.00%)	2 / 25 (8.00%)	12 / 226 (5.31%)
occurrences (all)	1	4	15
Pain			
subjects affected / exposed	1 / 5 (20.00%)	0 / 25 (0.00%)	6 / 226 (2.65%)
occurrences (all)	1	0	7
Non-cardiac chest pain			

subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	3 / 25 (12.00%) 3	14 / 226 (6.19%) 19
Pyrexia subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	3 / 25 (12.00%) 4	10 / 226 (4.42%) 11
Respiratory, thoracic and mediastinal disorders			
Dyspnoea subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	4 / 25 (16.00%) 7	19 / 226 (8.41%) 24
Pneumonitis subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 25 (0.00%) 0	1 / 226 (0.44%) 1
Cough subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	3 / 25 (12.00%) 4	15 / 226 (6.64%) 18
Pulmonary embolism subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	2 / 25 (8.00%) 2	0 / 226 (0.00%) 0
Psychiatric disorders			
Anxiety subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	2 / 25 (8.00%) 2	2 / 226 (0.88%) 2
Insomnia subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 25 (4.00%) 1	11 / 226 (4.87%) 14
Investigations			
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 3	5 / 25 (20.00%) 8	35 / 226 (15.49%) 59
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	3 / 25 (12.00%) 5	27 / 226 (11.95%) 41
Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 2	3 / 25 (12.00%) 4	19 / 226 (8.41%) 29
Gamma-glutamyltransferase			

increased			
subjects affected / exposed	1 / 5 (20.00%)	4 / 25 (16.00%)	10 / 226 (4.42%)
occurrences (all)	2	7	17
Weight decreased			
subjects affected / exposed	1 / 5 (20.00%)	9 / 25 (36.00%)	65 / 226 (28.76%)
occurrences (all)	2	11	112
Platelet count decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	9 / 226 (3.98%)
occurrences (all)	0	0	34
Neutrophil count decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	21 / 226 (9.29%)
occurrences (all)	0	0	46
White blood cell count decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	22 / 226 (9.73%)
occurrences (all)	0	0	46
Blood creatinine increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	19 / 226 (8.41%)
occurrences (all)	0	0	30
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 25 (4.00%)	11 / 226 (4.87%)
occurrences (all)	0	1	16
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 5 (0.00%)	2 / 25 (8.00%)	2 / 226 (0.88%)
occurrences (all)	0	4	2
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 5 (20.00%)	2 / 25 (8.00%)	11 / 226 (4.87%)
occurrences (all)	1	2	13
Dizziness			
subjects affected / exposed	0 / 5 (0.00%)	4 / 25 (16.00%)	12 / 226 (5.31%)
occurrences (all)	0	4	14
Somnolence			
subjects affected / exposed	0 / 5 (0.00%)	2 / 25 (8.00%)	3 / 226 (1.33%)
occurrences (all)	0	2	3
Blood and lymphatic system disorders			

Neutropenia			
subjects affected / exposed	3 / 5 (60.00%)	4 / 25 (16.00%)	41 / 226 (18.14%)
occurrences (all)	3	7	124
Thrombocytopenia			
subjects affected / exposed	0 / 5 (0.00%)	4 / 25 (16.00%)	11 / 226 (4.87%)
occurrences (all)	0	11	20
Anaemia			
subjects affected / exposed	2 / 5 (40.00%)	7 / 25 (28.00%)	82 / 226 (36.28%)
occurrences (all)	7	11	193
Coagulopathy			
subjects affected / exposed	1 / 5 (20.00%)	0 / 25 (0.00%)	0 / 226 (0.00%)
occurrences (all)	1	0	0
Lymphopenia			
subjects affected / exposed	1 / 5 (20.00%)	1 / 25 (4.00%)	22 / 226 (9.73%)
occurrences (all)	3	5	54
Leukopenia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	29 / 226 (12.83%)
occurrences (all)	0	0	82
Eye disorders			
Visual impairment			
subjects affected / exposed	0 / 5 (0.00%)	2 / 25 (8.00%)	0 / 226 (0.00%)
occurrences (all)	0	2	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	5 / 5 (100.00%)	22 / 25 (88.00%)	128 / 226 (56.64%)
occurrences (all)	17	80	393
Nausea			
subjects affected / exposed	3 / 5 (60.00%)	11 / 25 (44.00%)	96 / 226 (42.48%)
occurrences (all)	5	17	170
Abdominal pain			
subjects affected / exposed	2 / 5 (40.00%)	5 / 25 (20.00%)	41 / 226 (18.14%)
occurrences (all)	2	5	56
Constipation			
subjects affected / exposed	2 / 5 (40.00%)	3 / 25 (12.00%)	29 / 226 (12.83%)
occurrences (all)	3	4	42
Abdominal distension			

subjects affected / exposed	1 / 5 (20.00%)	0 / 25 (0.00%)	7 / 226 (3.10%)
occurrences (all)	1	0	8
Flatulence			
subjects affected / exposed	1 / 5 (20.00%)	0 / 25 (0.00%)	4 / 226 (1.77%)
occurrences (all)	1	0	4
Stomatitis			
subjects affected / exposed	1 / 5 (20.00%)	2 / 25 (8.00%)	6 / 226 (2.65%)
occurrences (all)	1	4	7
Vomiting			
subjects affected / exposed	1 / 5 (20.00%)	9 / 25 (36.00%)	47 / 226 (20.80%)
occurrences (all)	5	16	83
Abdominal pain upper			
subjects affected / exposed	0 / 5 (0.00%)	5 / 25 (20.00%)	11 / 226 (4.87%)
occurrences (all)	0	5	12
Dysphagia			
subjects affected / exposed	0 / 5 (0.00%)	3 / 25 (12.00%)	5 / 226 (2.21%)
occurrences (all)	0	3	6
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 25 (0.00%)	16 / 226 (7.08%)
occurrences (all)	1	0	20
Erythema			
subjects affected / exposed	1 / 5 (20.00%)	1 / 25 (4.00%)	0 / 226 (0.00%)
occurrences (all)	1	1	0
Hyperhidrosis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 25 (0.00%)	3 / 226 (1.33%)
occurrences (all)	1	0	9
Rash			
subjects affected / exposed	1 / 5 (20.00%)	0 / 25 (0.00%)	5 / 226 (2.21%)
occurrences (all)	1	0	8
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 5 (20.00%)	3 / 25 (12.00%)	2 / 226 (0.88%)
occurrences (all)	1	3	2
Endocrine disorders			

Adrenal insufficiency subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 25 (0.00%) 0	0 / 226 (0.00%) 0
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	3 / 5 (60.00%) 3	1 / 25 (4.00%) 1	11 / 226 (4.87%) 13
Back pain subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	8 / 25 (32.00%) 8	13 / 226 (5.75%) 15
Infections and infestations			
Diverticulitis subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 25 (0.00%) 0	0 / 226 (0.00%) 0
Herpes zoster subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	1 / 25 (4.00%) 1	2 / 226 (0.88%) 2
Upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	2 / 25 (8.00%) 2	1 / 226 (0.44%) 2
Urinary tract infection subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	3 / 25 (12.00%) 4	6 / 226 (2.65%) 6
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	4 / 5 (80.00%) 5	10 / 25 (40.00%) 17	81 / 226 (35.84%) 120
Hyperuricaemia subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 25 (0.00%) 0	13 / 226 (5.75%) 18
Hypocalcaemia subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	2 / 25 (8.00%) 2	17 / 226 (7.52%) 26
Hypokalaemia subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	7 / 25 (28.00%) 10	36 / 226 (15.93%) 53

Hypomagnesaemia			
subjects affected / exposed	1 / 5 (20.00%)	9 / 25 (36.00%)	19 / 226 (8.41%)
occurrences (all)	2	13	46
Hyponatraemia			
subjects affected / exposed	1 / 5 (20.00%)	2 / 25 (8.00%)	24 / 226 (10.62%)
occurrences (all)	1	2	43
Dehydration			
subjects affected / exposed	0 / 5 (0.00%)	3 / 25 (12.00%)	13 / 226 (5.75%)
occurrences (all)	0	5	15
Hyperglycaemia			
subjects affected / exposed	0 / 5 (0.00%)	3 / 25 (12.00%)	17 / 226 (7.52%)
occurrences (all)	0	3	21
Hypoalbuminaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 25 (0.00%)	23 / 226 (10.18%)
occurrences (all)	0	0	40

Non-serious adverse events	Part 2: Topotecan 1.5 mg/m ²		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	220 / 223 (98.65%)		
Vascular disorders			
Hypotension			
subjects affected / exposed	7 / 223 (3.14%)		
occurrences (all)	10		
Deep vein thrombosis			
subjects affected / exposed	0 / 223 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	50 / 223 (22.42%)		
occurrences (all)	90		
Fatigue			
subjects affected / exposed	43 / 223 (19.28%)		
occurrences (all)	58		
Oedema peripheral			
subjects affected / exposed	7 / 223 (3.14%)		
occurrences (all)	8		

Pain			
subjects affected / exposed	4 / 223 (1.79%)		
occurrences (all)	4		
Non-cardiac chest pain			
subjects affected / exposed	18 / 223 (8.07%)		
occurrences (all)	19		
Pyrexia			
subjects affected / exposed	16 / 223 (7.17%)		
occurrences (all)	18		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	27 / 223 (12.11%)		
occurrences (all)	35		
Pneumonitis			
subjects affected / exposed	1 / 223 (0.45%)		
occurrences (all)	2		
Cough			
subjects affected / exposed	19 / 223 (8.52%)		
occurrences (all)	23		
Pulmonary embolism			
subjects affected / exposed	0 / 223 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	3 / 223 (1.35%)		
occurrences (all)	3		
Insomnia			
subjects affected / exposed	15 / 223 (6.73%)		
occurrences (all)	15		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	22 / 223 (9.87%)		
occurrences (all)	30		
Aspartate aminotransferase increased			
subjects affected / exposed	14 / 223 (6.28%)		
occurrences (all)	17		

Blood alkaline phosphatase increased			
subjects affected / exposed	14 / 223 (6.28%)		
occurrences (all)	18		
Gamma-glutamyltransferase increased			
subjects affected / exposed	6 / 223 (2.69%)		
occurrences (all)	6		
Weight decreased			
subjects affected / exposed	26 / 223 (11.66%)		
occurrences (all)	43		
Platelet count decreased			
subjects affected / exposed	59 / 223 (26.46%)		
occurrences (all)	220		
Neutrophil count decreased			
subjects affected / exposed	45 / 223 (20.18%)		
occurrences (all)	115		
White blood cell count decreased			
subjects affected / exposed	34 / 223 (15.25%)		
occurrences (all)	102		
Blood creatinine increased			
subjects affected / exposed	9 / 223 (4.04%)		
occurrences (all)	21		
Blood lactate dehydrogenase increased			
subjects affected / exposed	13 / 223 (5.83%)		
occurrences (all)	23		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	3 / 223 (1.35%)		
occurrences (all)	3		
Nervous system disorders			
Headache			
subjects affected / exposed	13 / 223 (5.83%)		
occurrences (all)	16		
Dizziness			
subjects affected / exposed	20 / 223 (8.97%)		
occurrences (all)	24		
Somnolence			

subjects affected / exposed occurrences (all)	2 / 223 (0.90%) 2		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	137 / 223 (61.43%)		
occurrences (all)	532		
Thrombocytopenia			
subjects affected / exposed	131 / 223 (58.74%)		
occurrences (all)	487		
Anaemia			
subjects affected / exposed	177 / 223 (79.37%)		
occurrences (all)	773		
Coagulopathy			
subjects affected / exposed	0 / 223 (0.00%)		
occurrences (all)	0		
Lymphopenia			
subjects affected / exposed	27 / 223 (12.11%)		
occurrences (all)	133		
Leukopenia			
subjects affected / exposed	94 / 223 (42.15%)		
occurrences (all)	397		
Eye disorders			
Visual impairment			
subjects affected / exposed	1 / 223 (0.45%)		
occurrences (all)	1		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	43 / 223 (19.28%)		
occurrences (all)	70		
Nausea			
subjects affected / exposed	58 / 223 (26.01%)		
occurrences (all)	94		
Abdominal pain			
subjects affected / exposed	8 / 223 (3.59%)		
occurrences (all)	8		
Constipation			

subjects affected / exposed	35 / 223 (15.70%)		
occurrences (all)	46		
Abdominal distension			
subjects affected / exposed	2 / 223 (0.90%)		
occurrences (all)	2		
Flatulence			
subjects affected / exposed	0 / 223 (0.00%)		
occurrences (all)	0		
Stomatitis			
subjects affected / exposed	6 / 223 (2.69%)		
occurrences (all)	12		
Vomiting			
subjects affected / exposed	27 / 223 (12.11%)		
occurrences (all)	46		
Abdominal pain upper			
subjects affected / exposed	8 / 223 (3.59%)		
occurrences (all)	10		
Dysphagia			
subjects affected / exposed	5 / 223 (2.24%)		
occurrences (all)	6		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	27 / 223 (12.11%)		
occurrences (all)	34		
Erythema			
subjects affected / exposed	1 / 223 (0.45%)		
occurrences (all)	1		
Hyperhidrosis			
subjects affected / exposed	1 / 223 (0.45%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	6 / 223 (2.69%)		
occurrences (all)	8		
Renal and urinary disorders			
Renal failure			

subjects affected / exposed occurrences (all)	2 / 223 (0.90%) 2		
Endocrine disorders Adrenal insufficiency subjects affected / exposed occurrences (all)	1 / 223 (0.45%) 1		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all)	16 / 223 (7.17%) 19 12 / 223 (5.38%) 13		
Infections and infestations Diverticulitis subjects affected / exposed occurrences (all) Herpes zoster subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all)	1 / 223 (0.45%) 1 4 / 223 (1.79%) 5 5 / 223 (2.24%) 5 3 / 223 (1.35%) 3		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) Hyperuricaemia subjects affected / exposed occurrences (all) Hypocalcaemia subjects affected / exposed occurrences (all)	43 / 223 (19.28%) 56 11 / 223 (4.93%) 14 5 / 223 (2.24%) 12		

Hypokalaemia			
subjects affected / exposed	15 / 223 (6.73%)		
occurrences (all)	29		
Hypomagnesaemia			
subjects affected / exposed	19 / 223 (8.52%)		
occurrences (all)	30		
Hyponatraemia			
subjects affected / exposed	24 / 223 (10.76%)		
occurrences (all)	61		
Dehydration			
subjects affected / exposed	4 / 223 (1.79%)		
occurrences (all)	4		
Hyperglycaemia			
subjects affected / exposed	15 / 223 (6.73%)		
occurrences (all)	23		
Hypoalbuminaemia			
subjects affected / exposed	13 / 223 (5.83%)		
occurrences (all)	25		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 November 2017	Streamlined the phase II/III study design and allowed sufficient statistical power for interim analysis. Amended the design from 3 parts: Part 1a, Part 1b and Part 2 to two parts: Part 1 and Part 2. Clarified that safety and efficacy results from Part 1 determined if the study proceeded (or not) to Part 2. Disease stage (limited versus extensive) at diagnosis randomization stratification factor removed (However, the randomization scheme was designed with this stratification factor). Changed the study sponsor from Merrimack to Ipsen Bioscience.
14 September 2018	Incorporated country-specific requests from regulatory authorities received during the clinical trial submission process (this included those from France and Germany). Amended and clarified eligibility criteria and protocol procedures. Introduced serial Holter monitoring electrocardiogram recordings and time matched pharmacokinetic sampling for participants in Part 1. Defined OS for Part 2 as date from randomization. Updated to refer to National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 and Medical Dictionary for Regulatory Activities version 21.0 or later. Clarified sampling timepoints and dose modification rules. Allowed up to 3 dose reductions (rather than 2) of irinotecan liposome injection or up to 2 dose reductions of topotecan per participant due to toxicities.
04 December 2019	Provided justification for dose level chosen for Part 2. Clarified timepoints, protocol procedures and pregnancy follow-up period. Updated additional disease specific inclusion criteria. Statement added to clarify definition of platinum sensitivity. Updated recommendations for management of chemotherapy induced diarrhea. Revised adverse event management guidelines. Included that a subgroup analysis of safety by uridine diphosphate glucuronosyltransferase family 1 member A1 (UGT1A1)*28 allele status, based on accumulated data may be performed.
24 November 2020	Updated the statistical analysis to allow an assessment of the interim efficacy signal, confirming the promising results observed during the Part 1 by adding a descriptive analysis of ORR for efficacy at the time of the interim analysis of OS futility. 2 interim analyses were reduced to 1 futility analysis. Amended the secondary and exploratory objectives for participant-reported outcomes. Included reporting requirements and detail specific to conduct of the study during the Coronavirus Disease-2019 pandemic. Clarified protocol procedures. Amended additional disease specific inclusion criterion.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported