Clinical trial results:
An open-label multi-cohort Phase 1b/2 study of derazantinib and atezolizumab in patients with urothelial cancer expressing activating molecular FGFR aberrations (FIDES-02)

Summary

EudraCT number	2019-000359-15
Trial protocol	ES IT
Global end of trial date	04 October 2022

Results information

Result version number	v2 (current)
This version publication date	22 May 2024
First version publication date	07 October 2023
Version creation reason	• New data added to full data set There are no updates. This study has been opened by error

Trial information

Trial identification

Sponsor protocol code	DZB-CS-201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04045613
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Basilea Pharmaceutica International Ltd, Allschwil
Sponsor organisation address	Hegenheimermattweg 167b, Allschwil, Switzerland, 4123
Public contact	Manuel Haeckl, Basilea Pharmaceutica International Ltd, Allschwil, +41 76 302 53 10 , medical.information@basilea.com
Scientific contact	Study Director, Basilea Pharmaceutica International Ltd, Allschwil, +41 76 302 53 10 , manuel.haeckl@basilea.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	02 November 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 October 2022
Global end of trial reached?	Yes
Global end of trial date	04 October 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary objectives for Substudies 1, 3, 4 and 5

To evaluate the objective response rate (ORR) of derazantinib monotherapy (in Substudies 1 and 5, and Cohort 4a of Substudy 4) and of derazantinib-atezolizumab in combination (in Substudy 3 and Cohort 4b of Substudy 4) in patients with metastatic urothelial cancer (mUC) expressing fibroblast growth factor receptor genomic alterations (FGFR1–3 GAs).

Primary objective for Substudy 2
•To determine the recommended Phase 2 dose (RP2D) of derazantinib in combination with atezolizumab.

Protection of trial subjects:

The study was conducted according to the ethical principles that have their origins in the World Medical Association's Declaration of Helsinki, the International Council for Harmonisation (ICH) E6 Good Clinical Practice, and all applicable national and local laws and regulations for the conduct of clinical research.

Background therapy:

In this Phase 1b/2 study (FIDES-02), the FGFR inhibitor derazantinib, as monotherapy and in combination with the immune-checkpoint inhibitor (ICI) atezolizumab was evaluated in the treatment of patients with unresectable or mUC and FGFR1, FGFR2, or FGFR3 mutations and rearrangements/fusions. The addition of an FGFR inhibitor to an ICI was based on the assumption of an enhanced efficacy of checkpoint inhibition through immunomodulatory effects (CSF1R-inhibition by the kinase inhibitor derazantinib) on the tumor microenvironment.

Evidence for comparator:

Not applicable

Actual start date of recruitment	02 August 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 6
Country: Number of subjects enrolled	Spain: 16
Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	Switzerland: 3
Country: Number of subjects enrolled	United States: 15
Country: Number of subjects enrolled	Australia: 1
Country: Number of subjects enrolled	Korea, Republic of: 9
Country: Number of subjects enrolled	France: 15

Country: Number of subjects enrolled	Germany: 12
Country: Number of subjects enrolled	Hungary: 2
Country: Number of subjects enrolled	Italy: 8
Worldwide total number of subjects	95
EEA total number of subjects	59

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)	42
From 65 to 84 years	51
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

A total of 95 patients entered the study and were assigned treatment. All patients assigned treatment were dispensed study drug and received at least one dose of derazantinib or atezolizumab

Pre-assignment

Screening details:

From August, 2019 to September, 2022, 321 patients underwent molecular screening and 131 underwent clinical screening.

Period 1

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

Blinding implementation details:

Not applicable

Arms

Are arms mutually exclusive?	Yes
Arm title	Substudy 1: Derazantinib

Arm description:

Derazantinib 300 mg once daily monotherapy
Derazantinib was administered orally at a dose of 300 mg once daily

Arm type	Experimental
Investigational medicinal product name	Derazantinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Derazantinib was supplied as 100 mg immediate-release powder-filled capsules for oral administration.

Arm title	Substudy 2 (Dose-Level 1): Derazantinib + atezolizumab

Arm description:

Derazantinib 200 mg once daily + atezolizumab 1200 mg
Derazantinib was administered orally at a dose of 200 mg once daily in combination with atezolizumab 1200 mg every 3 weeks

Arm type	Experimental
Investigational medicinal product name	Derazantinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Derazantinib was supplied as 100 mg immediate-release powder-filled capsules for oral administration.

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

Dosage and administration details:

Atezolizumab is an authorised medicinal product which was supplied as 1200 mg/20 mL concentrate solution for intravenous (IV) infusion. The atezolizumab dose for all patients receiving the combination treatment was 1200 mg every 3 weeks

Arm title	Substudy 2 (Dose-Level 2): Derazantinib + atezolizumab

Arm description:

Derazantinib 300 mg once daily + atezolizumab 1200 mg
Derazantinib was administered orally at a dose of 300 mg once daily in combination with atezolizumab 1200 mg every 3 weeks

Arm type	Experimental
Investigational medicinal product name	Derazantinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Derazantinib was supplied as 100 mg immediate-release powder-filled capsules for oral administration.

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

Dosage and administration details:

Atezolizumab is an authorised medicinal product which was supplied as 1200 mg/20 mL concentrate solution for intravenous (IV) infusion. The atezolizumab dose for all patients receiving the combination treatment was 1200 mg every 3 weeks

Arm title	Substudy 3: Derazantinib + atezolizumab

Arm description:

Derazantinib 200 mg twice daily + atezolizumab 1200 mg
Derazantinib was administered orally at a dose of 200 mg twice daily in combination with atezolizumab 1200 mg every 3 weeks

Arm type	Experimental
Investigational medicinal product name	Derazantinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Derazantinib was supplied as 100 mg immediate-release powder-filled capsules for oral administration.

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

Dosage and administration details:

Atezolizumab is an authorised medicinal product which was supplied as 1200 mg/20 mL concentrate solution for intravenous (IV) infusion. The atezolizumab dose for all patients receiving the combination treatment was 1200 mg every 3 weeks

Arm title	Substudy 4 (Cohort 4a): Derazantinib

Arm description:

Derazantinib 300 mg once daily monotherapy (QD)
Derazantinib was administered orally at a dose of 300 mg once daily

Arm type	Experimental
Investigational medicinal product name	Derazantinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Derazantinib was supplied as 100 mg immediate-release powder-filled capsules for oral administration.

Arm title	Substudy 4 (Cohort 4b): Derazantinib + atezolizumab

Arm description:

Derazantinib 300 mg once daily + atezolizumab 1200 mg
Derazantinib was administered orally at a dose of 300 mg once daily in combination with atezolizumab 1200 mg every 3 weeks

Arm type	Experimental
Investigational medicinal product name	Derazantinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Derazantinib was supplied as 100 mg immediate-release powder-filled capsules for oral administration.

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

Dosage and administration details:

Atezolizumab is an authorised medicinal product which was supplied as 1200 mg/20 mL concentrate solution for intravenous (IV) infusion. The atezolizumab dose for all patients receiving the combination treatment was 1200 mg every 3 weeks

Arm title	Substudy 5: Derazantinib

Arm description:

Derazantinib 200 mg twice daily monotherapy
Derazantinib was administered orally at a dose of 200 mg twice daily

Arm type	Experimental
Investigational medicinal product name	Derazantinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Derazantinib was supplied as 100 mg immediate-release powder-filled capsules for oral administration.

Number of subjects in period 1	Substudy 1: Derazantinib	Substudy 2 (Dose-Level 1): Derazantinib + atezolizumab	Substudy 2 (Dose-Level 2): Derazantinib + atezolizumab
Started	32	14	12
Completed	0	0	0
Not completed	32	14	12
Adverse event, serious fatal	3	-	-
Physician decision	2	-	-
Consent withdrawn by subject	-	5	-
Adverse event, non-fatal	2	2	1
Other reasons	-	1	-
Progressive disease: Radiological progression	24	6	8
Progressive disease: Clinical progression	1	-	3

Number of subjects in period 1	Substudy 3: Derazantinib + atezolizumab	Substudy 4 (Cohort 4a): Derazantinib	Substudy 4 (Cohort 4b): Derazantinib + atezolizumab
Started	2	8	10
Completed	0	0	0
Not completed	2	8	10
Adverse event, serious fatal	-	-	-
Physician decision	-	1	-
Consent withdrawn by subject	-	-	1
Adverse event, non-fatal	1	-	-
Other reasons	-	-	-
Progressive disease: Radiological progression	-	6	6
Progressive disease: Clinical progression	1	1	3

Number of subjects in period 1	Substudy 5: Derazantinib
Started	17
Completed	0
Not completed	17
Adverse event, serious fatal	1
Physician decision	-
Consent withdrawn by subject	-
Adverse event, non-fatal	1
Other reasons	1
Progressive disease: Radiological progression	11
Progressive disease: Clinical progression	3

Baseline characteristics

Reporting groups	
Reporting group title	Substudy 1: Derazantinib
Reporting group description:	
Derazantinib 300 mg once daily monotherapy Derazantinib was administered orally at a dose of 300 mg once daily	

Reporting group title	Substudy 2 (Dose-Level 1): Derazantinib + atezolizumab
Reporting group description:	
Derazantinib 200 mg once daily + atezolizumab 1200 mg Derazantinib was administered orally at a dose of 200 mg once daily in combination with atezolizumab 1200 mg every 3 weeks	

Reporting group title	Substudy 2 (Dose-Level 2): Derazantinib + atezolizumab
Reporting group description:	
Derazantinib 300 mg once daily + atezolizumab 1200 mg Derazantinib was administered orally at a dose of 300 mg once daily in combination with atezolizumab 1200 mg every 3 weeks	

Reporting group title	Substudy 3: Derazantinib + atezolizumab
Reporting group description:	
Derazantinib 200 mg twice daily + atezolizumab 1200 mg Derazantinib was administered orally at a dose of 200 mg twice daily in combination with atezolizumab 1200 mg every 3 weeks	

Reporting group title	Substudy 4 (Cohort 4a): Derazantinib
Reporting group description:	
Derazantinib 300 mg once daily monotherapy (QD) Derazantinib was administered orally at a dose of 300 mg once daily	

Reporting group title	Substudy 4 (Cohort 4b): Derazantinib + atezolizumab
Reporting group description:	
Derazantinib 300 mg once daily + atezolizumab 1200 mg Derazantinib was administered orally at a dose of 300 mg once daily in combination with atezolizumab 1200 mg every 3 weeks	

Reporting group title	Substudy 5: Derazantinib
Reporting group description:	
Derazantinib 200 mg twice daily monotherapy Derazantinib was administered orally at a dose of 200 mg twice daily	

Reporting group values	Substudy 1: Derazantinib	Substudy 2 (Dose-Level 1): Derazantinib + atezolizumab	Substudy 2 (Dose-Level 2): Derazantinib + atezolizumab
Number of subjects	32	14	12
Age categorical Units: Subjects			
Adults (18-64 years)	7	5	11
From 65-84 years	23	9	1
85 years and over	2	0	0

Gender categorical Units: Subjects			
Female	11	4	8
Male	21	10	4
Site of primary tumor at diagnosis Units: Subjects			
Bladder	19	2	1
Renal pelvis	9	0	0
Ureter	3	0	1
Missing	1	0	0
Other site of primary tumor	0	12	10
Eastern Cooperative Oncology Group (ECOG) Performance Status (PS)			
Measure Description: The ECOG PS scale indicates increasing levels of disability, with 0 indicating fully active; 1, restricted in strenuous activity; 2, restricted in work activity but ambulatory and capable of self-care			
Units: Subjects			
Scale 0	14	4	2
Scale 1	15	8	9
Scale 2	3	2	1
Number of previous anti-cancer treatments Units: Subjects			
One treatment	5	4	3
Two treatments	9	4	4
Three or more treatments	18	6	5
No treatment	0	0	0
Prior immune checkpoint inhibitor treatment Units: Subjects			
Prior immune checkpoint inhibitor treatment	26	1	4
No prior immune checkpoint inhibitor treatment	6	13	8
Reason previous therapy ended Units: Subjects			
Treatment completed	4	2	0
Progressive disease	23	10	12
Toxicity	1	0	0
Other	2	1	0
Unknown	2	1	0
No previous therapy	0	0	0
Race Units: Subjects			
Asian	4	0	2
Native Hawaiian or Other Pacific Islander	1	0	0
Black or African American	0	1	0
White	18	12	5
More than one race	0	0	0
Unknown or Not Reported	9	1	5

Reporting group values	Substudy 3: Derazantinib + atezolizumab	Substudy 4 (Cohort 4a): Derazantinib	Substudy 4 (Cohort 4b): Derazantinib + atezolizumab

Number of subjects	2	8	10
Age categorical Units: Subjects			
Adults (18-64 years)	1	4	3
From 65-84 years	1	4	7
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	1	4	6
Male	1	4	4
Site of primary tumor at diagnosis Units: Subjects			
Bladder	2	7	7
Renal pelvis	0	0	2
Ureter	0	1	1
Missing	0	0	0
Other site of primary tumor	0	0	0
Eastern Cooperative Oncology Group (ECOG) Performance Status (PS)			
Measure Description: The ECOG PS scale indicates increasing levels of disability, with 0 indicating fully active; 1, restricted in strenuous activity; 2, restricted in work activity but ambulatory and capable of self-care			
Units: Subjects			
Scale 0	1	0	2
Scale 1	1	6	7
Scale 2	0	2	1
Number of previous anti-cancer treatments Units: Subjects			
One treatment	0	0	1
Two treatments	0	0	0
Three or more treatments	1	8	9
No treatment	1	0	0
Prior immune checkpoint inhibitor treatment Units: Subjects			
Prior immune checkpoint inhibitor treatment	0	8	10
No prior immune checkpoint inhibitor treatment	2	0	0
Reason previous therapy ended Units: Subjects			
Treatment completed	0	1	1
Progressive disease	0	6	8
Toxicity	1	1	0
Other	0	0	0
Unknown	0	0	1
No previous therapy	1	0	0
Race Units: Subjects			
Asian	0	2	1
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	1	0

White	2	2	7
More than one race	0	0	0
Unknown or Not Reported	0	3	2

Reporting group values	Substudy 5: Derazantinib	Total	
Number of subjects	17	95	
Age categorical Units: Subjects			
Adults (18-64 years)	11	42	
From 65-84 years	6	51	
85 years and over	0	2	
Gender categorical Units: Subjects			
Female	4	38	
Male	13	57	
Site of primary tumor at diagnosis Units: Subjects			
Bladder	11	49	
Renal pelvis	4	15	
Ureter	2	8	
Missing	0	1	
Other site of primary tumor	0	22	
Eastern Cooperative Oncology Group (ECOG) Performance Status (PS)			
Measure Description: The ECOG PS scale indicates increasing levels of disability, with 0 indicating fully active; 1, restricted in strenuous activity; 2, restricted in work activity but ambulatory and capable of self-care			
Units: Subjects			
Scale 0	8	31	
Scale 1	9	55	
Scale 2	0	9	
Number of previous anti-cancer treatments Units: Subjects			
One treatment	7	20	
Two treatments	6	23	
Three or more treatments	4	51	
No treatment	0	1	
Prior immune checkpoint inhibitor treatment Units: Subjects			
Prior immune checkpoint inhibitor treatment	12	61	
No prior immune checkpoint inhibitor treatment	5	34	
Reason previous therapy ended Units: Subjects			
Treatment completed	2	10	
Progressive disease	12	71	
Toxicity	0	3	
Other	2	5	
Unknown	1	5	
No previous therapy	0	1	

Race Units: Subjects			
Asian	0	9	
Native Hawaiian or Other Pacific Islander	0	1	
Black or African American	0	2	
White	12	58	
More than one race	1	1	
Unknown or Not Reported	4	24	

End points

End points reporting groups

Reporting group title	Substudy 1: Derazantinib
Reporting group description:	
Derazantinib 300 mg once daily monotherapy Derazantinib was administered orally at a dose of 300 mg once daily	

Reporting group title	Substudy 2 (Dose-Level 1): Derazantinib + atezolizumab
Reporting group description:	
Derazantinib 200 mg once daily + atezolizumab 1200 mg Derazantinib was administered orally at a dose of 200 mg once daily in combination with atezolizumab 1200 mg every 3 weeks	

Reporting group title	Substudy 2 (Dose-Level 2): Derazantinib + atezolizumab
Reporting group description:	
Derazantinib 300 mg once daily + atezolizumab 1200 mg Derazantinib was administered orally at a dose of 300 mg once daily in combination with atezolizumab 1200 mg every 3 weeks	

Reporting group title	Substudy 3: Derazantinib + atezolizumab
Reporting group description:	
Derazantinib 200 mg twice daily + atezolizumab 1200 mg Derazantinib was administered orally at a dose of 200 mg twice daily in combination with atezolizumab 1200 mg every 3 weeks	

Reporting group title	Substudy 4 (Cohort 4a): Derazantinib
Reporting group description:	
Derazantinib 300 mg once daily monotherapy (QD) Derazantinib was administered orally at a dose of 300 mg once daily	

Reporting group title	Substudy 4 (Cohort 4b): Derazantinib + atezolizumab
Reporting group description:	
Derazantinib 300 mg once daily + atezolizumab 1200 mg Derazantinib was administered orally at a dose of 300 mg once daily in combination with atezolizumab 1200 mg every 3 weeks	

Reporting group title	Substudy 5: Derazantinib
Reporting group description:	
Derazantinib 200 mg twice daily monotherapy Derazantinib was administered orally at a dose of 200 mg twice daily	

Subject analysis set title	mITT Population
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Efficacy analyses were performed using the modified Intent-to-Treat (mITT) population: all patients who received at least one dose of derazantinib or atezolizumab, and had at least one post-baseline imaging assessment in accordance with RECIST 1.1, or documented clinical progression	

Subject analysis set title	The safety/ITT population
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety/intent-to-treat (ITT) population consisted of all patients who received at least one dose of derazantinib or atezolizumab	

Subject analysis set title	Substudy 2 Combined (Dose-Level 1 and 2) ITT
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients with solid tumors were treated with derazantinib 200 mg or 300 mg once daily in combination	

with atezolizumab 1200 mg given every 3 weeks as IV infusion

Subject analysis set title	MTD-determining population
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The maximum tolerated dose (MTD)-determining population included all patients enrolled in the MTD Part of each dose level who met the following minimum criteria during the DLT period:

- received at least one dose of derazantinib and atezolizumab and has experienced a DLT;
- received ≥ 90% of the derazantinib and atezolizumab dose, respectively, in Cycle 1 and did not experience a DLT, have been observed for ≥ 21 days following the first dose, and have been evaluated for safety

Subject analysis set title	Substudy 2 Combined (Dose-Level 1 and 2) mITT
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Efficacy analyses were performed using the modified Intent-to-Treat (mITT) population: all patients who received at least one dose of derazantinib or atezolizumab, and had at least one post-baseline imaging assessment in accordance with RECIST 1.1, or documented clinical progression

Primary: Objective Response Rate (ORR) Based on RECIST 1.1 (Substudies 1,3,4 and 5)

End point title	Objective Response Rate (ORR) Based on RECIST 1.1 (Substudies 1,3,4 and 5)[1][2]

End point description:

ORR was defined as the proportion of patients who achieved a confirmed clinical response (CR) or partial response (PR) by blinded investigator central review (BICR) using the internationally recognized criteria for the radiological assessment in tumor response of solid tumors (RECIST) Version 1.1

End point type	Primary

End point timeframe:

From first dose up to 2 years

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: This study was not powered for formal statistical analysis

[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: This study was not powered for formal statistical analysis

End point values	Substudy 1: Derazantinib	Substudy 3: Derazantinib + atezolizumab	Substudy 4 (Cohort 4a): Derazantinib	Substudy 4 (Cohort 4b): Derazantinib + atezolizumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	32	2	7	10
Units: Proportion of patients				
number (confidence interval 95%)				
ORR	9.4 (2.0 to 25.0)	0.0 (0.0 to 84.2)	14.3 (0.4 to 57.9)	0.0 (0.0 to 30.8)

End point values	Substudy 5: Derazantinib	mITT Population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	17	91		
Units: Proportion of patients				
number (confidence interval 95%)				

ORR	5.9 (0.1 to 28.7)	7.7 (3.1 to 15.2)		

Statistical analyses

No statistical analyses for this end point

Primary: Recommended Phase 2 Dose (RP2D) of Derazantinib-atezolizumab in Combination Based on DLT Criteria, Safety and Efficacy Data (Substudy 2)

End point title	Recommended Phase 2 Dose (RP2D) of Derazantinib-atezolizumab in Combination Based on DLT Criteria, Safety and Efficacy Data (Substudy 2)[3]

End point description:

Patients with solid tumors were treated with derazantinib 200 mg or 300 mg once daily in combination with atezolizumab 1200 mg given every 3 weeks as IV infusion

End point type	Primary

End point timeframe:

From first dose up to 2 years

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: This study was not powered for formal statistical analysis

End point values	Substudy 2 Combined (Dose-Level 1 and 2) ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	26			
Units: mg				
number (not applicable)				
Recommended Phase 2 Dose (RP2D)	300			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Patients With Dose-limiting Toxicities (DLTs) in Substudy 2

End point title	Number of Patients With Dose-limiting Toxicities (DLTs) in Substudy 2[4][5]

End point description:

In Substudy 2, the primary endpoint was the number of patients with Dose-limiting Toxicities (DLTs=. A DLT was defined as a clinically-significant adverse event (AE) or abnormal laboratory value assessed as unrelated to disease progression, intercurrent illness, or concomitant medications. Any DLT had to be a toxicity considered at least possibly related to derazantinib or the combination of derazantinib and atezolizumab

End point type	Primary

End point timeframe:

From first dose up to 2 years

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: This study was not powered for formal statistical analysis

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This study was not powered for formal statistical analysis

End point values	Substudy 2 (Dose-Level 1): Derazantinib + atezolizumab	Substudy 2 (Dose-Level 2): Derazantinib + atezolizumab	MTD-determining population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	6	5	11	
Units: Subjects				
Number of Patients With DLTs	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: ORR Based on RECIST 1.1 (Substudy 2)

End point title	ORR Based on RECIST 1.1 (Substudy 2)[6]

End point description:

ORR was defined as the proportion of patients who achieved a confirmed clinical response (CR) or partial response (PR) by blinded investigator central review (BICR) using the internationally recognized criteria for the radiological assessment in tumor response of solid tumors (RECIST) Version 1.1

End point type	Secondary

End point timeframe:

From first dose up to 2 years

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: This study was not powered for formal statistical analysis

End point values	Substudy 2 (Dose-Level 1): Derazantinib + atezolizumab	Substudy 2 (Dose-Level 2): Derazantinib + atezolizumab	Substudy 2 Combined (Dose-Level 1 and 2) mITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	11	12	23	
Units: Percentage of participants				
number (confidence interval 95%)				
ORR Based on RECIST 1.1	0.0 (0.0 to 28.5)	16.7 (2.1 to 48.4)	8.7 (1.1 to 28.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival (PFS) by RECIST

End point title	Progression-free Survival (PFS) by RECIST

End point description:

PFS was calculated as the time from cohort assignment until disease progression as assessed by BICR, or death from any cause, whichever came first

End point type	Secondary

End point timeframe:

From first dose up to 2 years

End point values	Substudy 1: Derazantinib	Substudy 2 (Dose-Level 1): Derazantinib + atezolizumab	Substudy 2 (Dose-Level 2): Derazantinib + atezolizumab	Substudy 3: Derazantinib + atezolizumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	32	11	12	2
Units: Months				
median (confidence interval 95%)				
PFS	2.0 (1.9 to 2.1)	2.0 (1.5 to 2.1)	4.2 (0.7 to 10.8)	2.5 (0.6 to 4.4)

End point values	Substudy 4 (Cohort 4a): Derazantinib	Substudy 4 (Cohort 4b): Derazantinib + atezolizumab	Substudy 5: Derazantinib	mITT Population
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	7	10	17	91
Units: Months				
median (confidence interval 95%)				
PFS	2.0 (0.6 to 4.7)	1.9 (0.2 to 4.1)	2.1 (2.1 to 7.0)	2.1 (2.0 to 2.1)

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Patients With at Least Grade 3 Adverse Events (AEs)

End point title	Number of Patients With at Least Grade 3 Adverse Events (AEs)

End point description:

Common Terminology Criteria for Adverse Events (CTCAE) displayed by increasing severity grades 3 to 5 (CTCAE grade 3/4/5)

End point type	Secondary

End point timeframe:

From first dose and until 90 days following the last dose

End point values	Substudy 1: Derazantinib	Substudy 2 (Dose-Level 1): Derazantinib + atezolizumab	Substudy 2 (Dose-Level 2): Derazantinib + atezolizumab	Substudy 3: Derazantinib + atezolizumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	32	14	12	2
Units: Number of patients				
Number of patients with only unrelated CTCAE Grade	11	5	7	0
Number of patients with related CTCAE Grade ≥3	11	3	3	2
Number of patients without CTCAE Grade ≥3	10	6	2	0

End point values	Substudy 4 (Cohort 4a): Derazantinib	Substudy 4 (Cohort 4b): Derazantinib + atezolizumab	Substudy 5: Derazantinib	The safety/ITT population
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	8	10	17	95
Units: Number of patients				
Number of patients with only unrelated CTCAE Grade	2	5	3	33
Number of patients with related CTCAE Grade ≥3	2	4	9	34
Number of patients without CTCAE Grade ≥3	4	1	5	28

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From first administration of study medication up to 90 days after the last administration	
Adverse event reporting additional description:	
Treatment-emergent adverse events and serious adverse events	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups	
Reporting group title	SS2 - DZB 200 mg + AZB 1200 mg
Reporting group description:	
SS2 - DZB 200 mg + AZB 1200 mg	
Reporting group title	SS3 - DZB 200 mg BID + AZB 1200 mg
Reporting group description:	
SS3 - DZB 200 mg BID + AZB 1200 mg	
Reporting group title	SS5 - DZB 200 mg BID
Reporting group description:	
SS5 - DZB 200 mg BID	
Reporting group title	SS4 - DZB 300 mg
Reporting group description:	
SS4 - DZB 300 mg	
Reporting group title	SS4 - DZB 300 mg + AZB 1200 mg
Reporting group description:	
SS4 - DZB 300 mg + AZB 1200 mg	
Reporting group title	SS1 - DZB 300 mg
Reporting group description:	
SS1 - DZB 300 mg	
Reporting group title	SS2 - DZB 300 mg + AZB 1200 mg
Reporting group description:	
SS2 - DZB 300 mg + AZB 1200 mg	

Serious adverse events	SS2 - DZB 200 mg + AZB 1200 mg	SS3 - DZB 200 mg BID + AZB 1200 mg	SS5 - DZB 200 mg BID
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 14 (28.57%)	1 / 2 (50.00%)	8 / 17 (47.06%)
number of deaths (all causes)	7	2	10
number of deaths resulting from adverse events	3	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			

subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	1 / 17 (5.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Embolism			
subjects affected / exposed	1 / 14 (7.14%)	0 / 2 (0.00%)	0 / 17 (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
Hypertension			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Venous thrombosis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	1 / 17 (5.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	2 / 17 (11.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypothermia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	1 / 17 (5.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disease progression			
subjects affected / exposed	2 / 14 (14.29%)	1 / 2 (50.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 1	0 / 0
Pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	1 / 17 (5.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vaginal haemorrhage			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	1 / 14 (7.14%)	0 / 2 (0.00%)	0 / 17 (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
Pneumonitis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 2 (50.00%)	0 / 17 (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
Pleural effusion			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	1 / 17 (5.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alanine aminotransferase increased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			

subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eastern Cooperative Oncology Group performance status worsened			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fracture			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	1 / 17 (5.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus bradycardia			

subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	1 / 17 (5.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric haemorrhage			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal perforation			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			

subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	1 / 17 (5.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	1 / 17 (5.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatic cytolysis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	1 / 17 (5.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	1 / 17 (5.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephritis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 2 (0.00%)	0 / 17 (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
Haematuria			
subjects affected / exposed	0 / 14 (0.00%)	1 / 2 (50.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Acute kidney injury			
subjects affected / exposed	1 / 14 (7.14%)	0 / 2 (0.00%)	0 / 17 (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
Endocrine disorders			
Hypercalcaemia of malignancy			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	1 / 17 (5.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Flank pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neck pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Endocarditis			

subjects affected / exposed	1 / 14 (7.14%)	0 / 2 (0.00%)	0 / 17 (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
Sepsis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 2 (0.00%)	0 / 17 (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
Oral fungal infection			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 2 (0.00%)	0 / 17 (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
Pyelonephritis acute			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	1 / 17 (5.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cachexia			

subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypocalcaemia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypervolaemia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 2 (0.00%)	0 / 17 (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
Hyponatraemia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 2 (50.00%)	1 / 17 (5.88%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	SS4 - DZB 300 mg	SS4 - DZB 300 mg + AZB 1200 mg	SS1 - DZB 300 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 8 (37.50%)	6 / 10 (60.00%)	17 / 32 (53.13%)
number of deaths (all causes)	4	7	25
number of deaths resulting from adverse events	0	4	8
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Embolism			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			

subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Venous thrombosis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypothermia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disease progression			
subjects affected / exposed	0 / 8 (0.00%)	4 / 10 (40.00%)	7 / 32 (21.88%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 4	0 / 7
Pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vaginal haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 32 (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, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 32 (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
Alanine aminotransferase increased			
subjects affected / exposed	0 / 8 (0.00%)	2 / 10 (20.00%)	0 / 32 (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
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 8 (0.00%)	2 / 10 (20.00%)	0 / 32 (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
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eastern Cooperative Oncology Group performance status worsened			

subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	2 / 32 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fracture			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 32 (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
Bradycardia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus bradycardia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 8 (12.50%)	1 / 10 (10.00%)	2 / 32 (6.25%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal perforation			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Nausea			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			

subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	3 / 32 (9.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatic cytolysis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephritis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute kidney injury			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	2 / 32 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Hypercalcaemia of malignancy			

subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Flank pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neck pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Endocarditis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Oral fungal infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 8 (12.50%)	1 / 10 (10.00%)	0 / 32 (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
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cachexia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 32 (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
Hypocalcaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypervolaemia			

subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	SS2 - DZB 300 mg + AZB 1200 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 12 (50.00%)		
number of deaths (all causes)	8		
number of deaths resulting from adverse events	3		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Embolism			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypertension			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Venous thrombosis			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Fatigue			

subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypothermia				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Disease progression				
subjects affected / exposed	3 / 12 (25.00%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 3			
Pain				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast disorders				
Pelvic pain				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vaginal haemorrhage				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Respiratory failure				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonitis				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Pleural effusion				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Investigations				
Blood creatinine increased				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Alanine aminotransferase increased				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Aspartate aminotransferase increased				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood creatine phosphokinase increased				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Eastern Cooperative Oncology Group performance status worsened				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Fall				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Fracture				

subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bradycardia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sinus bradycardia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastric haemorrhage			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Constipation			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intestinal obstruction			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal perforation			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Small intestinal obstruction			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatic cytolysis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nephritis			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haematuria			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Acute kidney injury			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Hypercalcaemia of malignancy			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Back pain			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Flank pain			

subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Neck pain				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal pain				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Endocarditis				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oral fungal infection				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis acute				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infection				

subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Hypercalcaemia				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cachexia				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypocalcaemia				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypervolaemia				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hyponatraemia				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	SS2 - DZB 200 mg + AZB 1200 mg	SS3 - DZB 200 mg BID + AZB 1200 mg	SS5 - DZB 200 mg BID
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 14 (100.00%)	2 / 2 (100.00%)	17 / 17 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 14 (7.14%)	0 / 2 (0.00%)	3 / 17 (17.65%)
occurrences (all)	1	0	3
Lymphoedema			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 14 (14.29%)	0 / 2 (0.00%)	5 / 17 (29.41%)
occurrences (all)	2	0	5
Fatigue			
subjects affected / exposed	5 / 14 (35.71%)	0 / 2 (0.00%)	6 / 17 (35.29%)
occurrences (all)	5	0	6
Mucosal inflammation			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Oedema			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Oedema peripheral			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Pain			
subjects affected / exposed	0 / 14 (0.00%)	1 / 2 (50.00%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Pyrexia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0

Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Cough			
subjects affected / exposed	2 / 14 (14.29%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences (all)	2	0	0
Productive cough			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 2 (50.00%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	3 / 17 (17.65%)
occurrences (all)	0	0	3
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 14 (7.14%)	1 / 2 (50.00%)	2 / 17 (11.76%)
occurrences (all)	2	1	2
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 14 (14.29%)	0 / 2 (0.00%)	4 / 17 (23.53%)
occurrences (all)	2	0	4
Amylase increased			
subjects affected / exposed	1 / 14 (7.14%)	1 / 2 (50.00%)	0 / 17 (0.00%)
occurrences (all)	1	1	0
Alanine aminotransferase increased			
subjects affected / exposed	2 / 14 (14.29%)	0 / 2 (0.00%)	5 / 17 (29.41%)
occurrences (all)	2	0	5
Blood lactate dehydrogenase increased			

subjects affected / exposed	1 / 14 (7.14%)	0 / 2 (0.00%)	1 / 17 (5.88%)
occurrences (all)	1	0	1
Platelet count decreased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Transaminases increased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	2 / 17 (11.76%)
occurrences (all)	0	0	2
Weight decreased			
subjects affected / exposed	2 / 14 (14.29%)	0 / 2 (0.00%)	2 / 17 (11.76%)
occurrences (all)	2	0	2
Lipase increased			
subjects affected / exposed	2 / 14 (14.29%)	1 / 2 (50.00%)	1 / 17 (5.88%)
occurrences (all)	2	1	1
Haemoglobin decreased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	3
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 14 (7.14%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
C-reactive protein increased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Blood thyroid stimulating hormone increased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Blood phosphorus increased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	2
Injury, poisoning and procedural complications			

Contusion			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Balance disorder			
subjects affected / exposed	1 / 14 (7.14%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Tremor			
subjects affected / exposed	1 / 14 (7.14%)	0 / 2 (0.00%)	1 / 17 (5.88%)
occurrences (all)	1	0	1
Dizziness			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Dysgeusia			
subjects affected / exposed	2 / 14 (14.29%)	0 / 2 (0.00%)	1 / 17 (5.88%)
occurrences (all)	2	0	1
Sciatica			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 14 (14.29%)	0 / 2 (0.00%)	1 / 17 (5.88%)
occurrences (all)	2	0	1
Lymphopenia			
subjects affected / exposed	2 / 14 (14.29%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences (all)	2	0	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 14 (7.14%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
Cataract			

subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Central serous chorioretinopathy			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Dry eye			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Keratitis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	2
Maculopathy			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Punctate keratitis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Vision blurred			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Visual acuity reduced			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	2 / 17 (11.76%)
occurrences (all)	0	0	2
Xerophthalmia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	6 / 14 (42.86%)	1 / 2 (50.00%)	5 / 17 (29.41%)
occurrences (all)	7	2	7
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 14 (7.14%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Gastritis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0

Dyspepsia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 2 (0.00%)	2 / 17 (11.76%)
occurrences (all)	1	0	2
Dry mouth			
subjects affected / exposed	1 / 14 (7.14%)	0 / 2 (0.00%)	2 / 17 (11.76%)
occurrences (all)	1	0	2
Diarrhoea			
subjects affected / exposed	4 / 14 (28.57%)	1 / 2 (50.00%)	5 / 17 (29.41%)
occurrences (all)	4	1	7
Constipation			
subjects affected / exposed	1 / 14 (7.14%)	1 / 2 (50.00%)	3 / 17 (17.65%)
occurrences (all)	1	2	3
Ascites			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Abdominal pain upper			
subjects affected / exposed	1 / 14 (7.14%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Abdominal pain			
subjects affected / exposed	1 / 14 (7.14%)	0 / 2 (0.00%)	1 / 17 (5.88%)
occurrences (all)	1	0	1
Abdominal distension			
subjects affected / exposed	1 / 14 (7.14%)	0 / 2 (0.00%)	1 / 17 (5.88%)
occurrences (all)	1	0	1
Stomatitis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Vomiting			
subjects affected / exposed	4 / 14 (28.57%)	1 / 2 (50.00%)	4 / 17 (23.53%)
occurrences (all)	5	3	5
Hepatobiliary disorders			
Hepatic cytolysis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			

Rash			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	1 / 14 (7.14%)	1 / 2 (50.00%)	0 / 17 (0.00%)
occurrences (all)	1	2	0
Nail dystrophy			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	2 / 17 (11.76%)
occurrences (all)	0	0	2
Nail disorder			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Dry skin			
subjects affected / exposed	0 / 14 (0.00%)	1 / 2 (50.00%)	2 / 17 (11.76%)
occurrences (all)	0	1	2
Eczema			
subjects affected / exposed	1 / 14 (7.14%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Pollakiuria			
subjects affected / exposed	1 / 14 (7.14%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Haematuria			
subjects affected / exposed	1 / 14 (7.14%)	0 / 2 (0.00%)	2 / 17 (11.76%)
occurrences (all)	1	0	2
Dysuria			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Back pain			

subjects affected / exposed	1 / 14 (7.14%)	0 / 2 (0.00%)	3 / 17 (17.65%)
occurrences (all)	1	0	3
Groin pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Bone pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			
subjects affected / exposed	1 / 14 (7.14%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	3 / 17 (17.65%)
occurrences (all)	0	0	6
Pneumonia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Oral candidiasis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 2 (50.00%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 2 (50.00%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Hypoglycaemia			
subjects affected / exposed	2 / 14 (14.29%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences (all)	2	0	0
Hypocalcaemia			
subjects affected / exposed	2 / 14 (14.29%)	0 / 2 (0.00%)	1 / 17 (5.88%)
occurrences (all)	2	0	1
Hypoalbuminaemia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Hyperphosphataemia			

subjects affected / exposed	1 / 14 (7.14%)	0 / 2 (0.00%)	1 / 17 (5.88%)
occurrences (all)	2	0	1
Hyperkalaemia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 2 (0.00%)	1 / 17 (5.88%)
occurrences (all)	1	0	1
Hyperglycaemia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Hypercalcaemia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Dehydration			
subjects affected / exposed	4 / 14 (28.57%)	0 / 2 (0.00%)	1 / 17 (5.88%)
occurrences (all)	4	0	1
Decreased appetite			
subjects affected / exposed	3 / 14 (21.43%)	1 / 2 (50.00%)	6 / 17 (35.29%)
occurrences (all)	3	1	7
Cachexia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Hypomagnesaemia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Hyponatraemia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Hypophosphataemia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 2 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Vitamin D deficiency			
subjects affected / exposed	0 / 14 (0.00%)	0 / 2 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1

Non-serious adverse events	SS4 - DZB 300 mg	SS4 - DZB 300 mg + AZB 1200 mg	SS1 - DZB 300 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 8 (100.00%)	10 / 10 (100.00%)	30 / 32 (93.75%)

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	2 / 32 (6.25%)
occurrences (all)	1	0	2
Lymphoedema			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	2 / 32 (6.25%)
occurrences (all)	0	0	2
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 8 (37.50%)	3 / 10 (30.00%)	8 / 32 (25.00%)
occurrences (all)	4	4	8
Fatigue			
subjects affected / exposed	1 / 8 (12.50%)	3 / 10 (30.00%)	8 / 32 (25.00%)
occurrences (all)	1	3	9
Mucosal inflammation			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Oedema			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Oedema peripheral			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	1 / 32 (3.13%)
occurrences (all)	0	1	1
Pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	2 / 32 (6.25%)
occurrences (all)	0	0	2
Pyrexia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	1 / 32 (3.13%)
occurrences (all)	0	1	2
Respiratory, thoracic and mediastinal disorders			

Dyspnoea			
subjects affected / exposed	1 / 8 (12.50%)	1 / 10 (10.00%)	3 / 32 (9.38%)
occurrences (all)	1	1	3
Cough			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Productive cough			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 32 (3.13%)
occurrences (all)	0	0	1
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Investigations			
Blood creatinine increased			
subjects affected / exposed	1 / 8 (12.50%)	2 / 10 (20.00%)	6 / 32 (18.75%)
occurrences (all)	1	3	6
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	2 / 32 (6.25%)
occurrences (all)	0	0	2
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 8 (12.50%)	1 / 10 (10.00%)	4 / 32 (12.50%)
occurrences (all)	1	1	4
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 8 (25.00%)	2 / 10 (20.00%)	12 / 32 (37.50%)
occurrences (all)	2	3	12
Amylase increased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	4 / 32 (12.50%)
occurrences (all)	0	1	4
Alanine aminotransferase increased			
subjects affected / exposed	2 / 8 (25.00%)	2 / 10 (20.00%)	10 / 32 (31.25%)
occurrences (all)	2	2	10
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	4 / 32 (12.50%)
occurrences (all)	0	0	4

Platelet count decreased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	2 / 32 (6.25%)
occurrences (all)	0	0	2
Transaminases increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 32 (3.13%)
occurrences (all)	0	0	1
Weight decreased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	3 / 32 (9.38%)
occurrences (all)	0	1	3
Lipase increased			
subjects affected / exposed	1 / 8 (12.50%)	2 / 10 (20.00%)	4 / 32 (12.50%)
occurrences (all)	1	2	5
Haemoglobin decreased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	2 / 32 (6.25%)
occurrences (all)	0	1	2
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	4 / 32 (12.50%)
occurrences (all)	0	0	4
C-reactive protein increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	2 / 32 (6.25%)
occurrences (all)	0	0	2
Blood thyroid stimulating hormone increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	2 / 32 (6.25%)
occurrences (all)	0	0	2
Blood phosphorus increased			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	4 / 32 (12.50%)
occurrences (all)	1	0	4
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 32 (3.13%)
occurrences (all)	0	0	2
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			

Palpitations			
subjects affected / exposed	1 / 8 (12.50%)	1 / 10 (10.00%)	0 / 32 (0.00%)
occurrences (all)	1	1	0
Nervous system disorders			
Balance disorder			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Tremor			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	2 / 32 (6.25%)
occurrences (all)	0	1	2
Dizziness			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	1 / 32 (3.13%)
occurrences (all)	0	1	1
Dysgeusia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	3 / 32 (9.38%)
occurrences (all)	0	1	3
Sciatica			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 32 (3.13%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 8 (12.50%)	3 / 10 (30.00%)	7 / 32 (21.88%)
occurrences (all)	3	3	7
Lymphopenia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	3 / 32 (9.38%)
occurrences (all)	0	0	4
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Cataract			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	1 / 32 (3.13%)
occurrences (all)	0	1	1
Central serous chorioretinopathy			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	2 / 32 (6.25%)
occurrences (all)	0	0	2

Dry eye			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	3 / 32 (9.38%)
occurrences (all)	0	0	4
Keratitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 32 (3.13%)
occurrences (all)	0	0	2
Maculopathy			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	2 / 32 (6.25%)
occurrences (all)	0	0	2
Punctate keratitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	2 / 32 (6.25%)
occurrences (all)	0	0	2
Vision blurred			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	3 / 32 (9.38%)
occurrences (all)	0	0	3
Visual acuity reduced			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 32 (0.00%)
occurrences (all)	0	0	0
Xerophthalmia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	1 / 32 (3.13%)
occurrences (all)	0	1	1
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 8 (12.50%)	3 / 10 (30.00%)	14 / 32 (43.75%)
occurrences (all)	1	4	14
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Gastritis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	1 / 32 (3.13%)
occurrences (all)	0	1	1
Dyspepsia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	1 / 32 (3.13%)
occurrences (all)	1	0	1
Dry mouth			

subjects affected / exposed	1 / 8 (12.50%)	1 / 10 (10.00%)	7 / 32 (21.88%)
occurrences (all)	1	1	7
Diarrhoea			
subjects affected / exposed	2 / 8 (25.00%)	4 / 10 (40.00%)	7 / 32 (21.88%)
occurrences (all)	2	4	7
Constipation			
subjects affected / exposed	3 / 8 (37.50%)	3 / 10 (30.00%)	10 / 32 (31.25%)
occurrences (all)	3	4	10
Ascites			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 32 (0.00%)
occurrences (all)	0	0	0
Abdominal pain upper			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 32 (3.13%)
occurrences (all)	0	0	1
Abdominal pain			
subjects affected / exposed	1 / 8 (12.50%)	2 / 10 (20.00%)	2 / 32 (6.25%)
occurrences (all)	1	2	2
Abdominal distension			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 32 (0.00%)
occurrences (all)	0	0	0
Stomatitis			
subjects affected / exposed	1 / 8 (12.50%)	2 / 10 (20.00%)	1 / 32 (3.13%)
occurrences (all)	1	2	1
Vomiting			
subjects affected / exposed	0 / 8 (0.00%)	3 / 10 (30.00%)	6 / 32 (18.75%)
occurrences (all)	0	3	6
Hepatobiliary disorders			
Hepatic cytolysis			
subjects affected / exposed	1 / 8 (12.50%)	1 / 10 (10.00%)	0 / 32 (0.00%)
occurrences (all)	1	1	0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 8 (0.00%)	2 / 10 (20.00%)	1 / 32 (3.13%)
occurrences (all)	0	2	1
Pruritus			

subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 32 (3.13%)
occurrences (all)	0	0	1
Nail dystrophy			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 32 (0.00%)
occurrences (all)	0	0	0
Nail disorder			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	1 / 32 (3.13%)
occurrences (all)	0	1	1
Dry skin			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 32 (3.13%)
occurrences (all)	0	0	1
Eczema			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 32 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Pollakiuria			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 32 (3.13%)
occurrences (all)	0	0	1
Haematuria			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	2 / 32 (6.25%)
occurrences (all)	1	0	2
Dysuria			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	1 / 32 (3.13%)
occurrences (all)	0	1	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	3 / 32 (9.38%)
occurrences (all)	0	1	3
Back pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	4 / 32 (12.50%)
occurrences (all)	0	0	4
Groin pain			

subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 32 (3.13%)
occurrences (all)	0	0	1
Bone pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	2 / 32 (6.25%)
occurrences (all)	0	0	2
Pain in extremity			
subjects affected / exposed	1 / 8 (12.50%)	1 / 10 (10.00%)	0 / 32 (0.00%)
occurrences (all)	1	1	0
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	3 / 32 (9.38%)
occurrences (all)	0	2	3
Pneumonia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 32 (3.13%)
occurrences (all)	0	0	1
Oral candidiasis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 32 (3.13%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	1 / 32 (3.13%)
occurrences (all)	1	0	1
Hypoglycaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 32 (0.00%)
occurrences (all)	0	0	0
Hypocalcaemia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Hypoalbuminaemia			
subjects affected / exposed	2 / 8 (25.00%)	0 / 10 (0.00%)	1 / 32 (3.13%)
occurrences (all)	2	0	1
Hyperphosphataemia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	3 / 32 (9.38%)
occurrences (all)	0	1	3
Hyperkalaemia			

subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 32 (3.13%)
occurrences (all)	0	0	1
Hyperglycaemia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	2 / 32 (6.25%)
occurrences (all)	1	0	2
Hypercalcaemia			
subjects affected / exposed	1 / 8 (12.50%)	1 / 10 (10.00%)	3 / 32 (9.38%)
occurrences (all)	1	1	3
Dehydration			
subjects affected / exposed	2 / 8 (25.00%)	0 / 10 (0.00%)	0 / 32 (0.00%)
occurrences (all)	2	0	0
Decreased appetite			
subjects affected / exposed	1 / 8 (12.50%)	2 / 10 (20.00%)	9 / 32 (28.13%)
occurrences (all)	1	3	10
Cachexia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Hypomagnesaemia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	1 / 32 (3.13%)
occurrences (all)	1	0	2
Hyponatraemia			
subjects affected / exposed	3 / 8 (37.50%)	2 / 10 (20.00%)	4 / 32 (12.50%)
occurrences (all)	3	2	4
Hypophosphataemia			
subjects affected / exposed	1 / 8 (12.50%)	1 / 10 (10.00%)	1 / 32 (3.13%)
occurrences (all)	1	1	1
Vitamin D deficiency			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	1 / 32 (3.13%)
occurrences (all)	1	0	1

Non-serious adverse events	SS2 - DZB 300 mg + AZB 1200 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 12 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Tumour pain subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Vascular disorders Hypertension subjects affected / exposed occurrences (all) Lymphoedema subjects affected / exposed occurrences (all)	 0 / 12 (0.00%) 0 0 / 12 (0.00%) 0		
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all) Mucosal inflammation subjects affected / exposed occurrences (all) Oedema subjects affected / exposed occurrences (all) Oedema peripheral subjects affected / exposed occurrences (all) Pain subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all)	 5 / 12 (41.67%) 6 2 / 12 (16.67%) 2 2 / 12 (16.67%) 2 1 / 12 (8.33%) 1 0 / 12 (0.00%) 0 2 / 12 (16.67%) 2 3 / 12 (25.00%) 3		
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all)	 1 / 12 (8.33%) 1		

Cough			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Productive cough			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	3		
Amylase increased			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Alanine aminotransferase increased			
subjects affected / exposed	5 / 12 (41.67%)		
occurrences (all)	5		
Blood lactate dehydrogenase increased			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Platelet count decreased			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	2		

Transaminases increased			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Weight decreased			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Lipase increased			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Haemoglobin decreased			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
C-reactive protein increased			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Blood thyroid stimulating hormone increased			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Blood phosphorus increased			
subjects affected / exposed	4 / 12 (33.33%)		
occurrences (all)	4		
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	2		
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		

Nervous system disorders			
Balance disorder			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Tremor			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Dizziness			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Dysgeusia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Sciatica			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Lymphopenia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Eye disorders			
Cataract			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Central serous chorioretinopathy			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Dry eye			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		

Keratitis subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Maculopathy subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Punctate keratitis subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Vision blurred subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Visual acuity reduced subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Xerophthalmia subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	4 / 12 (33.33%) 5		
Gastrooesophageal reflux disease subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Gastritis subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Dyspepsia subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Dry mouth subjects affected / exposed occurrences (all)	2 / 12 (16.67%) 2		
Diarrhoea			

subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	4		
Constipation			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Ascites			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Abdominal pain upper			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Abdominal pain			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	3		
Abdominal distension			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Stomatitis			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Vomiting			
subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	3		
Hepatobiliary disorders			
Hepatic cytolysis			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Pruritus			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Nail dystrophy			

subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Nail disorder			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Dry skin			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Eczema			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Pollakiuria			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Haematuria			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Dysuria			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Back pain			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Groin pain			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Bone pain			

subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Pain in extremity			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Pneumonia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Oral candidiasis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Hypoglycaemia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Hypocalcaemia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Hypoalbuminaemia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Hyperphosphataemia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Hyperkalaemia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Hyperglycaemia			

subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Hypercalcaemia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Dehydration			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Decreased appetite			
subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	4		
Cachexia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Hypomagnesaemia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Hyponatraemia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Hypophosphataemia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Vitamin D deficiency			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 May 2019	Protocol amendment 1 was implemented in Protocol Version 2 prior to screening of the first study patient. This amendment included the following: • updated definition of a dose-limiting toxicity applicable to Substudy 2, • implemented a new dose modification and discontinuation criteria / additional information on hyperphosphatemia, • modified the schedule for ophthalmologic examinations and added a management of retinal AEs, • amended concomitant medications, • updated clinical safety laboratory blood tests, • clarification of inclusion criterion 4 in Substudy 4, • all references to impaired renal function were clarified as requiring calculation of creatinine clearance using the Cockcroft-Gault formula, • references to molecular testing protocols throughout the protocol were broadened, • rescreening timeframe for assessing the inclusion and exclusion criteria was specified for clarity, • procedures for on-treatment ECGs were clarified, • the storage and future use of biological samples was clarified, • a table listing the inducers, inhibitors and substrates of CYP2C8 was added to Appendix 6 and definitions amended.
04 October 2019	Protocol amendment 2 was implemented in Protocol Version 3. This amendment included the following: • broadened the target population for Substudy 2 by removing the requirement for patients to have a tumor harboring any FGFR genetic aberrations, • introduced time windows for PK sampling, • clarified that for enrollment in Substudy 3 patients needed PD-L1 expression < 5%, • requirements for molecular tests conducted in the EU were clarified, • appropriate methods of birth control were clarified, • an exclusion criterion was added for hypersensitivity to atezolizumab or to any of the excipients, • study drug discontinuation criteria were amended, • a tuberculosis blood test and serology for HCV/HBV/HIV at screening were added, • live, attenuated vaccines within 28 days prior to enrollment were added as a prohibited medication, • added a requirement for patients in Substudy 2 to have no 'standard' treatment alternative rather than no 'satisfactory' treatment alternative, • added serum electrolyte abnormalities as exclusion criterion 6, • addition of measurements of amylase and lipase to the clinical safety laboratory tests, • to provide continued study treatment at the time of study closure to patients who continued to derive benefit, • modification of the schedule for ophthalmologic examinations to require a complete ophthalmological examination at End of Treatment visit.

20 August 2020	Protocol amendment 3 was implemented in Protocol Version 4. This amendment included the following: • changes to potential risks for derazantinib, • removal of phototoxicity from the list of AEs of special interest (AESIs), • deletion of translational clinical study groups planned for Substudies 1, 3, and 4 and associated molecular translational analyses from the protocol, • clarification of inclusion criterion 4: the definition of 'PD-L1-low', a low PD-L1 expression level, • change to inclusion criterion 5: for enrollment into Substudy 4, a positive central FGFR1–3 genetic aberration test result was not required if the patient had documented FGFR1–3 GA status from prior FGFR inhibiting treatment, • clarification of which pathway-targeting agents were the subject of exclusion criteria 3 and 4, • clarification that the corneal or retinal disorder referred to in exclusion criterion 5 must be clinically significant and likely to increase the risk of eye toxicity, • clarification of exclusion criteria 14: revised to state that patients with chronic hepatitis B were only eligible with an HBV DNA < 100 IU/mL and if taking an antiviral therapy, • change to eligible FGFR genetic aberrations, • amendments to screening where local FGFR testing was performed as routine institutional practice, • change to estimated objective response rate for the Substudy 1 hypothesis, • clarification of the requirements for informed consent for pre-screening and study participation, • changes to requirements for bone scans, • clarification of the ethical basis of the study (GCP), • changes to administration of derazantinib with food in the event of nausea or vomiting.
08 March 2021	Protocol amendment 4 was implemented in Protocol Version 5. This amendment included the following: • addition of Substudy 5 (a new substudy in patients with advanced or mUC expressing FGFR1–3 GAs who had progressed on at least one standard chemotherapy and/or immune-checkpoint blockade and had not received prior FGFR inhibiting treatment), replacing Substudy 1, • modification of Substudy 3 (revised the strategy for exploring the efficacy of derazantinib in first-line cisplatin mUC patients expressing FGFR1–3 GAs and removing the monotherapy cohort in this patient population), • modification of inclusion criterion 4 for Substudy 3 (to permit enrolment of patients with mUC with any PD-L1 status), • addition of an exclusion criterion taking into account the prognostic 'Bellmunt score', • clarification of exclusion criterion 15 (patients with active/chronic hepatitis B and active hepatitis C), • addition of pharmacodynamics cohorts to Substudies 3, 4, and 5, • amendments to molecular testing for eligibility (to permit positive FGFR1–3 GA test results obtained from local NGS testing), • clarification of AST/ALT elevations (as DLT), • revised dose modifications guidance for atezolizumab.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

The following secondary endpoints could not be shown due to the restrictions of the EudraCT system; duration of response, overall survival and disease control rate. The figures are on CT.gov: https://clinicaltrials.gov/study/NCT04045613

Notes: