Clinical trial results:
A phase II, randomized, active-controlled, multicenter study comparing the efficacy and safety of targeted therapy or cancer immunotherapy guided by genomic profiling versus platinum-based chemotherapy in patients with cancer of unknown primary site who have received three cycles of platinum doublet chemotherapy

Summary

EudraCT number	2017-003040-20
Trial protocol	GB AT EE IE DE CZ FI LV HU PL FR ES BG PT HR NO NL DK CY IT RO
Global end of trial date	

Results information

Result version number	v2
This version publication date	19 July 2024
First version publication date	06 March 2024
Version creation reason	• Correction of full data set Previously uncalculated CIs were provided. Correction to deaths reported.

Trial information

Trial identification

Sponsor protocol code	MX39795

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03498521
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Hoffmann-La Roche
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, 4070
Public contact	F. Hoffmann-La Roche AG, Hoffmann-La Roche, +41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, Hoffmann-La Roche, +41 616878333, global.trial_information@roche.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Interim
Date of interim/final analysis	14 February 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 February 2023
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

Study MX39795 compared the efficacy and safety of molecularly-guided therapy versus standard platinum-containing chemotherapy in patients with poor prognosis cancer of unknown primary site (CUP; non-specific subset) who have achieved disease control (CR, PR or SD) after 3 cycles of first-line platinum-based induction chemotherapy. Molecularly-guided therapies included 10 targeted cancer therapy regimens and 2 cancer immunotherapy regimens and were chosen based on each participant's comprehensive genomic profile.

Protection of trial subjects:

All participants were required to sign an Informed Consent Form

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 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: 24
Country: Number of subjects enrolled	Austria: 3
Country: Number of subjects enrolled	Bulgaria: 3
Country: Number of subjects enrolled	Brazil: 29
Country: Number of subjects enrolled	Switzerland: 4
Country: Number of subjects enrolled	Chile: 8
Country: Number of subjects enrolled	Colombia: 6
Country: Number of subjects enrolled	Czechia: 17
Country: Number of subjects enrolled	Germany: 65
Country: Number of subjects enrolled	Denmark: 4
Country: Number of subjects enrolled	Spain: 54
Country: Number of subjects enrolled	Estonia: 3
Country: Number of subjects enrolled	Finland: 6
Country: Number of subjects enrolled	France: 50
Country: Number of subjects enrolled	United Kingdom: 59
Country: Number of subjects enrolled	Greece: 15
Country: Number of subjects enrolled	Croatia: 2
Country: Number of subjects enrolled	Hungary: 4

Country: Number of subjects enrolled	Ireland: 7
Country: Number of subjects enrolled	Israel: 11
Country: Number of subjects enrolled	Italy: 22
Country: Number of subjects enrolled	Japan: 13
Country: Number of subjects enrolled	Korea, Republic of: 22
Country: Number of subjects enrolled	Latvia: 6
Country: Number of subjects enrolled	Mexico: 6
Country: Number of subjects enrolled	Netherlands: 12
Country: Number of subjects enrolled	Norway: 5
Country: Number of subjects enrolled	Peru: 2
Country: Number of subjects enrolled	Poland: 1
Country: Number of subjects enrolled	Portugal: 4
Country: Number of subjects enrolled	Romania: 12
Country: Number of subjects enrolled	Thailand: 8
Country: Number of subjects enrolled	Türkiye: 41
Worldwide total number of subjects	528
EEA total number of subjects	295

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)	308
From 65 to 84 years	220
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Eligible participants included adults with poor prognosis cancer of unknown primary site (CUP).

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	Molecularly-Guided Therapy MGT) Category 1

Arm description:

Category 1 included participants with cancer of unknown primary site (CUP) with a complete response (CR), partial response (PR), or stable disease (SD) after 3 cycles of platinum induction chemotherapy (provided at the beginning of the study). MGT was chosen based on each participant's comprehensive genomic profile and administered until loss of clinical benefit, unacceptable toxicity, participant or investigator decision to discontinue, or death, whichever occurred first.

Arm type	Experimental
Investigational medicinal product name	Entrectinib
Investigational medicinal product code	
Other name	RO7102122
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Administered as recommended in its US label for patients with NTRK gene fusions or ROS1 gene rearrangements (600 mg QD) until loss of clinical benefit or unacceptable toxicity.

Investigational medicinal product name	Alectinib
Investigational medicinal product code	
Other name	RO5424802
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Administered as recommended for ALK-positive non-small cell lung cancer (NSCLC) (600 mg twice daily (BID) until loss of clinical benefit or unacceptable toxicity.

Investigational medicinal product name	Erlotinib
Investigational medicinal product code	
Other name	RO508231
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Administered as recommended in its EMA Summary of Product Characteristics (EU SmPC) for advanced NSCLC (150 mg per day (QD)) in combination with bevacizumab until loss of clinical benefit or unacceptable toxicity.

Investigational medicinal product name	Atezolizumab
Investigational medicinal product code	
Other name	RO5541267
Pharmaceutical forms	Solution for infusion

Routes of administration	Intravenous use

Dosage and administration details:

Administered alone or in combination with platinum-based chemotherapy as recommended for urinary carcinoma or NSCLC (1200 mg IV infusion over 60 min every three weeks (Q3W)) until loss of clinical benefit or unacceptable toxicity.

Investigational medicinal product name	Vismodegib
Investigational medicinal product code	
Other name	RO5450815
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Administered as recommended for metastatic basal cell carcinoma (150 mg QD) until loss of clinical benefit or toxicity.

Investigational medicinal product name	Pemigatinib
Investigational medicinal product code	
Other name	RO7496200
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Administered as recommended for advanced or metastatic cholangiocarcinoma with FGFR2 fusions or other rearrangements (13.5 mg QD) across a 21-day treatment cycle until loss of clinical benefit or unacceptable toxicity.

Investigational medicinal product name	Olaparib
Investigational medicinal product code	
Other name	RO5508245
Pharmaceutical forms	Capsule, Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Administered as recommended for patients with germline BRCA-mutated advanced ovarian cancer (400 mg twice-daily (BID) for capsules, or 300 mg BID for film-coated tablets) until loss of clinical benefit or unacceptable toxicity.

Investigational medicinal product name	Ivosidenib
Investigational medicinal product code	
Other name	RO7499824
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Administered as recommended in its US label for patients with newly-diagnosed or relapsed/refractory acute myeloid leukemia with a susceptible IDH1 mutation (500 mg QD across a 28-day treatment cycle) until loss of clinical benefit or unacceptable toxicity.

Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	RO0247506
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered at a dose of 175 mg/m^2 on Day 1
as part of platinum-based chemotherapy at induction (3 cycles) for all participants, then for a minimum of an additional 3 cycles for selected participants.

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	RO0232538
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered at a dose of 60-75 mg/m^2 on Day 1 as part of platinum-based chemotherapy at induction (3 cycles) for all participants, then for a minimum of an additional 3 cycles for selected participants.

Investigational medicinal product name	Carboplatin
Investigational medicinal product code	
Other name	RO4843791
Pharmaceutical forms	Solution for injection, Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered weekly as part of platinum-based chemotherapy at induction (3 cycles) at an AUC dose calculated by the Calvert formula for all participants, then for a minimum of an additional 3 cycles for selected participants.

Investigational medicinal product name	Pertuzumab
Investigational medicinal product code	
Other name	RO4368451
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered as recommended for advanced breast cancer with HER2 alterations (initial loading dose of 840 mg; thereafter 420 mg Q3W) in combination with trastuzumab and platinum-based chemotherapy.

Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	RO0452317
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered as recommended for advanced breast cancer with HER2 alterations (600 mg fixed-dose SC injection Q3W) in combination with pertuzumab and platinum-based chemotherapy.

Investigational medicinal product name	Cobimetinib
Investigational medicinal product code	
Other name	RO5514041
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Administered as recommended in its investigator's brochure for advanced melanoma (60 mg QD for the first 21 days of a 28-Day treatment cycle) in combination with vemurafenib until loss of clinical benefit or unacceptable toxicity.

Investigational medicinal product name	Vemurafenib
Investigational medicinal product code	
Other name	RO5185426
Pharmaceutical forms	Film-coated tablet and gastro-resistant granules in sachet, Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Administered as recommended in its investigator's brochure for advanced melanoma (960 mg BID) in combination with cobimetinib until loss of clinical benefit or unacceptable toxicity.

Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	RO0247506
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered at a dose of 80 mg/m^2 on Days 1, 8, and 15 of a 28-Day cycle for 3 cycles in combination with ipatasertib.

Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	RO0249587
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered at a dose of 1000 mg/m^2 on Day 1 and Day 8 of a 3-week cycle as part of platinum-based chemotherapy at induction (3 cycles) for all participants, then for a minimum of an additional 3 cycles for selected participants.

Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	RO4876646
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered as recommended in its EU SmPC for advanced NSCLC (15 mg/kg Q3W) in combination with erlotinib until loss of clinical benefit or unacceptable toxicity.

Investigational medicinal product name	Ipatasertib
Investigational medicinal product code	
Other name	RO5532961
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Administered at a dose of 400 mg QD on Days 1-21 of a 28-day cycle, first in combination with paclitaxel (3 cycles) and then as monotherapy until loss of clinical benefit or unacceptable toxicity.

Arm title	Chemotherapy Category 1

Arm description:

Category 1 included participants with cancer of unknown primary site (CUP) with a complete response (CR), partial response (PR), or stable disease (SD) after 3 cycles of platinum induction chemotherapy (provided at the beginning of the study). Participants in this arm continued to receive the same chemotherapy regimen used during induction for a minimum of 3 additional cycles.

Arm type	Control
Investigational medicinal product name	Carboplatin
Investigational medicinal product code	
Other name	RO4843791
Pharmaceutical forms	Solution for injection, Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered weekly as part of platinum-based chemotherapy at induction (3 cycles) at an AUC dose calculated by the Calvert formula for all participants, then for a minimum of an additional 3 cycles for selected participants.

Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	RO0249587
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered at a dose of 1000 mg/m^2 on Day 1 and Day 8 of a 3-week cycle as part of platinum-based chemotherapy at induction (3 cycles) for all participants, then for a minimum of an additional 3 cycles for selected participants.

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	RO0232538
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered at a dose of 60-75 mg/m^2 on Day 1 as part of platinum-based chemotherapy at induction (3 cycles) for all participants, then for a minimum of an additional 3 cycles for selected participants.

Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	RO0247506
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered at a dose of 175 mg/m^2 on Day 1
as part of platinum-based chemotherapy at induction (3 cycles) for all participants, then for a minimum of an additional 3 cycles for selected participants.

Arm title	Category 2

Arm description:

Category 2 included participants with progressive disease (PD) after 3 cycles of platinum induction chemotherapy. Participants in this arm received either MGT based on their comprehensive genomic profile until loss of clinical benefit, unacceptable toxicity, participant or investigator decision to discontinue, or death, whichever occurred first, or the same chemotherapy regimen used during induction for a minimum of 3 additional cycles.

Arm type	Experimental
Investigational medicinal product name	Carboplatin
Investigational medicinal product code	
Other name	RO4843791
Pharmaceutical forms	Solution for injection, Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered weekly as part of platinum-based chemotherapy at induction (3 cycles) at an AUC dose calculated by the Calvert formula for all participants, then for a minimum of an additional 3 cycles for selected participants.

Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	RO0247506
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered at a dose of 175 mg/m^2 on Day 1
as part of platinum-based chemotherapy at induction (3 cycles) for all participants, then for a minimum of an additional 3 cycles for selected participants.

Investigational medicinal product name	Atezolizumab
Investigational medicinal product code	
Other name	RO5541267
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered alone or in combination with platinum-based chemotherapy as recommended for urinary carcinoma or NSCLC (1200 mg IV infusion over 60 min every three weeks (Q3W)) until loss of clinical benefit or unacceptable toxicity.

Investigational medicinal product name	Vismodegib
Investigational medicinal product code	
Other name	RO5450815
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Administered as recommended for metastatic basal cell carcinoma (150 mg QD) until loss of clinical benefit or toxicity.

Investigational medicinal product name	Pemigatinib
Investigational medicinal product code	
Other name	RO7496200
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Administered as recommended for advanced or metastatic cholangiocarcinoma with FGFR2 fusions or other rearrangements (13.5 mg QD) across a 21-day treatment cycle until loss of clinical benefit or unacceptable toxicity.

Investigational medicinal product name	Olaparib
Investigational medicinal product code	
Other name	RO5508245
Pharmaceutical forms	Capsule, Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Administered as recommended for patients with germline BRCA-mutated advanced ovarian cancer (400 mg twice-daily (BID) for capsules, or 300 mg BID for film-coated tablets) until loss of clinical benefit or unacceptable toxicity.

Investigational medicinal product name	Ivosidenib
Investigational medicinal product code	
Other name	RO7499824
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Administered as recommended in its US label for patients with newly-diagnosed or relapsed/refractory acute myeloid leukemia with a susceptible IDH1 mutation (500 mg QD across a 28-day treatment cycle) until loss of clinical benefit or unacceptable toxicity.

Investigational medicinal product name	Entrectinib
Investigational medicinal product code	
Other name	RO7102122
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Administered as recommended in its US label for patients with NTRK gene fusions or ROS1 gene rearrangements (600 mg QD) until loss of clinical benefit or unacceptable toxicity.

Investigational medicinal product name	Alectinib
Investigational medicinal product code	
Other name	RO5424802
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Administered as recommended for ALK-positive non-small cell lung cancer (NSCLC) (600 mg twice daily (BID) until loss of clinical benefit or unacceptable toxicity.

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	RO0232538
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered at a dose of 60-75 mg/m^2 on Day 1 as part of platinum-based chemotherapy at induction (3 cycles) for all participants, then for a minimum of an additional 3 cycles for selected participants.

Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	RO0249587

Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered at a dose of 1000 mg/m^2 on Day 1 and Day 8 of a 3-week cycle as part of platinum-based chemotherapy at induction (3 cycles) for all participants, then for a minimum of an additional 3 cycles for selected participants.

Investigational medicinal product name	Vemurafenib
Investigational medicinal product code	
Other name	RO5185426
Pharmaceutical forms	Film-coated tablet and gastro-resistant granules in sachet, Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Administered as recommended in its investigator's brochure for advanced melanoma (960 mg BID) in combination with cobimetinib until loss of clinical benefit or unacceptable toxicity.

Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	RO0247506
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered at a dose of 80 mg/m^2 on Days 1, 8, and 15 of a 28-Day cycle for 3 cycles in combination with ipatasertib.

Investigational medicinal product name	Ipatasertib
Investigational medicinal product code	
Other name	RO5532961
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Administered at a dose of 400 mg QD on Days 1-21 of a 28-day cycle, first in combination with paclitaxel (3 cycles) and then as monotherapy until loss of clinical benefit or unacceptable toxicity.

Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	RO4876646
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered as recommended in its EU SmPC for advanced NSCLC (15 mg/kg Q3W) in combination with erlotinib until loss of clinical benefit or unacceptable toxicity.

Investigational medicinal product name	Erlotinib
Investigational medicinal product code	
Other name	RO508231
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Administered as recommended in its EMA Summary of Product Characteristics (EU SmPC) for advanced NSCLC (150 mg per day (QD)) in combination with bevacizumab until loss of clinical benefit or unacceptable toxicity.

Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	RO0452317
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered as recommended for advanced breast cancer with HER2 alterations (600 mg fixed-dose SC

injection Q3W) in combination with pertuzumab and platinum-based chemotherapy.

Investigational medicinal product name	Cobimetinib
Investigational medicinal product code	
Other name	RO5514041
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Administered as recommended in its investigator's brochure for advanced melanoma (60 mg QD for the first 21 days of a 28-Day treatment cycle) in combination with vemurafenib until loss of clinical benefit or unacceptable toxicity.

Investigational medicinal product name	Pertuzumab
Investigational medicinal product code	
Other name	RO4368451
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered as recommended for advanced breast cancer with HER2 alterations (initial loading dose of 840 mg; thereafter 420 mg Q3W) in combination with trastuzumab and platinum-based chemotherapy.

Number of subjects in period 1	Molecularly-Guided Therapy MGT) Category 1	Chemotherapy Category 1	Category 2
Started	326	110	92
Completed	0	0	0
Not completed	326	110	92
Adverse event, serious fatal	191	64	72
Consent withdrawn by subject	9	6	2
No profile due to technical failure	1	-	-
Study ongoing	121	36	15
Physician decision	-	1	-
Lost to follow-up	3	3	3
Exclusion criteria	1	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Molecularly-Guided Therapy MGT) Category 1
Reporting group description:	
Category 1 included participants with cancer of unknown primary site (CUP) with a complete response (CR), partial response (PR), or stable disease (SD) after 3 cycles of platinum induction chemotherapy (provided at the beginning of the study). MGT was chosen based on each participant's comprehensive genomic profile and administered until loss of clinical benefit, unacceptable toxicity, participant or investigator decision to discontinue, or death, whichever occurred first.	
Reporting group title	Chemotherapy Category 1
Reporting group description:	
Category 1 included participants with cancer of unknown primary site (CUP) with a complete response (CR), partial response (PR), or stable disease (SD) after 3 cycles of platinum induction chemotherapy (provided at the beginning of the study). Participants in this arm continued to receive the same chemotherapy regimen used during induction for a minimum of 3 additional cycles.	
Reporting group title	Category 2
Reporting group description:	
Category 2 included participants with progressive disease (PD) after 3 cycles of platinum induction chemotherapy. Participants in this arm received either MGT based on their comprehensive genomic profile until loss of clinical benefit, unacceptable toxicity, participant or investigator decision to discontinue, or death, whichever occurred first, or the same chemotherapy regimen used during induction for a minimum of 3 additional cycles.	

Reporting group values	Molecularly-Guided Therapy MGT) Category 1	Chemotherapy Category 1	Category 2
Number of subjects	326	110	92
Age categorical Units: Subjects			
Adults (18-64 years)	188	61	59
From 65-84 years	138	49	33
Age Continuous Units: Years			
arithmetic mean	60.5	61.1	59.4
standard deviation	± 11.5	± 11.3	± 12.7
Sex: Female, Male Units: Participants			
Female	161	53	43
Male	165	57	49
Race, Customized Units: Subjects			
American Indian or Alaska Native	4	3	1
Asian	31	12	7
Black or African American	5	0	0
Unknown	43	14	15
White	242	81	69
Missing	1	0	0
Ethnicity, Customized Units: Subjects			
Hispanic or Latino	22	9	4
Not Hispanic or Latino	252	85	75
Not Stated	31	11	7

Unknown	21	5	6

Reporting group values	Total		
Number of subjects	528		
Age categorical Units: Subjects			
Adults (18-64 years)	308		
From 65-84 years	220		
Age Continuous Units: Years arithmetic mean standard deviation	 -		
Sex: Female, Male Units: Participants			
Female	257		
Male	271		
Race, Customized Units: Subjects			
American Indian or Alaska Native	8		
Asian	50		
Black or African American	5		
Unknown	72		
White	392		
Missing	1		
Ethnicity, Customized Units: Subjects			
Hispanic or Latino	35		
Not Hispanic or Latino	412		
Not Stated	49		
Unknown	32		

End points

End points reporting groups

Reporting group title	Molecularly-Guided Therapy MGT) Category 1

Reporting group description:

Category 1 included participants with cancer of unknown primary site (CUP) with a complete response (CR), partial response (PR), or stable disease (SD) after 3 cycles of platinum induction chemotherapy (provided at the beginning of the study). MGT was chosen based on each participant's comprehensive genomic profile and administered until loss of clinical benefit, unacceptable toxicity, participant or investigator decision to discontinue, or death, whichever occurred first.

Reporting group title	Chemotherapy Category 1

Reporting group description:

Category 1 included participants with cancer of unknown primary site (CUP) with a complete response (CR), partial response (PR), or stable disease (SD) after 3 cycles of platinum induction chemotherapy (provided at the beginning of the study). Participants in this arm continued to receive the same chemotherapy regimen used during induction for a minimum of 3 additional cycles.

Reporting group title	Category 2

Reporting group description:

Category 2 included participants with progressive disease (PD) after 3 cycles of platinum induction chemotherapy. Participants in this arm received either MGT based on their comprehensive genomic profile until loss of clinical benefit, unacceptable toxicity, participant or investigator decision to discontinue, or death, whichever occurred first, or the same chemotherapy regimen used during induction for a minimum of 3 additional cycles.

Primary: Progression Free Survival (PFS) as Assessed by the Investigator According to Response Evaluation Criteria In Solid Tumors v1.1 (RECIST v1.1)

End point title	Progression Free Survival (PFS) as Assessed by the Investigator According to Response Evaluation Criteria In Solid Tumors v1.1 (RECIST v1.1)[1]

End point description:

This efficacy objective was to evaluate the efficacy of MGT vs platinum chemotherapy in term of PFS in participants with CUP whose best response to 3 cycles of platinum induction chemotherapy was assessed CR, PR, or SD.

End point type	Primary

End point timeframe:

From randomization to the first occurrence of disease progression or death from any cause, until 330 PFS events were observed (approx. 4.3 years for MGT Cat 1 and 3.4 years for Chemotherapy Cat 1).

Notes:

[1] - 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: Endpoints for Category 2 were exploratory and were not included in this analysis.

End point values	Molecularly-Guided Therapy MGT) Category 1	Chemotherapy Category 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	326	110		
Units: Months				
median (confidence interval 95%)	6.05 (4.70 to 6.47)	4.40 (4.14 to 5.59)		

Statistical analyses

Statistical analysis title	PFS ITT Category 1
Comparison groups	Molecularly-Guided Therapy MGT) Category 1 v Chemotherapy Category 1
Number of subjects included in analysis	436
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0079
Method	Stratified log-rank
Parameter estimate	Stratified Cox proportional hazard
Point estimate	0.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	0.92

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)[2]

End point description:

The intent-to-treat (ITT) population included all Category 1 randomized participants, whether or not the assigned study treatment was received. Endpoints for Category 2 were exploratory and were not included in this analysis.

End point type	Secondary

End point timeframe:

From randomization to death from any cause, through the end of study (approximately 4 years)

Notes:

[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: Endpoints for Category 2 were exploratory and were not included in this analysis.

End point values	Molecularly-Guided Therapy MGT) Category 1	Chemotherapy Category 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	189	64		
Units: Months				
median (confidence interval 95%)	14.65 (13.31 to 17.25)	11.04 (9.72 to 15.38)		

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)[3]

End point description:

The intent-to-treat (ITT) population included all Category 1 randomized participants, whether or not the assigned study treatment was received. Endpoints for Category 2 were exploratory and were not included in this analysis.

End point type	Secondary

End point timeframe:

Two consecutive occurrences of complete or partial response >/=4 weeks apart

Notes:

[3] - 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: Endpoints for Category 2 were exploratory and were not included in this analysis.

End point values	Molecularly-Guided Therapy MGT) Category 1	Chemotherapy Category 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	326[4]	110[5]		
Units: Percentage of participants				
number (confidence interval 95%)				
Complete response (CR)	4.9 (2.83 to 7.85)	3.6 (1.00 to 9.05)		
Partial response (PR)	12.9 (9.45 to 17.01)	4.5 (1.49 to 10.29)		
Stable disease (SD)	44.5 (39.00 to 50.06)	49.1 (39.43 to 58.80)		
Non-CR/Non-PD	7.1 (4.52 to 10.40)	6.4 (2.60 to 12.67)		
NA	2.5 (1.07 to 4.78)	2.7 (0.57 to 7.76)		
Progressive disease (PD)	17.8 (13.80 to 22.38)	21.8 (14.51 to 30.70)		
Not evaluable	0.6 (0.07 to 2.20)	0 (0.00 to 3.30)		
Missing	9.8 (6.81 to 13.57)	11.8 (6.45 to 19.36)		

Notes:

[4] - 9999 values indicate not evaluable or missing data

[5] - 9999 values indicate not evaluable or missing data

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)[6]

End point description:

End point type	Secondary

End point timeframe:

From the first documentation of a complete response (CR) or partial response (PR) to disease progression or death from any cause, whichever occurs first (up to approximately 70 months)

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoints for Category 2 were exploratory and were not included in this analysis.

End point values	Molecularly-Guided Therapy MGT) Category 1	Chemotherapy Category 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58[7]	9[8]		
Units: Months				
median (confidence interval 95%)	16.39 (8.08 to 9999)	9999 (4.14 to 9999)		

Notes:

[7] - 9999 = Value is NA due to insufficient no. of participants with the event.

[8] - 9999 = Value is NA due to insufficient no. of participants with the event.

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR1)

End point title	Disease Control Rate (DCR1)[9]

End point description:

End point type	Secondary

End point timeframe:

From randomization to death from any cause, through the end of study (approximately 70 months)

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: Endpoints for Category 2 were exploratory and were not included in this analysis.

End point values	Molecularly-Guided Therapy MGT) Category 1	Chemotherapy Category 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	326	110		
Units: Percentage of responders				
number (confidence interval 95%)	64.7 (59.27 to 69.91)	60.0 (50.22 to 69.22)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Approximately 4.5 years

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	Molecularly-Guided Therapy

Reporting group description:

Category 1 included participants with cancer of unknown primary site (CUP) with a complete response (CR), partial response (PR), or stable disease (SD) after 3 cycles of platinum induction chemotherapy (provided at the beginning of the study). MGT was chosen based on each participant's comprehensive genomic profile and administered until loss of clinical benefit, unacceptable toxicity, participant or investigator decision to discontinue, or death, whichever occurred first.

Reporting group title	Category 2

Reporting group description:

Category 2 included participants with progressive disease (PD) after 3 cycles of platinum induction chemotherapy. Participants in this arm received either MGT based on their comprehensive genomic profile until loss of clinical benefit, unacceptable toxicity, participant or investigator decision to discontinue, or death, whichever occurred first, or the same chemotherapy regimen used during induction for a minimum of 3 additional cycles.

Reporting group title	Chemotherapy

Reporting group description:

Category 1 included participants with cancer of unknown primary site (CUP) with a complete response (CR), partial response (PR), or stable disease (SD) after 3 cycles of platinum induction chemotherapy (provided at the beginning of the study).
Participants in this arm continued to receive the same chemotherapy regimen used during induction for a minimum of 3 additional cycles.

Serious adverse events	Molecularly-Guided Therapy	Category 2	Chemotherapy
Total subjects affected by serious adverse events			
subjects affected / exposed	112 / 312 (35.90%)	37 / 92 (40.22%)	14 / 101 (13.86%)
number of deaths (all causes)	191	72	64
number of deaths resulting from adverse events	14	12	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cholangiocarcinoma			
subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (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
Prostatic adenoma			

subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (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
Tumour associated fever			
subjects affected / exposed	0 / 312 (0.00%)	1 / 92 (1.09%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 312 (0.00%)	0 / 92 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shock haemorrhagic			
subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (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
Vena cava thrombosis			
subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (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
Circulatory collapse			
subjects affected / exposed	0 / 312 (0.00%)	1 / 92 (1.09%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pain			
subjects affected / exposed	1 / 312 (0.32%)	1 / 92 (1.09%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	1 / 312 (0.32%)	1 / 92 (1.09%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

General physical health deterioration			
subjects affected / exposed	1 / 312 (0.32%)	1 / 92 (1.09%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	1 / 1	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	3 / 312 (0.96%)	1 / 92 (1.09%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 1	0 / 0
Pyrexia			
subjects affected / exposed	7 / 312 (2.24%)	2 / 92 (2.17%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	1 / 8	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	3 / 312 (0.96%)	0 / 92 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	2 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (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
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 312 (0.32%)	2 / 92 (2.17%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (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
Pneumonitis			
subjects affected / exposed	4 / 312 (1.28%)	0 / 92 (0.00%)	2 / 101 (1.98%)
occurrences causally related to treatment / all	1 / 4	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0

Pulmonary oedema			
subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (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
Respiratory failure			
subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (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
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (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
Pleural effusion			
subjects affected / exposed	0 / 312 (0.00%)	1 / 92 (1.09%)	0 / 101 (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
Haemoptysis			
subjects affected / exposed	0 / 312 (0.00%)	1 / 92 (1.09%)	0 / 101 (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
Psychiatric disorders			
Psychiatric decompensation			
subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (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
Suicide attempt			
subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (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
Anxiety			
subjects affected / exposed	0 / 312 (0.00%)	1 / 92 (1.09%)	0 / 101 (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

Delirium			
subjects affected / exposed	0 / 312 (0.00%)	1 / 92 (1.09%)	0 / 101 (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
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (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
Neutrophil count decreased			
subjects affected / exposed	2 / 312 (0.64%)	0 / 92 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver function test abnormal			
subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Hip fracture			
subjects affected / exposed	1 / 312 (0.32%)	1 / 92 (1.09%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (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
Femoral neck fracture			
subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (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
Lumbar vertebral fracture			
subjects affected / exposed	2 / 312 (0.64%)	0 / 92 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Spinal compression fracture			
subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (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
Stoma site haemorrhage			
subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (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
Subdural haematoma			
subjects affected / exposed	0 / 312 (0.00%)	0 / 92 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wrist fracture			
subjects affected / exposed	0 / 312 (0.00%)	1 / 92 (1.09%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	2 / 312 (0.64%)	0 / 92 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			
subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (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
Myocardial infarction			
subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (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
Endocarditis noninfective			
subjects affected / exposed	0 / 312 (0.00%)	0 / 92 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			

subjects affected / exposed	0 / 312 (0.00%)	3 / 92 (3.26%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	0 / 312 (0.00%)	1 / 92 (1.09%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure chronic			
subjects affected / exposed	0 / 312 (0.00%)	1 / 92 (1.09%)	0 / 101 (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
Cardio-respiratory arrest			
subjects affected / exposed	0 / 312 (0.00%)	1 / 92 (1.09%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	0 / 312 (0.00%)	1 / 92 (1.09%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cerebral ischaemia			
subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (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
Dysarthria			
subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (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
Haemorrhage intracranial			
subjects affected / exposed	2 / 312 (0.64%)	0 / 92 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Subarachnoid haemorrhage			

subjects affected / exposed	0 / 312 (0.00%)	0 / 92 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune-mediated encephalitis			
subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (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
Mononeuritis			
subjects affected / exposed	0 / 312 (0.00%)	0 / 92 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myasthenic syndrome			
subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (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
Seizure			
subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (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
Hydrocephalus			
subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (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
Transient ischaemic attack			
subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (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
Vestibular migraine			

subjects affected / exposed	0 / 312 (0.00%)	0 / 92 (0.00%)	1 / 101 (0.99%)
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 / 312 (0.00%)	2 / 92 (2.17%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Syncope			
subjects affected / exposed	0 / 312 (0.00%)	1 / 92 (1.09%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	2 / 312 (0.64%)	1 / 92 (1.09%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia			
subjects affected / exposed	4 / 312 (1.28%)	5 / 92 (5.43%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	2 / 4	5 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombotic microangiopathy			
subjects affected / exposed	0 / 312 (0.00%)	0 / 92 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Agranulocytosis			
subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (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
Pancytopenia			
subjects affected / exposed	4 / 312 (1.28%)	0 / 92 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	4 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			

subjects affected / exposed	0 / 312 (0.00%)	0 / 92 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone marrow failure			
subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Autoimmune haemolytic anaemia			
subjects affected / exposed	2 / 312 (0.64%)	0 / 92 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	2 / 312 (0.64%)	0 / 92 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Periorbital oedema			
subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (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
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	2 / 312 (0.64%)	0 / 92 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	2 / 312 (0.64%)	0 / 92 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	4 / 4	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal fistula			

subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (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
Abdominal pain upper			
subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (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
Abdominal pain			
subjects affected / exposed	2 / 312 (0.64%)	0 / 92 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal incarcerated hernia			
subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (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
Duodenal ulcer perforation			
subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (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
Vomiting			
subjects affected / exposed	6 / 312 (1.92%)	0 / 92 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	5 / 8	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal haemorrhage			
subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (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
Duodenitis			

subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (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
Oesophageal varices haemorrhage			
subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (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
Neutropenic colitis			
subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (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
Nausea			
subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (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
Intestinal obstruction			
subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer haemorrhage			
subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (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
Pneumatosis intestinalis			
subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (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
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 312 (0.00%)	1 / 92 (1.09%)	0 / 101 (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
Ascites			

subjects affected / exposed	0 / 312 (0.00%)	1 / 92 (1.09%)	0 / 101 (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
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 312 (0.00%)	0 / 92 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice cholestatic			
subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (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
Gallbladder rupture			
subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (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
Cholestasis			
subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (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
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (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
Pruritus			
subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (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
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 312 (0.64%)	0 / 92 (0.00%)	2 / 101 (1.98%)
occurrences causally related to treatment / all	0 / 2	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0

Tubulointerstitial nephritis			
subjects affected / exposed	2 / 312 (0.64%)	0 / 92 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydronephrosis			
subjects affected / exposed	0 / 312 (0.00%)	1 / 92 (1.09%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	0 / 312 (0.00%)	2 / 92 (2.17%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Endocrine disorders			
Secondary adrenocortical insufficiency			
subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (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
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (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
Hyperthyroidism			
subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (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
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	2 / 312 (0.64%)	0 / 92 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal pain			

subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (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
Myalgia			
subjects affected / exposed	0 / 312 (0.00%)	1 / 92 (1.09%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	6 / 312 (1.92%)	1 / 92 (1.09%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	1 / 6	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 312 (0.00%)	1 / 92 (1.09%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Sepsis			
subjects affected / exposed	3 / 312 (0.96%)	4 / 92 (4.35%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	1 / 3	1 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 3	0 / 0
Pneumonia			
subjects affected / exposed	5 / 312 (1.60%)	1 / 92 (1.09%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	2 / 5	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	1 / 312 (0.32%)	1 / 92 (1.09%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			
subjects affected / exposed	6 / 312 (1.92%)	2 / 92 (2.17%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 6	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 2	0 / 0
Anal abscess			

subjects affected / exposed	1 / 312 (0.32%)	1 / 92 (1.09%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (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
Cystitis			
subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (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
Clostridium difficile colitis			
subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (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
Cholecystitis infective			
subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (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
Campylobacter gastroenteritis			
subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (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
Abscess jaw			
subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (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
Abdominal infection			
subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (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
Abdominal abscess			

subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (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
Encephalitis			
subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (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
Escherichia sepsis			
subjects affected / exposed	0 / 312 (0.00%)	0 / 92 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	2 / 312 (0.64%)	0 / 92 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis salmonella			
subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (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
Infection			
subjects affected / exposed	3 / 312 (0.96%)	0 / 92 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (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
Lower respiratory tract infection			
subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (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
Peritonitis bacterial			

subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (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
Pneumonia bacterial			
subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (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
Post procedural infection			
subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (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
Pyonephrosis			
subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection viral			
subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (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
Staphylococcal abscess			
subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (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
Upper respiratory tract infection			
subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (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
Respiratory tract infection fungal			
subjects affected / exposed	0 / 312 (0.00%)	1 / 92 (1.09%)	0 / 101 (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
Abdominal sepsis			

subjects affected / exposed	0 / 312 (0.00%)	1 / 92 (1.09%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Gastroenteritis viral			
subjects affected / exposed	0 / 312 (0.00%)	1 / 92 (1.09%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 312 (0.00%)	1 / 92 (1.09%)	0 / 101 (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
Wound infection			
subjects affected / exposed	0 / 312 (0.00%)	1 / 92 (1.09%)	0 / 101 (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
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (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
Diabetes mellitus			
subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (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
Hyponatraemia			
subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (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
Type 1 diabetes mellitus			
subjects affected / exposed	1 / 312 (0.32%)	0 / 92 (0.00%)	0 / 101 (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

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

Non-serious adverse events	Molecularly-Guided Therapy	Category 2	Chemotherapy
Total subjects affected by non-serious adverse events			
subjects affected / exposed	276 / 312 (88.46%)	73 / 92 (79.35%)	79 / 101 (78.22%)
Vascular disorders			
Hypertension			
subjects affected / exposed	18 / 312 (5.77%)	0 / 92 (0.00%)	2 / 101 (1.98%)
occurrences (all)	24	0	2
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	57 / 312 (18.27%)	14 / 92 (15.22%)	15 / 101 (14.85%)
occurrences (all)	76	16	19
Fatigue			
subjects affected / exposed	65 / 312 (20.83%)	19 / 92 (20.65%)	13 / 101 (12.87%)
occurrences (all)	99	25	17
Oedema peripheral			
subjects affected / exposed	22 / 312 (7.05%)	7 / 92 (7.61%)	3 / 101 (2.97%)
occurrences (all)	27	7	6
Pyrexia			
subjects affected / exposed	26 / 312 (8.33%)	10 / 92 (10.87%)	3 / 101 (2.97%)
occurrences (all)	42	10	5
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	21 / 312 (6.73%)	0 / 92 (0.00%)	4 / 101 (3.96%)
occurrences (all)	31	0	4
Cough			
subjects affected / exposed	22 / 312 (7.05%)	0 / 92 (0.00%)	3 / 101 (2.97%)
occurrences (all)	37	0	3
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 312 (0.00%)	5 / 92 (5.43%)	0 / 101 (0.00%)
occurrences (all)	0	5	0
Investigations			
Neutrophil count decreased			

subjects affected / exposed	32 / 312 (10.26%)	8 / 92 (8.70%)	9 / 101 (8.91%)
occurrences (all)	55	20	12
Weight decreased			
subjects affected / exposed	18 / 312 (5.77%)	6 / 92 (6.52%)	3 / 101 (2.97%)
occurrences (all)	18	7	3
Platelet count decreased			
subjects affected / exposed	37 / 312 (11.86%)	9 / 92 (9.78%)	8 / 101 (7.92%)
occurrences (all)	73	11	17
Alanine aminotransferase increased			
subjects affected / exposed	16 / 312 (5.13%)	0 / 92 (0.00%)	7 / 101 (6.93%)
occurrences (all)	23	0	7
Aspartate aminotransferase increased			
subjects affected / exposed	17 / 312 (5.45%)	0 / 92 (0.00%)	6 / 101 (5.94%)
occurrences (all)	20	0	6
White blood cell count decreased			
subjects affected / exposed	0 / 312 (0.00%)	6 / 92 (6.52%)	0 / 101 (0.00%)
occurrences (all)	0	7	0
Nervous system disorders			
Headache			
subjects affected / exposed	17 / 312 (5.45%)	0 / 92 (0.00%)	3 / 101 (2.97%)
occurrences (all)	18	0	5
Neuropathy peripheral			
subjects affected / exposed	35 / 312 (11.22%)	0 / 92 (0.00%)	14 / 101 (13.86%)
occurrences (all)	42	0	17
Peripheral sensory neuropathy			
subjects affected / exposed	21 / 312 (6.73%)	0 / 92 (0.00%)	7 / 101 (6.93%)
occurrences (all)	25	0	8
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	105 / 312 (33.65%)	35 / 92 (38.04%)	30 / 101 (29.70%)
occurrences (all)	160	49	37
Leukopenia			
subjects affected / exposed	12 / 312 (3.85%)	5 / 92 (5.43%)	9 / 101 (8.91%)
occurrences (all)	19	5	13
Neutropenia			

subjects affected / exposed	59 / 312 (18.91%)	11 / 92 (11.96%)	23 / 101 (22.77%)
occurrences (all)	90	13	38
Thrombocytopenia			
subjects affected / exposed	47 / 312 (15.06%)	13 / 92 (14.13%)	13 / 101 (12.87%)
occurrences (all)	75	20	23
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	73 / 312 (23.40%)	8 / 92 (8.70%)	5 / 101 (4.95%)
occurrences (all)	109	10	7
Nausea			
subjects affected / exposed	81 / 312 (25.96%)	21 / 92 (22.83%)	19 / 101 (18.81%)
occurrences (all)	114	29	32
Vomiting			
subjects affected / exposed	38 / 312 (12.18%)	8 / 92 (8.70%)	12 / 101 (11.88%)
occurrences (all)	54	9	16
Constipation			
subjects affected / exposed	39 / 312 (12.50%)	11 / 92 (11.96%)	12 / 101 (11.88%)
occurrences (all)	49	11	13
Abdominal pain			
subjects affected / exposed	33 / 312 (10.58%)	9 / 92 (9.78%)	3 / 101 (2.97%)
occurrences (all)	38	10	3
Abdominal pain upper			
subjects affected / exposed	18 / 312 (5.77%)	0 / 92 (0.00%)	5 / 101 (4.95%)
occurrences (all)	20	0	5
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	33 / 312 (10.58%)	0 / 92 (0.00%)	1 / 101 (0.99%)
occurrences (all)	44	0	2
Pruritus			
subjects affected / exposed	25 / 312 (8.01%)	0 / 92 (0.00%)	0 / 101 (0.00%)
occurrences (all)	34	0	0
Alopecia			
subjects affected / exposed	23 / 312 (7.37%)	0 / 92 (0.00%)	1 / 101 (0.99%)
occurrences (all)	23	0	1
Endocrine disorders			

Hypothyroidism			
subjects affected / exposed	0 / 312 (0.00%)	5 / 92 (5.43%)	0 / 101 (0.00%)
occurrences (all)	0	5	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	22 / 312 (7.05%)	7 / 92 (7.61%)	2 / 101 (1.98%)
occurrences (all)	24	8	3
Arthralgia			
subjects affected / exposed	42 / 312 (13.46%)	0 / 92 (0.00%)	6 / 101 (5.94%)
occurrences (all)	53	0	6
Myalgia			
subjects affected / exposed	20 / 312 (6.41%)	0 / 92 (0.00%)	7 / 101 (6.93%)
occurrences (all)	28	0	7
Pain in extremity			
subjects affected / exposed	20 / 312 (6.41%)	0 / 92 (0.00%)	3 / 101 (2.97%)
occurrences (all)	32	0	3
Bone pain			
subjects affected / exposed	0 / 312 (0.00%)	5 / 92 (5.43%)	0 / 101 (0.00%)
occurrences (all)	0	5	0
Infections and infestations			
COVID-19			
subjects affected / exposed	21 / 312 (6.73%)	5 / 92 (5.43%)	2 / 101 (1.98%)
occurrences (all)	21	5	2
Urinary tract infection			
subjects affected / exposed	23 / 312 (7.37%)	0 / 92 (0.00%)	5 / 101 (4.95%)
occurrences (all)	25	0	6
Metabolism and nutrition disorders			
Hypomagnesaemia			
subjects affected / exposed	22 / 312 (7.05%)	0 / 92 (0.00%)	4 / 101 (3.96%)
occurrences (all)	35	0	6
Decreased appetite			
subjects affected / exposed	54 / 312 (17.31%)	11 / 92 (11.96%)	9 / 101 (8.91%)
occurrences (all)	66	14	11
Hyponatraemia			
subjects affected / exposed	0 / 312 (0.00%)	6 / 92 (6.52%)	0 / 101 (0.00%)
occurrences (all)	0	6	0

Hypoalbuminaemia subjects affected / exposed occurrences (all)	0 / 312 (0.00%) 0	5 / 92 (5.43%) 5	0 / 101 (0.00%) 0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 May 2018	Amended eligibility criteria.
13 July 2018	Updated eligibility criteria.
05 November 2018	Amended eligibility criteria.
29 July 2019	Added a new treatment (entrectinib). Replaced ipatasertib monotherapy with ipatasertib + paclitaxel combination therapy. Amended eligibility criteria.
11 February 2020	Amended eligibility criteria. Added the option for additional chemotherapy for eligible participants. Re-added ipatasertib monotherapy for participants that had started ipatasertib monotherapy under previous protocol versions.
19 February 2021	Added pemigatinib and ivosidenib as treatments. Replaced duration of clinical benefit endpoint with duration of response (DOR) and disease control rate (DCR). Category 1 participants deemed ineligible for MGT were allowed to continue with platinum-based chemotherapy. Amended eligibility criteria.
16 August 2021	Change to olaparib dose and formulation. Amended eligibility criteria.
24 January 2022	Addition of efficacy analysis population for Category 2 participants.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported