



Clinical trial results:

An international, multicenter, Phase 1b/2 study of rogaratinib (BAY 1163877) in combination with atezolizumab as first-line treatment in cisplatin-ineligible patients with FGFR-positive locally advanced or metastatic urothelial carcinoma

Summary

EudraCT number	2017-001483-38
Trial protocol	DE ES FR AT
Global end of trial date	10 July 2024

Results information

Result version number	v1 (current)
This version publication date	07 March 2025
First version publication date	07 March 2025

Trial information

Trial identification

Sponsor protocol code	BAY1163877/19131
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03473756
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser-Wilhelm-Allee, Leverkusen, Germany, 51368
Public contact	Bayer Clinical Trials Contact, Bayer AG, clinical-trials-contact@bayer.com
Scientific contact	Bayer Clinical Trials Contact, Bayer AG, clinical-trials-contact@bayer.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	07 August 2024
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	10 July 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- To determine the safety and tolerability of rogaratinib in combination with atezolizumab in patients with FGFR-positive locally advanced or metastatic urothelial carcinoma
- To determine the recommended Phase 2 dose (RP2D) of rogaratinib in combination with atezolizumab in this patient population.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and the International Council for Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent was read by and explained to all the subjects. Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 May 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 9
Country: Number of subjects enrolled	Austria: 3
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	Japan: 2
Country: Number of subjects enrolled	Korea, Republic of: 6
Country: Number of subjects enrolled	United States: 4
Worldwide total number of subjects	37
EEA total number of subjects	25

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)	4
From 65 to 84 years	32
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 30 study centers in 8 countries (4 in Austria, 3 in France, 3 in Germany, 5 in Italy, 4 in Japan, 3 in South Korea, 4 in Spain, and 4 in the US) between 15 May 2018 (first informed consent) and 10 July 2024 (last participant last visit).

Pre-assignment

Screening details:

A total of 54 FGFR mRNA-positive subjects (35.3%) successfully completed the prescreening. Of these, 37 subjects (68.5%) completed the screening and were assigned to treatment and 31.5% prematurely discontinued the screening: 29.6% due to screening failure and 1.9% (1 subject) due to withdrawal by subject.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Rogaratinib 800 mg BID + Atezolizumab

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Rogaratinib
Investigational medicinal product code	
Other name	BAY 1163877 / rogaratinib / pan FGFR inhibitor
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Starting dose level of rogaratinib was 800 mg twice daily (BID), in continuous 21-day cycles. Suggested by safety findings, the dose was lowered to rogaratinib 600 mg BID when given in combination with 1200 mg atezolizumab every 21 days.

Arm title	Rogaratinib 600 mg BID + Atezolizumab
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Arm description: -

Arm type	Experimental
Investigational medicinal product name	Rogaratinib
Investigational medicinal product code	
Other name	BAY 1163877 / rogaratinib / pan FGFR inhibitor
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Starting dose level of rogaratinib was 800 mg twice daily (BID), in continuous 21-day cycles. Suggested by safety findings, the dose was lowered to rogaratinib 600 mg BID when given in combination with 1200 mg atezolizumab every 21 days.

Number of subjects in period 1	Rogaratinib 800 mg BID + Atezolizumab	Rogaratinib 600 mg BID + Atezolizumab
Started	11	26
Completed	1	0
Not completed	10	26
Consent withdrawn by subject	1	4
Physician decision	-	2
Adverse event, non-fatal	6	7
End of study treatment	-	2
Lost to follow-up	-	1
Lack of efficacy	3	10

Baseline characteristics

Reporting groups

Reporting group title	Rogaratinib 800 mg BID + Atezolizumab
Reporting group description: -	
Reporting group title	Rogaratinib 600 mg BID + Atezolizumab
Reporting group description: -	

Reporting group values	Rogaratinib 800 mg BID + Atezolizumab	Rogaratinib 600 mg BID + Atezolizumab	Total
Number of subjects	11	26	37
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	2	2	4
From 65-84 years	9	23	32
85 years and over	0	1	1
Gender categorical			
Units: Subjects			
Female	2	3	5
Male	9	23	32

Subject analysis sets

Subject analysis set title	All participants assigned to treatment
Subject analysis set type	Safety analysis
Subject analysis set description:	
All participants, who successfully passed screening and were assigned to study treatment and received at least one dose of study treatment:	

Reporting group values	All participants assigned to treatment		
Number of subjects	37		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	4		

From 65-84 years	32		
85 years and over	1		

Gender categorical			
Units: Subjects			
Female	5		
Male	32		

End points

End points reporting groups

Reporting group title	Rogaratinib 800 mg BID + Atezolizumab
Reporting group description: -	
Reporting group title	Rogaratinib 600 mg BID + Atezolizumab
Reporting group description: -	
Subject analysis set title	All participants assigned to treatment
Subject analysis set type	Safety analysis
Subject analysis set description:	
All participants, who successfully passed screening and were assigned to study treatment and received at least one dose of study treatment:	

Primary: Number of participants with Dose-limiting toxicities(DLTs)

End point title	Number of participants with Dose-limiting toxicities(DLTs) ^[1]
End point description:	
End point type	Primary
End point timeframe:	
Up to 21 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: Due to the limited number of patients, statistical analyses included in this study focused on descriptive statistics only.

Comparisons between Rogaratinib 800 mg and Rogaratinib 600 mg are not considered meaningful

End point values	Rogaratinib 800 mg BID + Atezolizumab	Rogaratinib 600 mg BID + Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	26		
Units: participants	1	4		

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with treatment-emergent adverse events (TEAEs)

End point title	Number of participants with treatment-emergent adverse events (TEAEs) ^[2]
End point description:	
End point type	Primary
End point timeframe:	
Up to 30 days after the last dose of rogaratinib or 90 days after the last atezolizumab administration, whichever comes later	

Notes:

[2] - 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: Due to the limited number of patients, statistical analyses included in this study focused on descriptive statistics only.

Comparisons between Rogaratinib 800 mg and Rogaratinib 600 mg are not considered meaningful

End point values	Rogaratinib 800 mg BID + Atezolizumab	Rogaratinib 600 mg BID + Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	26		
Units: participants	11	26		

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with drug-related TEAEs

End point title	Number of participants with drug-related TEAEs ^[3]
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End point description:

End point type	Primary
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End point timeframe:

Up to 30 days after the last dose of rogaratinib or 90 days after the last atezolizumab administration, whichever comes later

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: Due to the limited number of patients, statistical analyses included in this study focused on descriptive statistics only.

Comparisons between Rogaratinib 800 mg and Rogaratinib 600 mg are not considered meaningful

End point values	Rogaratinib 800 mg BID + Atezolizumab	Rogaratinib 600 mg BID + Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	26		
Units: participants	11	26		

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with treatment-emergent serious adverse events(TESAEs)

End point title	Number of participants with treatment-emergent serious adverse events(TESAEs) ^[4]
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End point description:

End point type	Primary
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End point timeframe:

Up to 30 days after the last dose of rogaratinib or 90 days after the last atezolizumab administration, whichever comes later

Notes:

[4] - 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: Due to the limited number of patients, statistical analyses included in this study focused on descriptive statistics only.

Comparisons between Rogaratinib 800 mg and Rogaratinib 600 mg are not considered meaningful

End point values	Rogaratinib 800 mg BID + Atezolizumab	Rogaratinib 600 mg BID + Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	26		
Units: participants	8	14		

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate(ORR)

End point title	Objective Response Rate(ORR)
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End point description:

Objective response rate (ORR) was defined as the percentage of patients with complete response (CR) or partial response (PR). Patients for whom best overall tumor response was not CR or PR, as well as patients without any post-baseline tumor assessment were considered non-responders. For all patients, the best overall tumor response was determined locally by investigators using the RECIST (Response Evaluation Criteria In Solid Tumors) criteria.

End point type	Secondary
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End point timeframe:

Up to 5 months

End point values	Rogaratinib 800 mg BID + Atezolizumab	Rogaratinib 600 mg BID + Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	26		
Units: participants				
complete response	1	4		
partial response	1	10		
no response	9	12		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximal plasma concentration (Cmax) of rogaratinib

End point title Maximal plasma concentration (Cmax) of rogaratinib

End point description:

End point type Secondary

End point timeframe:

At cycle 1 Day 1

End point values	Rogaratinib 800 mg BID + Atezolizumab	Rogaratinib 600 mg BID + Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	25 ^[5]		
Units: µg/l				
geometric mean (standard deviation)	13207.846 (± 1.379)	10372.864 (± 1.404)		

Notes:

[5] - Pharmacokinetic analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the rogaratinib concentration versus time curve (AUC)

End point title Area under the rogaratinib concentration versus time curve (AUC)

End point description:

End point type Secondary

End point timeframe:

At cycle 1 Day 1, 0-t(last)

End point values	Rogaratinib 800 mg BID + Atezolizumab	Rogaratinib 600 mg BID + Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	25 ^[6]		
Units: µg*h/l				
geometric mean (standard deviation)	59187.389 (± 1.513)	45094.877 (± 1.463)		

Notes:

[6] - pharmacokinetic analysis set

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events (TEAEs) were defined as any event arising or worsening after the start of study drug administration until 30 days after the last rogaratinib intake or 90 days after the last atezolizumab administration

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	27.0

Reporting groups

Reporting group title	Rogaratib 800 mg BID + Atezolizumab
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Reporting group description:

Subjects received Rogaratib 800 mg twice daily (b.i.d.) continuously twice daily on all 21 days in each cycle and 1200 mg Atezolizumab through intravenous (i.v.) infusion on Day 1 of each 21-day cycle.

Reporting group title	Rogaratib 600 mg BID + Atezolizumab
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Reporting group description:

Subjects received Rogaratib 600 mg twice daily (b.i.d.) continuously twice daily on all 21 days in each cycle and 1200 mg Atezolizumab through intravenous (i.v.) infusion on Day 1 of each 21-day cycle.

Serious adverse events	Rogaratib 800 mg BID + Atezolizumab	Rogaratib 600 mg BID + Atezolizumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 11 (72.73%)	14 / 26 (53.85%)	
number of deaths (all causes)	9	11	
number of deaths resulting from adverse events	1	3	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Chronic lymphocytic leukaemia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour haemorrhage			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Deep vein thrombosis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Renal cyst aspiration			
subjects affected / exposed	1 / 11 (9.09%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 11 (9.09%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			

subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 11 (9.09%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 11 (9.09%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal function test abnormal			
subjects affected / exposed	1 / 11 (9.09%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Vascular pseudoaneurysm			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haematoma			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Craniocerebral injury			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac disorders			
Angina unstable			

subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Supraventricular tachycardia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 11 (9.09%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea haemorrhagic			

subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 11 (9.09%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal vascular malformation haemorrhagic			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatitis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatotoxicity			
subjects affected / exposed	1 / 11 (9.09%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal impairment			
subjects affected / exposed	1 / 11 (9.09%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations Urinary tract infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 11 (9.09%) 0 / 1 0 / 0	1 / 26 (3.85%) 0 / 4 0 / 0	
Sepsis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 11 (0.00%) 0 / 0 0 / 0	1 / 26 (3.85%) 0 / 2 0 / 1	
Pyelonephritis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 11 (9.09%) 0 / 1 0 / 0	0 / 26 (0.00%) 0 / 0 0 / 0	
Respiratory tract infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 11 (9.09%) 0 / 1 0 / 0	0 / 26 (0.00%) 0 / 0 0 / 0	
Metabolism and nutrition disorders Dehydration subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 11 (0.00%) 0 / 0 0 / 0	1 / 26 (3.85%) 1 / 1 0 / 0	

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

Non-serious adverse events	Rogaratinib 800 mg BID + Atezolizumab	Rogaratinib 600 mg BID + Atezolizumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 11 (100.00%)	26 / 26 (100.00%)	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 11 (9.09%)	1 / 26 (3.85%)	
occurrences (all)	1	2	
Hypotension			
subjects affected / exposed	0 / 11 (0.00%)	3 / 26 (11.54%)	
occurrences (all)	0	3	

Erythromelalgia subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 26 (3.85%) 1	
Hypertension subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	4 / 26 (15.38%) 4	
Embolism subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 26 (3.85%) 1	
Peripheral arterial occlusive disease subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 26 (3.85%) 2	
Surgical and medical procedures Astringent therapy subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 26 (3.85%) 4	
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all)	4 / 11 (36.36%) 13	7 / 26 (26.92%) 11	
Fatigue subjects affected / exposed occurrences (all)	4 / 11 (36.36%) 6	11 / 26 (42.31%) 26	
Chills subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 26 (3.85%) 1	
Chest pain subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 26 (3.85%) 1	
Hyperpyrexia subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 26 (3.85%) 4	
Influenza like illness subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 26 (3.85%) 1	
Injection site reaction			

subjects affected / exposed	1 / 11 (9.09%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Mucosal inflammation			
subjects affected / exposed	2 / 11 (18.18%)	2 / 26 (7.69%)	
occurrences (all)	3	4	
Pain			
subjects affected / exposed	1 / 11 (9.09%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Oedema peripheral			
subjects affected / exposed	0 / 11 (0.00%)	5 / 26 (19.23%)	
occurrences (all)	0	5	
Oedema			
subjects affected / exposed	1 / 11 (9.09%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Pyrexia			
subjects affected / exposed	4 / 11 (36.36%)	7 / 26 (26.92%)	
occurrences (all)	13	10	
Early satiety			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Secretion discharge			
subjects affected / exposed	1 / 11 (9.09%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
General physical health deterioration			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Erectile dysfunction			
subjects affected / exposed	1 / 11 (9.09%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Breast pain			

subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Cough			
subjects affected / exposed	0 / 11 (0.00%)	3 / 26 (11.54%)	
occurrences (all)	0	4	
Dysphonia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Dyspnoea			
subjects affected / exposed	0 / 11 (0.00%)	3 / 26 (11.54%)	
occurrences (all)	0	3	
Lower respiratory tract congestion			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	3	
Pneumothorax			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Epistaxis			
subjects affected / exposed	0 / 11 (0.00%)	3 / 26 (11.54%)	
occurrences (all)	0	4	
Hiccups			
subjects affected / exposed	0 / 11 (0.00%)	2 / 26 (7.69%)	
occurrences (all)	0	2	
Nasal inflammation			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Pleural effusion			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	2	
Psychiatric disorders			

Anxiety subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 26 (3.85%) 1	
Personality change subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	0 / 26 (0.00%) 0	
Insomnia subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	0 / 26 (0.00%) 0	
Depression subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 26 (3.85%) 1	
Product issues Thrombosis in device subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 26 (3.85%) 1	
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 13	8 / 26 (30.77%) 11	
Amylase increased subjects affected / exposed occurrences (all)	3 / 11 (27.27%) 7	5 / 26 (19.23%) 38	
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 22	6 / 26 (23.08%) 7	
Blood bilirubin increased subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	1 / 26 (3.85%) 1	
Blood creatinine increased subjects affected / exposed occurrences (all)	3 / 11 (27.27%) 14	2 / 26 (7.69%) 4	
Blood thyroid stimulating hormone decreased subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	0 / 26 (0.00%) 0	
Blood potassium increased			

subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	1
Neutrophil count decreased		
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	1
Platelet count decreased		
subjects affected / exposed	1 / 11 (9.09%)	3 / 26 (11.54%)
occurrences (all)	1	4
Weight decreased		
subjects affected / exposed	1 / 11 (9.09%)	3 / 26 (11.54%)
occurrences (all)	2	3
Blood phosphorus increased		
subjects affected / exposed	1 / 11 (9.09%)	0 / 26 (0.00%)
occurrences (all)	1	0
Glomerular filtration rate decreased		
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	3
Lipase increased		
subjects affected / exposed	1 / 11 (9.09%)	6 / 26 (23.08%)
occurrences (all)	1	39
Lymphocyte count decreased		
subjects affected / exposed	1 / 11 (9.09%)	0 / 26 (0.00%)
occurrences (all)	2	0
Lymphocyte count increased		
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	1
Liver function test increased		
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	1
N-terminal prohormone brain natriuretic peptide increased		
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	1
Calcium phosphate product increased		
subjects affected / exposed	2 / 11 (18.18%)	0 / 26 (0.00%)
occurrences (all)	4	0

Renal function test abnormal subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	0 / 26 (0.00%) 0	
Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 2	1 / 26 (3.85%) 2	
Transaminases increased subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	0 / 26 (0.00%) 0	
Electrocardiogram ST-T segment abnormal subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 26 (3.85%) 1	
Injury, poisoning and procedural complications			
Subcutaneous haematoma subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 26 (3.85%) 1	
Fall subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 26 (3.85%) 1	
Stoma site ulcer subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	0 / 26 (0.00%) 0	
Stoma site inflammation subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 26 (3.85%) 1	
Post-traumatic pain subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 26 (3.85%) 1	
Procedural pain subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	2 / 26 (7.69%) 2	
Post procedural fever subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	0 / 26 (0.00%) 0	
Chest injury			

subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 26 (3.85%) 1	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Pericardial effusion			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	2	
Sinus tachycardia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	1 / 11 (9.09%)	6 / 26 (23.08%)	
occurrences (all)	1	11	
Dizziness			
subjects affected / exposed	0 / 11 (0.00%)	3 / 26 (11.54%)	
occurrences (all)	0	4	
Amnesia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Headache			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	2	
Hyperaesthesia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Hypoaesthesia			
subjects affected / exposed	0 / 11 (0.00%)	2 / 26 (7.69%)	
occurrences (all)	0	8	
Hypotonia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Loss of consciousness			

subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Taste disorder			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	2	
Paraesthesia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	2	
Memory impairment			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 11 (36.36%)	4 / 26 (15.38%)	
occurrences (all)	12	14	
Lymphopenia			
subjects affected / exposed	1 / 11 (9.09%)	1 / 26 (3.85%)	
occurrences (all)	3	1	
Neutropenia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Neutrophilia			
subjects affected / exposed	1 / 11 (9.09%)	1 / 26 (3.85%)	
occurrences (all)	1	1	
Leukocytosis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	2	
Thrombocytopenia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Hypereosinophilic syndrome			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	2	
Ear and labyrinth disorders			
Ear pain			

subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Vertigo			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Eye disorders			
Cataract			
subjects affected / exposed	0 / 11 (0.00%)	2 / 26 (7.69%)	
occurrences (all)	0	2	
Blepharitis			
subjects affected / exposed	1 / 11 (9.09%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Chalazion			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Diplopia			
subjects affected / exposed	0 / 11 (0.00%)	2 / 26 (7.69%)	
occurrences (all)	0	2	
Dry eye			
subjects affected / exposed	0 / 11 (0.00%)	2 / 26 (7.69%)	
occurrences (all)	0	2	
Eye irritation			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Keratitis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Keratopathy			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Macular degeneration			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Lacrimation increased			
subjects affected / exposed	1 / 11 (9.09%)	1 / 26 (3.85%)	
occurrences (all)	1	1	

Maculopathy			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Photopsia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Retinal detachment			
subjects affected / exposed	1 / 11 (9.09%)	2 / 26 (7.69%)	
occurrences (all)	1	2	
Retinopathy			
subjects affected / exposed	1 / 11 (9.09%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Vision blurred			
subjects affected / exposed	0 / 11 (0.00%)	4 / 26 (15.38%)	
occurrences (all)	0	6	
Visual acuity reduced			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Detachment of retinal pigment epithelium			
subjects affected / exposed	0 / 11 (0.00%)	2 / 26 (7.69%)	
occurrences (all)	0	2	
Xerophthalmia			
subjects affected / exposed	1 / 11 (9.09%)	1 / 26 (3.85%)	
occurrences (all)	1	1	
Vitreous floaters			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Visual impairment			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Corneal toxicity			
subjects affected / exposed	1 / 11 (9.09%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Ocular rosacea			

subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Detachment of macular retinal pigment epithelium			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	2	
Meibomian gland dysfunction			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	2	
Retinoschisis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Serous retinopathy			
subjects affected / exposed	0 / 11 (0.00%)	4 / 26 (15.38%)	
occurrences (all)	0	5	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Constipation			
subjects affected / exposed	1 / 11 (9.09%)	7 / 26 (26.92%)	
occurrences (all)	1	8	
Colitis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Ascites			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Aphthous ulcer			
subjects affected / exposed	1 / 11 (9.09%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Abdominal pain			
subjects affected / exposed	3 / 11 (27.27%)	7 / 26 (26.92%)	
occurrences (all)	3	7	
Diarrhoea			

subjects affected / exposed	7 / 11 (63.64%)	16 / 26 (61.54%)
occurrences (all)	20	51
Dry mouth		
subjects affected / exposed	3 / 11 (27.27%)	7 / 26 (26.92%)
occurrences (all)	3	10
Dyspepsia		
subjects affected / exposed	1 / 11 (9.09%)	4 / 26 (15.38%)
occurrences (all)	1	5
Eructation		
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	2
Flatulence		
subjects affected / exposed	0 / 11 (0.00%)	2 / 26 (7.69%)
occurrences (all)	0	2
Gastrooesophageal reflux disease		
subjects affected / exposed	1 / 11 (9.09%)	1 / 26 (3.85%)
occurrences (all)	1	2
Haematochezia		
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	1
Haemorrhoids		
subjects affected / exposed	1 / 11 (9.09%)	1 / 26 (3.85%)
occurrences (all)	1	1
Inguinal hernia		
subjects affected / exposed	1 / 11 (9.09%)	0 / 26 (0.00%)
occurrences (all)	1	0
Rectal haemorrhage		
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	1
Oral pain		
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	1
Oral lichen planus		
subjects affected / exposed	1 / 11 (9.09%)	0 / 26 (0.00%)
occurrences (all)	3	0
Nausea		

subjects affected / exposed	3 / 11 (27.27%)	10 / 26 (38.46%)	
occurrences (all)	7	15	
Stomatitis			
subjects affected / exposed	1 / 11 (9.09%)	2 / 26 (7.69%)	
occurrences (all)	1	4	
Anal erythema			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Tongue erosion			
subjects affected / exposed	1 / 11 (9.09%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Toothache			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	2 / 11 (18.18%)	7 / 26 (26.92%)	
occurrences (all)	6	7	
Rectal discharge			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Abdominal hernia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Hepatobiliary disorders			
Hepatic function abnormal			
subjects affected / exposed	1 / 11 (9.09%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Hepatitis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Hyperbilirubinaemia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 26 (0.00%)	
occurrences (all)	3	0	
Hypertransaminasaemia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 26 (0.00%)	
occurrences (all)	2	0	

Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 11 (0.00%)	5 / 26 (19.23%)	
occurrences (all)	0	7	
Nail disorder			
subjects affected / exposed	1 / 11 (9.09%)	3 / 26 (11.54%)	
occurrences (all)	1	3	
Nail discolouration			
subjects affected / exposed	0 / 11 (0.00%)	2 / 26 (7.69%)	
occurrences (all)	0	5	
Hyperkeratosis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Erythema			
subjects affected / exposed	1 / 11 (9.09%)	1 / 26 (3.85%)	
occurrences (all)	1	1	
Eczema			
subjects affected / exposed	1 / 11 (9.09%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Dry skin			
subjects affected / exposed	1 / 11 (9.09%)	5 / 26 (19.23%)	
occurrences (all)	1	7	
Nail dystrophy			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	7	
Decubitus ulcer			
subjects affected / exposed	1 / 11 (9.09%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 11 (0.00%)	4 / 26 (15.38%)	
occurrences (all)	0	14	
Palmar erythema			
subjects affected / exposed	1 / 11 (9.09%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Onycholysis			

subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	3
Nail hypertrophy		
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	1
Pruritus		
subjects affected / exposed	1 / 11 (9.09%)	5 / 26 (19.23%)
occurrences (all)	2	5
Rash		
subjects affected / exposed	2 / 11 (18.18%)	5 / 26 (19.23%)
occurrences (all)	10	8
Psoriasis		
subjects affected / exposed	1 / 11 (9.09%)	0 / 26 (0.00%)
occurrences (all)	1	0
Rash macular		
subjects affected / exposed	1 / 11 (9.09%)	0 / 26 (0.00%)
occurrences (all)	5	0
Rash papular		
subjects affected / exposed	1 / 11 (9.09%)	0 / 26 (0.00%)
occurrences (all)	1	0
Rash pruritic		
subjects affected / exposed	1 / 11 (9.09%)	0 / 26 (0.00%)
occurrences (all)	1	0
Seborrhoeic dermatitis		
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	1
Skin exfoliation		
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	1
Skin lesion		
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	1
Xeroderma		
subjects affected / exposed	1 / 11 (9.09%)	0 / 26 (0.00%)
occurrences (all)	1	0
Onychomadesis		

subjects affected / exposed	0 / 11 (0.00%)	4 / 26 (15.38%)	
occurrences (all)	0	12	
Diabetic foot			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Nail bed inflammation			
subjects affected / exposed	1 / 11 (9.09%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	2 / 11 (18.18%)	4 / 26 (15.38%)	
occurrences (all)	2	6	
Urinary retention			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	3	
Renal pain			
subjects affected / exposed	1 / 11 (9.09%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Renal failure			
subjects affected / exposed	0 / 11 (0.00%)	2 / 26 (7.69%)	
occurrences (all)	0	2	
Hydronephrosis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Nocturia			
subjects affected / exposed	0 / 11 (0.00%)	2 / 26 (7.69%)	
occurrences (all)	0	2	
Pollakiuria			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Proteinuria			
subjects affected / exposed	1 / 11 (9.09%)	2 / 26 (7.69%)	
occurrences (all)	1	3	
Leukocyturia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	2	

Renal impairment subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 26 (3.85%) 1	
Endocrine disorders			
Adrenal insufficiency subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 26 (3.85%) 1	
Hypothyroidism subjects affected / exposed occurrences (all)	2 / 11 (18.18%) 2	2 / 26 (7.69%) 2	
Musculoskeletal and connective tissue disorders			
Joint swelling subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	2 / 26 (7.69%) 2	
Groin pain subjects affected / exposed occurrences (all)	2 / 11 (18.18%) 2	1 / 26 (3.85%) 1	
Flank pain subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	2 / 26 (7.69%) 2	
Bone pain subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 26 (3.85%) 1	
Back pain subjects affected / exposed occurrences (all)	4 / 11 (36.36%) 5	6 / 26 (23.08%) 6	
Arthralgia subjects affected / exposed occurrences (all)	3 / 11 (27.27%) 4	6 / 26 (23.08%) 14	
Muscle spasms subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	2 / 26 (7.69%) 4	
Musculoskeletal pain subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	0 / 26 (0.00%) 0	
Spinal pain			

subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Tendon pain			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Rotator cuff syndrome			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	2	
Pain in jaw			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Neck pain			
subjects affected / exposed	1 / 11 (9.09%)	3 / 26 (11.54%)	
occurrences (all)	1	3	
Myalgia			
subjects affected / exposed	1 / 11 (9.09%)	2 / 26 (7.69%)	
occurrences (all)	2	3	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Atypical pneumonia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Conjunctivitis			
subjects affected / exposed	1 / 11 (9.09%)	2 / 26 (7.69%)	
occurrences (all)	2	2	
Cystitis			
subjects affected / exposed	1 / 11 (9.09%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Diverticulitis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	

Fungal skin infection		
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	1
Herpes simplex		
subjects affected / exposed	1 / 11 (9.09%)	0 / 26 (0.00%)
occurrences (all)	1	0
Influenza		
subjects affected / exposed	1 / 11 (9.09%)	1 / 26 (3.85%)
occurrences (all)	1	2
Oesophageal candidiasis		
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	1
Onychomycosis		
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	2
Oral candidiasis		
subjects affected / exposed	0 / 11 (0.00%)	4 / 26 (15.38%)
occurrences (all)	0	5
Paronychia		
subjects affected / exposed	1 / 11 (9.09%)	0 / 26 (0.00%)
occurrences (all)	1	0
Escherichia urinary tract infection		
subjects affected / exposed	1 / 11 (9.09%)	0 / 26 (0.00%)
occurrences (all)	1	0
Urinary tract infection		
subjects affected / exposed	4 / 11 (36.36%)	9 / 26 (34.62%)
occurrences (all)	8	29
Pyelonephritis		
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	1
Tooth abscess		
subjects affected / exposed	0 / 11 (0.00%)	2 / 26 (7.69%)
occurrences (all)	0	2
Upper respiratory tract infection		
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	1

Anorectal infection subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 26 (3.85%) 1	
Respiratory tract infection subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	1 / 26 (3.85%) 1	
Herpes dermatitis subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	1 / 26 (3.85%) 1	
Device related infection subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 26 (3.85%) 1	
Oral herpes subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 3	0 / 26 (0.00%) 0	
Klebsiella urinary tract infection subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	0 / 26 (0.00%) 0	
COVID-19 subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 2	2 / 26 (7.69%) 2	
Candida infection subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 26 (3.85%) 1	
Gastrointestinal viral infection subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	0 / 26 (0.00%) 0	
Metabolism and nutrition disorders			
Hypertriglyceridaemia subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	0 / 26 (0.00%) 0	
Hyperphosphataemia subjects affected / exposed occurrences (all)	4 / 11 (36.36%) 5	15 / 26 (57.69%) 45	
Hyperkalaemia			

subjects affected / exposed	0 / 11 (0.00%)	4 / 26 (15.38%)
occurrences (all)	0	4
Hyperglycaemia		
subjects affected / exposed	2 / 11 (18.18%)	1 / 26 (3.85%)
occurrences (all)	2	1
Hypercholesterolaemia		
subjects affected / exposed	1 / 11 (9.09%)	0 / 26 (0.00%)
occurrences (all)	1	0
Hypercalcaemia		
subjects affected / exposed	1 / 11 (9.09%)	3 / 26 (11.54%)
occurrences (all)	1	5
Dehydration		
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	1
Hypoalbuminaemia		
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	2
Hypocalcaemia		
subjects affected / exposed	0 / 11 (0.00%)	2 / 26 (7.69%)
occurrences (all)	0	2
Hypomagnesaemia		
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	1
Hyperlipasaemia		
subjects affected / exposed	1 / 11 (9.09%)	1 / 26 (3.85%)
occurrences (all)	6	1
Hypercreatininaemia		
subjects affected / exposed	1 / 11 (9.09%)	1 / 26 (3.85%)
occurrences (all)	1	2
Decreased appetite		
subjects affected / exposed	3 / 11 (27.27%)	8 / 26 (30.77%)
occurrences (all)	7	12
Metabolic acidosis		
subjects affected / exposed	0 / 11 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	1
Hypophosphataemia		

subjects affected / exposed	1 / 11 (9.09%)	2 / 26 (7.69%)	
occurrences (all)	1	15	
Hyponatraemia			
subjects affected / exposed	0 / 11 (0.00%)	2 / 26 (7.69%)	
occurrences (all)	0	5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 December 2018	<ul style="list-style-type: none">- Immune-related nephritis was added as new identified risk for atezolizumab- Management guideline of rogaratinib-induced hyperphosphatemia was updated.- The option of transferring patients to a roll-over study was included.- Wording was clarified for the tumor biopsy procedure for biomarker testing.
10 February 2021	<ul style="list-style-type: none">- Immune-related myositis and severe cutaneous adverse reactions were added as new identified risks for atezolizumab together with respective management guidelines .- The option of continuing post-study therapy in any other form of continued study drug supply with no cost to the patient was included.
04 October 2021	<ul style="list-style-type: none">- After primary completion, study procedures were reduced to decrease burden to patients and sites- The updated schedule of events is intended to mimic standard of care- Immune-related myositis and severe cutaneous adverse reactions were added as new identified risks for atezolizumab- After primary completion, pregnancy tests were no longer required because there were no female patients of childbearing potential left in the study- The interval for tumor assessments was prolonged during the treatment and active follow-up periods- The decision to not conduct Part B of the study was communicated on 25 OCT 2021 as part of the submission of this amendment to ethical committees/health authorities, and sites, and duly implemented under this amendment.
09 November 2022	<ul style="list-style-type: none">- Immune-mediated pericardial disorders was added as new identified risk -- Management guidelines for atezolizumab-specific adverse events were revised -- active and long-term follow-ups were concluded.
23 May 2023	<ul style="list-style-type: none">- Immune-mediated myelitis and immune-mediated facial paresis were added as new identified risks for atezolizumab -- Management guidelines were revised for atezolizumab-specific adverse events.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/36240478>

<http://www.ncbi.nlm.nih.gov/pubmed/39298147>