Clinical trial results:
A Randomized, Open-Label (formerly Double-Blind), Phase 2 Trial to Assess Safety and Efficacy of Lenvatinib at Two Different Starting Doses (18 mg vs 14 mg QD) in Combination With Everolimus (5 mg QD) in Renal Cell Carcinoma Following One Prior VEGF-Targeted Treatment

Summary

EudraCT number	2016-002778-11
Trial protocol	CZ GB NL GR FI PL ES PT IT RO
Global end of trial date	20 June 2024

Results information

Result version number	v1 (current)
This version publication date	04 April 2025
First version publication date	04 April 2025

Trial information

Trial identification

Sponsor protocol code	E7080-G000-218

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03173560
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Eisai, Inc.
Sponsor organisation address	200 Metro Boulevard, Nutley, New Jersey, United States, 07110
Public contact	Eisai Medical Information, Eisai, Inc., +18 882742378, esi_oncmedinfo@eisai.com
Scientific contact	Eisai Medical Information, Eisai, Inc., +18 882742378, esi_oncmedinfo@eisai.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 August 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 June 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to assess whether a starting dose of lenvatinib 14 milligram (mg) in combination with everolimus 5 mg once daily (QD) will provide comparable efficacy (based on objective response rate [ORR]at 24 weeks [ORR24W]) with an improved safety profile compared to lenvatinib 18 mg in combination with everolimus 5 mg (based on treatment emergent intolerable Grade 2, or any greater than or equal to (>=) Grade 3 adverse events (AEs) in the first 24 weeks after randomization).

Protection of trial subjects:

This study was conducted in accordance with standard operating procedures of the sponsor (or designee), which are designed to ensure adherence to Good Clinical Practice (GCP) guidelines as required by the following: Principles of the World Medical Association Declaration of Helsinki (2013), ICH E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Title 21 of the United States Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312, European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any EU country.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 August 2017
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	Netherlands: 4
Country: Number of subjects enrolled	Poland: 35
Country: Number of subjects enrolled	Portugal: 12
Country: Number of subjects enrolled	Spain: 47
Country: Number of subjects enrolled	United Kingdom: 11
Country: Number of subjects enrolled	Czechia: 8
Country: Number of subjects enrolled	Finland: 19
Country: Number of subjects enrolled	Greece: 22
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	Australia: 16
Country: Number of subjects enrolled	Korea, Republic of: 47
Country: Number of subjects enrolled	Taiwan: 9

Country: Number of subjects enrolled	Romania: 21
Country: Number of subjects enrolled	Russian Federation: 49
Country: Number of subjects enrolled	Canada: 11
Country: Number of subjects enrolled	United States: 26
Worldwide total number of subjects	343
EEA total number of subjects	174

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)	215
From 65 to 84 years	127
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Subjects took part in the study at 82 investigative sites in Australia, Korea, Taiwan, Czech, Poland, Romania, Russia, Finland, Greece, Italy, Netherlands, Portugal, Spain, United Kingdom, Canada and the United States from 17 August 2017 to 20 June 2024.

Pre-assignment

Screening details:

A total of 489 subjects were screened, of which 146 were screen failures and 343 were enrolled and randomized, out of which 341 subjects were treated.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Lenvatinib 14 mg + Everolimus 5 mg

Arm description:

Subjects received lenvatinib 14 mg, capsule, orally, once daily along with everolimus 5 mg, tablet, orally, once daily as the starting dose in a 28-day treatment cycle until progressive disease (PD), development of unacceptable toxicity, subject requested to discontinue treatment, withdrew consent or lost to follow-up, until the end of the study, or until study termination by the sponsor, whichever occurred first. Subjects who had no intolerable Grade 2 or any greater than or equal to (>=) Grade 3 treatment-emergent adverse events (TEAEs) that required dose reduction in the first 28-day cycle (that is, the first 4 weeks of treatment), had lenvatinib dose titrated to 18 mg once daily (along with everolimus 5 mg) beginning in Cycle 2 or later (cycle length equals to (=) 28 days) during randomization phase.

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

Dosage and administration details:

Everolimus 5 mg, tablet, orally, once daily in each 28-day treatment cycle.

Investigational medicinal product name	Lenvatinib
Investigational medicinal product code	
Other name	E7080
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Lenvatinib 14 mg, capsule, orally, once daily in each 28-day treatment cycle.

Arm title	Lenvatinib 18 mg + Everolimus 5 mg

Arm description:

Subjects received lenvatinib 18 mg, capsule, orally, once daily along with everolimus 5 mg, tablet, orally, once daily as the starting dose in a 28-day treatment cycle until PD, development of unacceptable toxicity, subject requested to discontinue treatment, withdrew consent or lost to follow-up, until the end of the study, or until study termination by the sponsor, whichever occurred first.

Arm type	Experimental

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

Dosage and administration details:

Everolimus 5 mg, tablet, orally, once daily in each 28-day treatment cycle.

Investigational medicinal product name	Lenvatinib
Investigational medicinal product code	
Other name	E7080
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Lenvatinib 18 mg capsule, orally, once daily in each 28-day treatment cycle.

Number of subjects in period 1	Lenvatinib 14 mg + Everolimus 5 mg	Lenvatinib 18 mg + Everolimus 5 mg
Started	172	171
Treated Subjects	172	169
Completed	91	101
Not completed	81	70
Consent withdrawn by subject	10	5
Death	70	60
Unspecified	-	1
Lost to follow-up	1	4

Baseline characteristics

Reporting groups

Reporting group title	Lenvatinib 14 mg + Everolimus 5 mg

Reporting group description:

Subjects received lenvatinib 14 mg, capsule, orally, once daily along with everolimus 5 mg, tablet, orally, once daily as the starting dose in a 28-day treatment cycle until progressive disease (PD), development of unacceptable toxicity, subject requested to discontinue treatment, withdrew consent or lost to follow-up, until the end of the study, or until study termination by the sponsor, whichever occurred first. Subjects who had no intolerable Grade 2 or any greater than or equal to (>=) Grade 3 treatment-emergent adverse events (TEAEs) that required dose reduction in the first 28-day cycle (that is, the first 4 weeks of treatment), had lenvatinib dose titrated to 18 mg once daily (along with everolimus 5 mg) beginning in Cycle 2 or later (cycle length equals to (=) 28 days) during randomization phase.

Reporting group title	Lenvatinib 18 mg + Everolimus 5 mg

Reporting group description:

Subjects received lenvatinib 18 mg, capsule, orally, once daily along with everolimus 5 mg, tablet, orally, once daily as the starting dose in a 28-day treatment cycle until PD, development of unacceptable toxicity, subject requested to discontinue treatment, withdrew consent or lost to follow-up, until the end of the study, or until study termination by the sponsor, whichever occurred first.

Reporting group values	Lenvatinib 14 mg + Everolimus 5 mg	Lenvatinib 18 mg + Everolimus 5 mg	Total
Number of subjects	172	171	343
Age categorical Units: subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	114	101	215
From 65-84 years	58	69	127
85 years and over	0	1	1
Age Continuous Units: years			
arithmetic mean	60.5	61.5	
standard deviation	± 9.59	± 9.90	-
Sex: Female, Male Units: subjects			
Female	39	42	81
Male	133	129	262
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	4	8	12
Not Hispanic or Latino	168	163	331
Unknown or Not Reported	0	0	0
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0

Asian	33	27	60
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	137	140	277
More than one race	0	0	0
Unknown or Not Reported	2	4	6

End points reporting groups

Reporting group title	Lenvatinib 14 mg + Everolimus 5 mg

Reporting group description:

Subjects received lenvatinib 14 mg, capsule, orally, once daily along with everolimus 5 mg, tablet, orally, once daily as the starting dose in a 28-day treatment cycle until progressive disease (PD), development of unacceptable toxicity, subject requested to discontinue treatment, withdrew consent or lost to follow-up, until the end of the study, or until study termination by the sponsor, whichever occurred first. Subjects who had no intolerable Grade 2 or any greater than or equal to (>=) Grade 3 treatment-emergent adverse events (TEAEs) that required dose reduction in the first 28-day cycle (that is, the first 4 weeks of treatment), had lenvatinib dose titrated to 18 mg once daily (along with everolimus 5 mg) beginning in Cycle 2 or later (cycle length equals to (=) 28 days) during randomization phase.

Reporting group title	Lenvatinib 18 mg + Everolimus 5 mg

Reporting group description:

Subjects received lenvatinib 18 mg, capsule, orally, once daily along with everolimus 5 mg, tablet, orally, once daily as the starting dose in a 28-day treatment cycle until PD, development of unacceptable toxicity, subject requested to discontinue treatment, withdrew consent or lost to follow-up, until the end of the study, or until study termination by the sponsor, whichever occurred first.

Subject analysis set title	Lenvatinib 18 mg
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects with RCC received lenvatinib 18 mg, capsule, orally, once daily until PD, development of unacceptable toxicity, participant requested to discontinue treatment, withdrew consent or lost to follow-up or until the end of the study, whichever occurred first in studies E7080-G000-205 (NCT01136733), E7080-M001-221 (NCT02915783), E7080-J081-112 (NCT02454478) and in this current study E7080-G000-218 (NCT03173560).

Subject analysis set title	Everolimus 10 mg
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects with RCC received everolimus 10 mg, capsule, orally, once daily until PD, development of unacceptable toxicity, participant requested to discontinue treatment, withdrew consent or lost to follow-up or until the end of the study, whichever occurred first in studies E7080-G000-205 (NCT01136733), E7080-M001-221 (NCT02915783), E7080-J081-112 (NCT02454478) or in this current study E7080-G000-218 (NCT03173560).

Subject analysis set title	Lenvatinib 18 mg + Everolimus 5 mg
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects with RCC received lenvatinib 18 mg, capsule, orally, once daily along with everolimus 5 mg, tablet, orally, once daily until PD, development of unacceptable toxicity, participant requested to discontinue treatment, withdrew consent or lost to follow-up or until the end of the study, whichever occurred first in studies E7080-G000-205 (NCT01136733), E7080-M001-221 (NCT02915783), E7080-J081-112 (NCT02454478) and in this current study E7080-G000-218 (NCT03173560).

Subject analysis set title	Lenvatinib + Everolimus 5 mg
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects with RCC received lenvatinib 18 mg, capsule, orally, once daily along with everolimus 5 mg, tablet, orally, once daily until PD, development of unacceptable toxicity, participant requested to discontinue treatment, withdrew consent or lost to follow-up or until the end of the study, whichever occurred first in studies E7080-G000-205 (NCT01136733), E7080-M001-221 (NCT02915783), E7080-J081-112 (NCT02454478) or in this current study E7080-G000-218 (NCT03173560).

Subject analysis set title	Lenvatinib 14 mg + Everolimus 5 mg
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects received lenvatinib 14 mg, capsule, orally, once daily along with everolimus 5 mg, tablet, orally, once daily as the starting dose in a 28-day treatment cycle until PD, development of unacceptable toxicity, participant requested to discontinue treatment, withdrew consent or lost to follow-up, until the end of the study, or until study termination by the sponsor, whichever occurred first.

Subjects who had no intolerable Grade 2 or any >=Grade 3 TEAEs that required dose reduction in the first 28-day cycle (that is, the first 4 weeks of treatment), had lenvatinib dose titrated to 18 mg once daily (along with everolimus 5 mg) beginning in Cycle 2 or later (cycle length =28 days) during randomization phase.

Subject analysis set title	Lenvatinib 18 mg + Everolimus 5 mg
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects received lenvatinib 18 mg, capsule, orally, once daily along with everolimus 5 mg, tablet, orally, once daily as the starting dose in a 28-day treatment cycle until PD, development of unacceptable toxicity, participant requested to discontinue treatment, withdrew consent or lost to follow-up, until the end of the study, or until study termination by the sponsor, whichever occurred first.

Primary: Objective Response Rate at Week 24 (ORR24W)

End point title	Objective Response Rate at Week 24 (ORR24W)

End point description:

ORR24W: percentage of subjects with best overall response(BOR) of complete response(CR) or partial response(PR) at Week 24(after randomization), during treatment or within 28 days after last dose date but on or prior to start of new anticancer therapy based on investigator assessment according to Response Evaluation Criteria In Solid Tumors(RECIST) version 1.1.CR: disappearance of all target and non-target lesions(non-lymph nodes). All pathological lymph nodes(whether target or non-target) must have reduction in their short axis to less than (<) 10 millimeters(mm).PR: at least a 30 percent(%) decrease in sum of diameters of target lesions, taking as reference baseline sum diameters. To be considered BOR, all responses had to be confirmed no <4 weeks after initial assessment of response. Per-protocol analysis set 1(PPAS1) included all randomized subjects minus the 32 subjects who had received >=2 incorrect lenvatinib doses due to interactive voice and web response system(IxRS) issues.

End point type	Primary

End point timeframe:

At Week 24

End point values	Lenvatinib 14 mg + Everolimus 5 mg	Lenvatinib 18 mg + Everolimus 5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	156	155		
Units: percentage of subjects				
number (confidence interval 95%)	32.1 (24.7 to 39.4)	34.8 (27.3 to 42.3)		

Statistical analyses

Statistical analysis title	Statistical analysis
Comparison groups	Lenvatinib 14 mg + Everolimus 5 mg v Lenvatinib 18 mg + Everolimus 5 mg
Number of subjects included in analysis	311
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2676
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.88

Confidence interval	
level	90 %
sides	2-sided
lower limit	0.59
upper limit	1.32

Primary: Percentage of Participants With Intolerable Grade 2 or Any Grade >=Grade 3 TEAEs Within 24 Weeks

End point title	Percentage of Participants With Intolerable Grade 2 or Any Grade >=Grade 3 TEAEs Within 24 Weeks

End point description:

TEAE was defined as an adverse event (AE) with an onset that had occurred after receiving study drug. A severity grade was defined by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03. As per NCI-CTCAE, Grade 1 scales as Mild; Grade 2 scales as Moderate; Grade 3 scales as severe or medically significant but not immediately life threatening; Grade 4 scales as life-threatening consequences; and Grade 5 scales as death related to AE. Per-protocol safety analysis set included all randomized and treated participants minus 32 participants who had received >=2 incorrect lenvatinib doses due to IxRS issues according to actual treatment received.

End point type	Primary

End point timeframe:

Up to Week 24

End point values	Lenvatinib 14 mg + Everolimus 5 mg	Lenvatinib 18 mg + Everolimus 5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	157	152		
Units: percentage of subjects				
number (confidence interval 95%)	82.8 (76.9 to 88.7)	79.6 (73.2 to 86.0)		

Statistical analyses

Statistical analysis title	Statistical analysis
Comparison groups	Lenvatinib 14 mg + Everolimus 5 mg v Lenvatinib 18 mg + Everolimus 5 mg
Number of subjects included in analysis	309
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4763
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference
Point estimate	3.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.5
upper limit	11.9

Secondary: Progression-free Survival (PFS)

End point title	Progression-free Survival (PFS)

End point description:

PFS was defined as the time from the date of randomization to the date of the first documentation of PD by investigator assessment or date of death, whichever occurred first according to RECIST v1.1. PD: at least 20% increase (including an absolute increase of at least 5 millimeter [mm]) in the sum of diameter (SOD) of target lesions, taking as reference the smallest sum and/or unequivocal progression of existing non-target lesions and/or appearance of 1 or more new lesions. Median PFS was analyzed using the Kaplan-Meier product-limit estimates for each treatment group and presented with 2-sided 95% confidence interval (CI). PPAS1 included all randomized subjects minus the 32 participants who had received >=2 incorrect lenvatinib doses due to IxRS issues. As pre-specified in the protocol, data for this secondary endpoint was collected and analyzed till the primary analysis only.

End point type	Secondary

End point timeframe:

From the date of randomization to the date of the first documentation of PD or date of death, whichever occurred first or up to date of data cutoff for the primary analysis (up to 29 months)

End point values	Lenvatinib 14 mg + Everolimus 5 mg	Lenvatinib 18 mg + Everolimus 5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	156	155		
Units: months				
median (confidence interval 95%)	11.1 (9.0 to 12.9)	14.7 (11.1 to 20.3)		

Statistical analyses

Statistical analysis title	Statistical analysis
Comparison groups	Lenvatinib 14 mg + Everolimus 5 mg v Lenvatinib 18 mg + Everolimus 5 mg
Number of subjects included in analysis	311
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	1.42
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.08
upper limit	1.86

Secondary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)

End point description:

ORR was defined as the percentage of subjects with a BOR of CR or PR at the at the end of treatment based on investigator assessment according to RECIST v1.1. CR: defined as the disappearance of all target and non-target lesions (non-lymph nodes). All pathological lymph nodes (whether target or non-target) must have a reduction in their short axis to <10 mm. PR: defined as at least a 30 % decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. To be considered a BOR, all responses had to be confirmed no less than 4 weeks after the initial assessment of response. PPAS1 included all randomized subjects minus the 32 subjects who had received >=2 incorrect lenvatinib doses due to IxRS issues. As pre-specified in the protocol, data for this secondary endpoint was collected and analyzed till the primary analysis only.

End point type	Secondary

End point timeframe:

From date of randomization up to first documentation of PD or date of death, whichever occurred first or up to the date of data cut off for the primary analysis (up to 29 months)

End point values	Lenvatinib 14 mg + Everolimus 5 mg	Lenvatinib 18 mg + Everolimus 5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	156	155		
Units: percentage of subjects				
number (confidence interval 95%)	34.6 (27.1 to 42.1)	40.6 (32.9 to 48.4)		

Statistical analyses

Statistical analysis title	Statistical analysis
Comparison groups	Lenvatinib 14 mg + Everolimus 5 mg v Lenvatinib 18 mg + Everolimus 5 mg
Number of subjects included in analysis	311
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Odds ratio (OR)
Point estimate	0.77
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.52
upper limit	1.14

Secondary: Number of Subjects with TEAEs and Serious TEAEs

End point title	Number of Subjects with TEAEs and Serious TEAEs

End point description:

TEAEs were defined as those adverse events (AEs) that occurred (or worsened, if present at Baseline) after the first dose of study drug through 28 days after the last dose of study drug. An AE was defined as any untoward medical occurrence in a subjects or clinical investigation participant administered an investigational product. An AE does not necessarily have a causal relationship with medicinal product. A serious adverse event (SAE) was defined as any AE if it resulted in death or life-threatening AE or required inpatient hospitalization or prolongation of existing hospitalization or resulted in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions or was a congenital anomaly/birth defect. Safety analysis set (SAS) included all subjects who were randomized and received at least 1 dose of study drug according to the treatment starting dose actually received.

End point type	Secondary

End point timeframe:

From date of first dose of study drug up to 28 days after last dose of study drug (up to 71 months)

End point values	Lenvatinib 14 mg + Everolimus 5 mg	Lenvatinib 18 mg + Everolimus 5 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	173	168		
Units: subjects				
Subjects With TEAEs	173	167		
Subjects With Serious TEAEs	92	87		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Treatment Failure due to Toxicity

End point title	Time to Treatment Failure due to Toxicity

End point description:

Time to treatment failure due to toxicity was defined as the time from the date of randomization to the date that a subject discontinued study treatment due to TEAEs. Toxicity (except hypertension and non-infectious pneumonitis) was assessed according to CTCAE v4.03. FAS included all randomized subjects. As planned, data for this secondary endpoint was collected and analyzed till the primary analysis only.

End point type	Secondary

End point timeframe:

From the date of randomization to the date of discontinuation of study treatment due to TEAEs, or date of data cut off for the primary analysis (up to 29 months)

End point values	Lenvatinib 14 mg + Everolimus 5 mg	Lenvatinib 18 mg + Everolimus 5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	172	171		
Units: months				
median (full range (min-max))	3.15 (0.5 to	5.70 (0.8 to		

12.7)	24.6)

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration of Lenvatinib

End point title	Plasma Concentration of Lenvatinib

End point description:

PK sparse sampling was performed. As planned, the post-dose plasma sample was collected anytime between 0.5 to 4 hours at Cycle 1 Days 1 and 15, between 6 to 10 hours at Cycle 1 Days 1 and 15, and between 2 to 12 hours at Cycle 2 Day 1. Only one sample was collected for each post-dose category between specified timepoints. Pharmacokinetic (PK) analysis set included all subjects who received at least 1 dose of study drug with documented dosing history and had at least 1 evaluable lenvatinib plasma or everolimus whole blood concentration data. Here, "number of subjects analyzed" are the subjects who were evaluable for the endpoint and "n" were the subjects who were evaluable for this endpoint at given time points.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1: 0.5-4 hours and 6-10 hours post-dose; Cycle 1 Day 15: pre-dose, 0.5-4 hours and 6-10 hours post-dose; Cycle 2 Day 1: pre-dose and 2-12 hours post-dose (each cycle length =28 days)

End point values	Lenvatinib 14 mg + Everolimus 5 mg	Lenvatinib 18 mg + Everolimus 5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	168	160		
Units: nanogram per milliliter (ng/mL)				
arithmetic mean (standard deviation)				
Cycle 1 Day 1: 0.5-4 hours post-dose (n=168,160)	57.9 (± 96.54)	82.3 (± 119.89)		
Cycle 1 Day 1: 6-10 hours post-dose (n=166,154)	136.3 (± 66.53)	193.7 (± 93.08)		
Cycle 1 Day 15: Pre-dose (n=154,149)	53.7 (± 62.31)	64.0 (± 59.71)		
Cycle 1 Day 15: 0.5-4 hours post-dose (n=147,147)	99.6 (± 102.54)	133.4 (± 125.65)		
Cycle 1 Day 15: 6-10 hours post-dose (n=148,143)	177.8 (± 89.42)	236.2 (± 135.21)		
Cycle 2 Day 1: Pre-dose (n=160,151)	42.8 (± 42.84)	50.6 (± 46.06)		
Cycle 2 Day 1: 2-12 hours post-dose (154,143)	172.8 (± 130.90)	190.3 (± 114.85)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects who Discontinued Treatment due to Toxicity

End point title	Percentage of Subjects who Discontinued Treatment due to Toxicity

End point description:

Percentage of subjects who discontinued treatment due to toxicity, defined as the percentage of subjects who discontinued study treatment due to TEAEs. Toxicity (except hypertension and non-infectious pneumonitis) was assessed according to NCI-CTCAE v4.03. FAS included all randomized subjects.

End point type	Secondary

End point timeframe:

From date of first dose of study drug up to 28 days after last dose of study drug (up to 71 months)

End point values	Lenvatinib 14 mg + Everolimus 5 mg	Lenvatinib 18 mg + Everolimus 5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	172	171		
Units: percentage of subjects				
number (not applicable)	17.4	25.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Whole Blood Concentration of Everolimus

End point title	Whole Blood Concentration of Everolimus

End point description:

PK sparse sampling was performed. As planned, the post-dose whole blood sample was collected anytime between 0.5 to 4 hours at Cycle 1 Days 1 and 15, between 6 to 10 hours at Cycle 1 Days 1 and 15, and between 2 to 12 hours at Cycle 2 Day 1. Only one sample was collected for each post-dose category between specified timepoints. PK analysis set included all subjects who received at least 1 dose of study drug with documented dosing history and had at least 1 evaluable lenvatinib plasma or everolimus whole blood concentration data. Here, "number of subjects analyzed" are the subjects who were evaluable for the endpoint and "n" were the subjects who were evaluable at given time points.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1: 0.5-4 hours and 6-10 hours post-dose; Cycle 1 Day 15: pre-dose, 0.5-4 hours and 6-10 hours post-dose; Cycle 2 Day 1: pre-dose and 2-12 hours post-dose (each cycle length =28 days)

End point values	Lenvatinib 14 mg + Everolimus 5 mg	Lenvatinib 18 mg + Everolimus 5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120	117		
Units: ng/mL				
arithmetic mean (standard deviation)				

Cycle 1 Day 1: 0.5-4 hours post-dose (n=106,117)	18.3 (± 15.89)	18.6 (± 16.39)		
Cycle 1 Day 1: 6-10 hours post-dose (n=103,115)	9.2 (± 6.60)	8.4 (± 5.64)		
Cycle 1 Day 15: Pre-dose (n=110,111)	8.4 (± 4.84)	7.4 (± 5.51)		
Cycle 1 Day 15: 0.5-4 hours post-dose (n=106,111)	23.7 (± 15.41)	23.4 (± 16.96)		
Cycle 1 Day 15: 6-10 hours post-dose (n=107,106)	14.3 (± 5.83)	14.3 (± 9.22)		
Cycle 2 Day 1: Pre-dose (n=120,117)	7.8 (± 5.44)	5.9 (± 4.02)		
Cycle 2 Day 1: 2-12 hours post-dose (n=112,112)	22.9 (± 12.67)	19.5 (± 9.74)		

Statistical analyses

No statistical analyses for this end point

Secondary: Model Predicted Apparent Total Clearance (CL/F) for Lenvatinib Alone and When Coadministration With Everolimus in Renal Cell Carcinoma (RCC) Subjects to Assess Drug-Drug Interaction

End point title	Model Predicted Apparent Total Clearance (CL/F) for Lenvatinib Alone and When Coadministration With Everolimus in Renal Cell Carcinoma (RCC) Subjects to Assess Drug-Drug Interaction

End point description:

Sparse PK samples were collected and analyzed using a population PK approach to estimate PK parameters. The lenvatinib concentration data was pooled from studies E7080-G000-205 (NCT01136733), E7080-M001-221 (NCT02915783), E7080-J081-112 (NCT02454478) and from current study E7080-G000-218 (NCT03173560). A previously developed 3-compartment PK model for lenvatinib was fitted to the pooled dataset. Individual lenvatinib CL/F value was derived from the final PK model. The endpoint was assessed for lenvatinib 18 mg dose only. PK analysis set included all subjects who received at least 1 dose of study drug with documented dosing history and had at least 1 evaluable lenvatinib plasma concentration data. Population included subjects from E7080-G000-205 (NCT01136733), E7080-M001-221 (NCT02915783), E7080-J081-112 (NCT02454478) and current study E7080-G000-218 (NCT03173560). Here, "number of subjects analyzed" are the subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1: 0.5-4 hours and 6-10 hours post-dose; Cycle 1 Day 15: pre-dose, 0.5-4 hours and 6-10 hours post-dose; Cycle 2 Day 1: pre-dose and 2-12 hours post-dose (each cycle length =28 days)

End point values	Lenvatinib 18 mg	Lenvatinib 18 mg + Everolimus 5 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	48	443		
Units: liter per hour (L/h)				
arithmetic mean (standard deviation)	6.37 (± 2.01)	5.77 (± 2.01)		

Statistical analyses

No statistical analyses for this end point

Secondary: Model Predicted Dose Normalized AUC for Everolimus Alone and When Coadministration With Lenvatinib in RCC Subjects to Assess Drug-Drug Interaction

End point title	Model Predicted Dose Normalized AUC for Everolimus Alone and When Coadministration With Lenvatinib in RCC Subjects to Assess Drug-Drug Interaction

End point description:

Sparse PK samples were collected and analyzed using a population PK approach to estimate PK parameters. The everolimus concentration data was pooled from studies E7080 -G000-205 (NCT01136733), E7080-M001-221 (NCT02915783), E7080-J081-112 (NCT02454478) or from current study E7080-G000-218 (NCT03173560). A previously developed 3-compartment PK model for everolimus was fitted to the pooled dataset. Individual everolimus AUC at steady state based on the starting dose was derived as a function of starting dose from the final PK model. PK analysis set included all subjects who received at least 1 dose of study drug with documented dosing history and had at least 1 evaluable everolimus whole blood concentration data. Population included subjects from E7080-G000-205 (NCT01136733), E7080-M001-221 (NCT02915783), E7080-J081-112 (NCT02454478) or current study E7080-G000-218 (NCT03173560). "N" are the subjects who were evaluable for endpoint.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1: 0.5-4 hours and 6-10 hours post-dose; Cycle 1 Day 15: pre-dose, 0.5-4 hours and 6-10 hours post-dose; Cycle 2 Day 1: pre-dose and 2-12 hours post-dose (each cycle length =28 days)

End point values	Everolimus 10 mg	Lenvatinib + Everolimus 5 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	33	345		
Units: ng*hour/mL				
arithmetic mean (standard deviation)	507.4 (± 176.6)	305.5 (± 174.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Model Predicted Dose Normalized Area Under the Plasma Drug Concentration-time Curve (AUC) for Lenvatinib Alone and When Coadministration With Everolimus in RCC Subjects to Assess Drug-Drug Interaction

End point title	Model Predicted Dose Normalized Area Under the Plasma Drug Concentration-time Curve (AUC) for Lenvatinib Alone and When Coadministration With Everolimus in RCC Subjects to Assess Drug-Drug Interaction

End point description:

Sparse PK samples were collected and analyzed using population PK approach to estimate PK parameters. The lenvatinib concentration data was pooled from studies E7080-G000-205 (NCT01136733), E7080-M001-221 (NCT02915783), E7080-J081-112 (NCT02454478) and from current study E7080-G000-218 (NCT03173560). A previously developed 3-compartment PK model for lenvatinib was fitted to the pooled dataset. Individual lenvatinib AUC at steady state based on the starting dose was derived as a function of starting dose from the final PK model. The endpoint was assessed for lenvatinib 18 mg dose only. PK analysis set included all subjects who received at least 1 dose of study drug with documented dosing history and had at least 1 evaluable lenvatinib plasma concentration data. Population included subjects from E7080-G000-205 (NCT01136733), E7080-M001-221 (NCT02915783), E7080-J081-112 (NCT02454478) and current study E7080-G000-218 (NCT03173560). "N" are the

subjects who were evaluable for endpoint.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1: 0.5-4 hours and 6-10 hours post-dose; Cycle 1 Day 15: pre-dose, 0.5-4 hours and 6-10 hours post-dose; Cycle 2 Day 1: pre-dose and 2-12 hours post-dose (each cycle length =28 days)

End point values	Lenvatinib 18 mg	Lenvatinib 18 mg + Everolimus 5 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	48	443		
Units: nanogram*hour per milliliter (ng*h/mL)				
arithmetic mean (standard deviation)	3693 (± 1295)	4350 (± 2934)		

Statistical analyses

No statistical analyses for this end point

Secondary: Model Predicted CL/F for Everolimus Alone and When Coadministration With Lenvatinib in RCC Subjects to Assess Drug-Drug Interaction

End point title	Model Predicted CL/F for Everolimus Alone and When Coadministration With Lenvatinib in RCC Subjects to Assess Drug-Drug Interaction

End point description:

Sparse PK samples were collected and analyzed using a population PK approach to estimate PK parameters. The everolimus concentration data was pooled from studies E7080 -G000-205 (NCT01136733), E7080-M001-221 (NCT02915783), E7080-J081-112 (NCT02454478) or from current study E7080-G000-218 (NCT03173560). A previously developed 3-compartment PK model for everolimus was fitted to the pooled dataset. Individual everolimus CL/F value was derived from the final PK model. PK analysis set included all subjects who received at least 1 dose of study drug with documented dosing history and had at least 1 evaluable everolimus whole blood concentration data. Population included subjects from E7080-G000-205 (NCT01136733), E7080-M001-221 (NCT02915783), E7080-J081-112 (NCT02454478) or current study E7080-G000-218 (NCT03173560). Here, "number of subjects analyzed” are the subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1: 0.5-4 hours and 6-10 hours post-dose; Cycle 1 Day 15: pre-dose, 0.5-4 hours and 6-10 hours post-dose; Cycle 2 Day 1: pre-dose and 2-12 hours post-dose (each cycle length =28 days)

End point values	Everolimus 10 mg	Lenvatinib + Everolimus 5 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	33	345		
Units: liter per hour (L/h)				
arithmetic mean (standard deviation)	22.3 (± 10.5)	19.4 (± 7.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as the time from the date of randomization until the date of death from any cause. In the absence of confirmation of death, subjects will be censored either at the date that the subject was last known to be alive or the date of data cutoff for the primary analysis, whichever comes earlier. Median OS was to be calculated using Kaplan-Meier estimate and presented with 2-sided 95% confidence interval. Here, 99999 indicates median, upper limit of 95% CI was not estimable because insufficient number of subjects had events. PPAS1 included all randomized subjects minus the 32 subjects who had received >=2 incorrect lenvatinib doses due to IxRS issues. As pre-specified in the protocol, data for this secondary endpoint was collected and analyzed till the primary analysis only.

End point type	Secondary

End point timeframe:

From the date of randomization until the date of death from any cause, or up to date of data cut off for the primary analysis (up to 29 months)

End point values	Lenvatinib 14 mg + Everolimus 5 mg	Lenvatinib 18 mg + Everolimus 5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	156	155		
Units: months				
median (confidence interval 95%)	27.0 (18.3 to 99999)	99999 (23.8 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Health-Related Quality of Life (HRQoL) Assessed by Functional Assessment of Cancer Therapy Kidney Syndrome Index-Disease-Related Symptoms (FKSI-DRS) Scores

End point title	Health-Related Quality of Life (HRQoL) Assessed by Functional Assessment of Cancer Therapy Kidney Syndrome Index-Disease-Related Symptoms (FKSI-DRS) Scores

End point description:

The FKSI-DRS consisted of 9 items that experts and subjects had indicated are important targets for the treatment of advanced kidney cancer, and that clinical experts had indicated are primarily disease-related, as opposed to treatment-related. Symptoms assessed on the FKSI-DRS included lack of energy, fatigue, weight loss, pain, bone pain, shortness of breath, cough, fever, or hematuria. Each item was

scored on a 5-point Likert-type scale (0 = not at all; 4 = very much) where total score ranged from 0 (worst) to 36 (best), where higher scores correspond to better outcomes. Quality of Life (QoL) analysis set consisted of all subjects who had any QoL data. Here "number of subjects analyzed" are the subjects who were evaluable for the endpoint; "n" were the subjects who were evaluable at given time points and 99999 = no data was calculated due to less subjects. As pre-specified in the protocol, data for this secondary endpoint was collected and analyzed till the primary analysis only.

End point type	Secondary

End point timeframe:

At baseline (prior to first dose of study drug), on Day 1 of each subsequent cycle (cycle length =28 days), and at the Off-treatment visit (up to 29 months)

End point values	Lenvatinib 14 mg + Everolimus 5 mg	Lenvatinib 18 mg + Everolimus 5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	169	162		
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline (n=169,162)	29.69 (± 4.819)	29 (± 5.886)		
Cycle 2 Day 1 (n=156,152)	28.43 (± 5.269)	28.31 (± 5.162)		
Cycle 3 Day 1 (n=146,140)	28.26 (± 5.344)	28.80 (± 5.455)		
Cycle 4 Day 1 (n=133,137)	27.97 (± 5.524)	29.11 (± 5.183)		
Cycle 5 Day 1 (n=125,127)	28 (± 5.680)	29.14 (± 5.081)		
Cycle 6 Day 1 (n=120,120)	28.63 (± 5.185)	29.46 (± 5.107)		
Cycle 7 Day 1 (n=105,103)	28.31 (± 5.486)	29.58 (± 4.803)		
Cycle 8 Day 1 (n=96,97)	28.36 (± 6.204)	29.85 (± 4.610)		
Cycle 9 Day 1 (n=89,92)	28.58 (± 5.562)	29.84 (± 5.005)		
Cycle 10 Day 1 (n=79,75)	29.10 (± 5.294)	30.70 (± 4.297)		
Cycle 11 Day 1 (n=68,72)	29.56 (± 5.035)	30.09 (± 5.316)		
Cycle 12 Day 1 (n=64,61)	29.34 (± 5.149)	30.75 (± 5.127)		
Cycle 13 Day 1 (n=56,53)	29.26 (± 4.851)	30.93 (± 4.201)		
Cycle 14 Day 1 (n=48,52)	29.81 (± 4.752)	31.06 (± 4.830)		
Cycle 15 Day 1 (n=44,51)	30.09 (± 5.121)	30.52 (± 4.417)		
Cycle 16 Day 1 (n=41,47)	29.93 (± 5.293)	30.91 (± 4.704)		
Cycle 17 Day 1 (n=36.40)	29.36 (± 5.233)	31.52 (± 4.875)		
Cycle 18 Day 1 (n=31,34)	29.81 (± 4.293)	31.41 (± 4.639)		
Cycle 19 Day 1 (n=27,34)	28.48 (± 6.216)	30.82 (± 4.469)		

Cycle 20 Day 1 (n=27,31)	28.77 (± 6.058)	30.69 (± 4.575)		
Cycle 21 Day 1 (n=26,28)	29.35 (± 4.707)	32 (± 3.243)		
Cycle 22 Day 1 (n=19,27)	30.32 (± 4.978)	30.59 (± 5.168)		
Cycle 23 Day 1 (n=15,24)	30.53 (± 3.998)	30.29 (± 5.544)		
Cycle 24 Day 1 (n=15,19)	29.47 (± 5.041)	31.58 (± 3.977)		
Cycle 25 Day 1 (n=12,16)	27.92 (± 6.388)	31.69 (± 4.270)		
Cycle 26 Day 1 (n=8,13)	28.75 (± 4.862)	29.82 (± 6.422)		
Cycle 27 Day 1 (n=6,7)	29.83 (± 5.345)	32.86 (± 2.854)		
Cycle 28 Day 1 (n=4,6)	30.50 (± 4.435)	33.67 (± 1.862)		
Cycle 29 Day 1 (n=4,5)	29.50 (± 4.359)	33.40 (± 1.342)		
Cycle 30 Day 1 (n=4,1)	30.75 (± 4.031)	36 (± 99999)		
Cycle 31 Day 1 (n=1,0)	31 (± 99999)	99999 (± 99999)		
Off-treatment Visit (n=78,74)	27.42 (± 5.953)	27.86 (± 6.500)		

Statistical analyses

No statistical analyses for this end point

Secondary: HRQoL assessed by European Organization for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 scores

End point title	HRQoL assessed by European Organization for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 scores

End point description:

In EQ-5D-3L, subjects rate 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) by choosing from 3 answering options (1=no problems; 2=some problems; 3=extreme problems). Summed score ranges from 5-15, "5" =no problems "15" =severe problems in 5 dimensions. EQ-5D index calculated by applying preference-based weights (tariffs) to scores of 5 health state dimensions. Index values range from -1 to 1, 0 =health state equivalent to death and 1=perfect health. EQ-5D-3L also included EQVAS ranges between 100 (best imaginable health) and 0 (worst imaginable health). Decrease in EQ-5D-3L =improvement. Total index EQ-5D-3L score was weighted with range of -0.594 (worst) to 1.0 (best). QoL analysis set. "N"=subjects evaluable for endpoint; "n”=subjects evaluable at given time points and 99999=no data was calculated due to less subjects. As pre-specified in protocol, data for this endpoint was collected and analyzed till primary analysis only.

End point type	Secondary

End point timeframe:

At baseline (prior to first dose of study drug), on Day 1 of each subsequent cycle (cycle length =28 days), and at the Off-treatment visit (up to 29 months)

End point values	Lenvatinib 14 mg + Everolimus 5 mg	Lenvatinib 18 mg + Everolimus 5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	162		
Units: score on a scale				
arithmetic mean (standard deviation)				
Global Health Status/QoL; Baseline(n=171,162)	63.35 (± 22.020)	63.58 (± 21.340)		
Global Health Status/QoL;Cycle 2 Day 1(n=157,151)	58.60 (± 21.234)	60.93 (± 20.280)		
Global Health Status/QoL;Cycle 3 Day 1(n=149,142)	56.43 (± 24.065)	61.85 (± 20.202)		
Global Health Status/QoL;Cycle 4 Day 1(n=133,136)	58.71 (± 19.754)	62.62 (± 19.641)		
Global Health Status/QoL;Cycle 5 Day 1(n=127,126)	59.38 (± 21.670)	63.76 (± 20.339)		
Global Health Status/QoL;Cycle 6 Day 1(n=120,119)	58.75 (± 21.028)	63.73 (± 19.756)		
Global Health Status/QoL;Cycle 7 Day 1(n=107,105)	58.72 (± 20.134)	62.54 (± 20.153)		
Global Health Status/QoL;Cycle 8 Day 1(n=97,97)	58.68 (± 20.409)	62.11 (± 20.271)		
Global Health Status/QoL;Cycle 9 Day 1(n=91,92)	58.97 (± 18.726)	63.77 (± 20.429)		
Global Health Status/QoL;Cycle 10 Day 1(n=80,74)	63.13 (± 19.612)	66.44 (± 19.012)		
Global Health Status/QoL;Cycle 11 Day 1(n=69,72)	60.87 (± 18.705)	65.86 (± 21.173)		
Global Health Status/QoL;Cycle 12 Day 1(n=64,60)	57.81 (± 18.891)	66.94 (± 18.409)		
Global Health Status/QoL;Cycle 13 Day 1(n=55,55)	59.39 (± 19.047)	68.94 (± 18.388)		
Global Health Status/QoL;Cycle 14 Day 1(n=49,52)	61.56 (± 17.498)	70.35 (± 15.605)		
Global Health Status/QoL;Cycle 15 Day 1(n=43,51)	62.98 (± 16.795)	66.83 (± 16.955)		
Global Health Status/QoL;Cycle 16 Day 1(n=41,47)	61.59 (± 17.567)	64.54 (± 19.386)		
Global Health Status/QoL;Cycle 17 Day 1(n=36,40)	60.88 (± 16.882)	67.71 (± 18.794)		
Global Health Status/QoL;Cycle 18 Day 1(n=31,34)	59.68 (± 16.258)	68.38 (± 17.859)		
Global Health Status/QoL;Cycle 19 Day 1(n=27,34)	58.33 (± 19.747)	66.67 (± 15.215)		
Global Health Status/QoL;Cycle 20 Day 1(n=27,31)	58.95 (± 18.479)	66.40 (± 15.736)		
Global Health Status/QoL;Cycle 21 Day 1(n=26,28)	57.05 (± 18.362)	71.13 (± 15.463)		
Global Health Status/QoL;Cycle 22 Day 1(n=19,27)	62.72 (± 14.532)	66.05 (± 17.438)		
Global Health Status/QoL;Cycle 23 Day 1(n=15,24)	60 (± 15.494)	66.67 (± 14.948)		
Global Health Status/QoL;Cycle 24 Day 1 (n=15,19)	64.44 (± 17.385)	65.79 (± 18.818)		
Global Health Status/QoL;Cycle 25 Day 1(n=12,16)	58.33 (± 16.667)	69.79 (± 14.868)		
Global Health Status/QoL;Cycle 26 Day 1(n=8,13)	59.38 (± 15.064)	60.90 (± 18.442)		

Global Health Status/QoL;Cycle 27 Day 1(n=6,7)	59.72 (± 18.572)	71.43 (± 18.545)		
Global Health Status/QoL;Cycle 28 Day 1(n=4,6)	58.33 (± 21.517)	77.78 (± 13.608)		
Global Health Status/QoL;Cycle 29 Day 1(n=4,5)	56.25 (± 18.478)	75 (± 16.667)		
Global Health Status/QoL;Cycle 30 Day 1(n-4,1)	54.17 (± 15.957)	66.67 (± 99999)		
Global Health Status/QoL;Cycle 31 Day 19(n=1,0)	33.33 (± 99999)	99999 (± 99999)		
Global Health Status/QoL;Off-treatment(n=80,73)	51.04 (± 23.133)	56.05 (± 22.363)		
Physical Functioning; Baseline(n=171,162)	76.36 (± 19.282)	76.60 (± 21.855)		
Physical Functioning; Cycle 2 Day 1(n=158,150)	73.54 (± 19.857)	75.38 (± 19.706)		
Physical Functioning; Cycle 3 Day 1(n=148,142)	72.74 (± 21.227)	76.15 (± 19.160)		
Physical Functioning; Cycle 4 Day 1(n=135,137)	70.90 (± 20.873)	75.40 (± 20.155)		
Physical Functioning; Cycle 5 Day 1(n=128,127)	72.80 (± 19.284)	77.85 (± 18.342)		
Physical Functioning; Cycle 6 Day 1(n=123,120)	72.17 (± 21.694)	77.76 (± 18.562)		
Physical Functioning; Cycle 7 Day 1(n=107,105)	73.02 (± 20.769)	78.41 (± 18.034)		
Physical Functioning; Cycle 8 Day 1(n=98,97)	72.77 (± 20.422)	79.11 (± 17.707)		
Physical Functioning; Cycle 9 Day 1(n=91,92)	74.54 (± 19.389)	80.60 (± 16.041)		
Physical Functioning; Cycle 10 Day 1(n=81,75)	75.06 (± 18.908)	81.20 (± 16.271)		
Physical Functioning; Cycle 11 Day 1(n=69,71)	73.72 (± 18.073)	81.13 (± 16.638)		
Physical Functioning; Cycle 12 Day 1(n=65,62)	75.52 (± 17.080)	83.01 (± 15.254)		
Physical Functioning; Cycle 13 Day 1(n=55,55)	74.55 (± 17.874)	80.24 (± 16.873)		
Physical Functioning; Cycle 14 Day 1(n=49,53)	75.78 (± 16.925)	82.39 (± 16.387)		
Physical Functioning; Cycle 15 Day 1(n=44,51)	75.45 (± 16.629)	80.92 (± 17.283)		
Physical Functioning; Cycle 16 Day 1(n=41,47)	73.46 (± 17.129)	81.74 (± 15.982)		
Physical Functioning; Cycle 17 Day 1(n=36,40)	71.85 (± 17.896)	82.33 (± 15.657)		
Physical Functioning; Cycle 18 Day 1(n=31,34)	75.48 (± 17.838)	81.52 (± 16.135)		
Physical Functioning; Cycle 19 Day 1(n=27,34)	76.67 (± 15.771)	81.57 (± 16.002)		
Physical Functioning; Cycle 20 Day 1(n=27,31)	73.09 (± 22.071)	82.80 (± 13.854)		
Physical Functioning; Cycle 21 Day 1(n=26,28)	74.62 (± 18.668)	84.29 (± 12.335)		
Physical Functioning; Cycle 22 Day 1(n=19,27)	80.35 (± 14.483)	82.72 (± 15.164)		
Physical Functioning; Cycle 23 Day 1(n=15,24)	79.56 (± 14.357)	81.39 (± 17.248)		
Physical Functioning; Cycle 24 Day 1(n=15,19)	77.33 (± 16.676)	83.86 (± 13.755)		
Physical Functioning; Cycle 25 Day 1(n=12,16)	72.78 (± 15.688)	84.17 (± 15.753)		

Physical Functioning; Cycle 26 Day 1(n=8,13)	76.67 (± 6.172)	71.79 (± 29.833)		
Physical Functioning; Cycle 27 Day 1(n=6,7)	76.67 (± 6.992)	85.71 (± 16.523)		
Physical Functioning; Cycle 28 Day 1(n=4,6)	78.33 (± 3.333)	90 (± 15.635)		
Physical Functioning; Cycle 29 Day 1(n=4,5)	78.33 (± 3.333)	86.67 (± 16.330)		
Physical Functioning; Cycle 30 Day 1(n=4,1)	76.67 (± 3.849)	100 (± 99999)		
Physical Functioning; Cycle 31 Day 1(n=1,0)	80 (± 99999)	99999 (± 99999)		
Physical Functioning; Off-treatment(n=80,74)	64.50 (± 25.891)	70.41 (± 25.139)		
Role Functioning; Baseline(n=171,162)	73.78 (± 27.471)	75.72 (± 27.932)		
Role Functioning; Cycle 2 Day 1(n=158,150)	68.25 (± 27.951)	69.33 (± 27.449)		
Role Functioning; Cycle 3 Day 1(n=148,142)	67 (± 28.136)	72.18 (± 25.630)		
Role Functioning; Cycle 4 Day 1(n=135,137)	66.67 (± 27.993)	73.60 (± 26.169)		
Role Functioning; Cycle 5 Day 1(n=128,127)	67.32 (± 28.479)	72.44 (± 25.143)		
Role Functioning; Cycle 6 Day 1(n=123,120)	68.16 (± 27.245)	73.75 (± 27.557)		
Role Functioning; Cycle 7 Day 1(n=107,105)	66.51 (± 27.424)	73.97 (± 25.205)		
Role Functioning; Cycle 8 Day 1(n=98,97)	68.20 (± 27.712)	75.60 (± 26.139)		
Role Functioning; Cycle 9 Day 1(n=91,92)	67.58 (± 26.101)	75.91 (± 25.242)		
Role Functioning; Cycle 10 Day 1(n=81,75)	68.52 (± 27.131)	76.89 (± 24.027)		
Role Functioning; Cycle 11 Day 1(n=69,71)	69.57 (± 25.237)	79.11 (± 23.691)		
Role Functioning; Cycle 12 Day 1(n=65,62)	70.51 (± 24.785)	80.91 (± 22.953)		
Role Functioning; Cycle 13 Day 1(n=56,55)	69.64 (± 24.434)	80 (± 24.721)		
Role Functioning; Cycle 14 Day 1(n=49,53)	71.09 (± 24.242)	81.13 (± 23.121)		
Role Functioning; Cycle 15 Day 1(n=44,51)	72.73 (± 22.184)	74.84 (± 25.685)		
Role Functioning; Cycle 16 Day 1(n=41,47)	70.33 (± 23.426)	79.08 (± 21.272)		
Role Functioning; Cycle 17 Day 1(n=36,40)	65.74 (± 22.868)	83.75 (± 18.292)		
Role Functioning; Cycle 18 Day 1(n=31,34)	67.74 (± 20.609)	82.35 (± 22.073)		
Role Functioning; Cycle 19 Day 1(n=27,34)	67.28 (± 28.300)	77.45 (± 23.883)		
Role Functioning; Cycle 20 Day 1(n=27,31)	70.37 (± 23.266)	79.57 (± 24.612)		
Role Functioning; Cycle 21 Day 1(n=26,28)	69.23 (± 21.956)	81.55 (± 19.948)		
Role Functioning; Cycle 22 Day 1(n=19,27)	75.44 (± 20.313)	77.78 (± 22.169)		
Role Functioning; Cycle 23 Day 1(n=15,24)	73.33 (± 25.040)	79.86 (± 23.560)		
Role Functioning; Cycle 24 Day 1(n=15,19)	78.89 (± 16.019)	83.33 (± 19.245)		

Role Functioning; Cycle 25 Day 1(n=12,16)	77.78 (± 17.885)	82.29 (± 23.936)		
Role Functioning; Cycle 26 Day 1(n=8,13)	75 (± 12.599)	69.23 (± 31.066)		
Role Functioning; Cycle 27 Day 1(n=6,7)	77.78 (± 13.608)	90.48 (± 16.265)		
Role Functioning; Cycle 28 Day 1(n=4,6)	79.17 (± 15.957)	97.22 (± 6.804)		
Role Functioning; Cycle 29 Day 1(n=4,5)	75 (± 9.623)	96.67 (± 7.454)		
Role Functioning; Cycle 30 Day 1(n=4,1)	87.50 (± 15.957)	100 (± 99999)		
Role Functioning; Cycle 31 Day 1(n=1,0)	66.67 (± 99999)	99999 (± 99999)		
Role Functioning; Off-treatment(n=79,74)	60.97 (± 31.790)	63.51 (± 31.656)		
Emotional Functioning; Baseline(n=171,162)	79.35 (± 19.704)	80.06 (± 19.729)		
Emotional Functioning; Cycle 2 Day 1(n=157,151)	79.41 (± 19.465)	82.06 (± 19.167)		
Emotional Functioning; Cycle 3 Day 1(n=149,141)	78.47 (± 21.642)	82.90 (± 19.314)		
Emotional Functioning; Cycle 4 Day 1(n=133,136)	78.26 (± 18.854)	84.19 (± 18.517)		
Emotional Functioning; Cycle 5 Day 1(n=127,126)	75.85 (± 21.767)	84.52 (± 15.766)		
Emotional Functioning; Cycle 6 Day 1(n=121,119)	80.60 (± 18.703)	84.38 (± 18.365)		
Emotional Functioning; Cycle 7 Day 1(n=107,105)	77.18 (± 19.571)	84.29 (± 16.356)		
Emotional Functioning; Cycle 8 Day 1(n=98,97)	79.08 (± 19.744)	84.88 (± 18.215)		
Emotional Functioning; Cycle 9 Day 1(n=91,92)	78.75 (± 22.127)	85.96 (± 17.512)		
Emotional Functioning; Cycle 10 Day 1(n=81,74)	80.04 (± 19.440)	87.84 (± 15.433)		
Emotional Functioning; Cycle 11 Day 1(n=69,72)	82.25 (± 20.558)	87.15 (± 16.247)		
Emotional Functioning; Cycle 12 Day 1(n=64,60)	81.51 (± 19.157)	86.67 (± 15.358)		
Emotional Functioning; Cycle 13 Day 1(n=56,55)	79.32 (± 17.908)	87.27 (± 15.783)		
Emotional Functioning; Cycle 14 Day 1(n=49,52)	81.35 (± 16.782)	87.50 (± 17.110)		
Emotional Functioning; Cycle 15 Day 1(n=44,51)	80.30 (± 18.336)	87.25 (± 15.398)		
Emotional Functioning; Cycle 16 Day 1(n=41,47)	81.50 (± 17.432)	87.41 (± 14.935)		
Emotional Functioning; Cycle 17 Day 1(n=36,40)	79.63 (± 19.664)	87.08 (± 16.118)		
Emotional Functioning; Cycle 18 Day 1(n=31,34)	81.90 (± 15.330)	86.76 (± 16.555)		
Emotional Functioning; Cycle 19 Day 1(n=27,34)	81.17 (± 15.945)	84.80 (± 18.403)		
Emotional Functioning; Cycle 20 Day 1(n=27,31)	80.25 (± 17.925)	86.56 (± 17.437)		
Emotional Functioning; Cycle 21 Day 1(n=26,28)	81.73 (± 15.279)	88.99 (± 14.174)		
Emotional Functioning; Cycle 22 Day 1(n=19,27)	85.09 (± 16.096)	89.20 (± 15.644)		
Emotional Functioning; Cycle 23 Day 1(n=15,24)	86.67 (± 15.366)	87.15 (± 15.922)		

Emotional Functioning; Cycle 24 Day 1(n=15,19)	88.89 (± 14.319)	87.28 (± 13.712)		
Emotional Functioning; Cycle 25 Day 1(n=12,16)	83.33 (± 18.119)	90.63 (± 12.500)		
Emotional Functioning; Cycle 26 Day 1(n=8,13)	77.08 (± 23.038)	85.26 (± 23.362)		
Emotional Functioning; Cycle 27 Day 1(n=6,7)	80.56 (± 16.387)	95.24 (± 12.599)		
Emotional Functioning; Cycle 28 Day 1(n=4,6)	75 (± 16.667)	100 (± 0)		
Emotional Functioning; Cycle 29 Day 1(n=4,5)	75 (± 16.667)	100 (± 0)		
Emotional Functioning; Cycle 30 Day 1(n=4,1)	75 (± 16.667)	100 (± 99999)		
Emotional Functioning; Cycle 31 Day 1(n=1,0)	66.67 (± 99999)	99999 (± 99999)		
Emotional Functioning;Off-treatment Visit(n=80,74)	69.62 (± 27.304)	73.87 (± 25.145)		
Cognitive Functioning; Baseline(n=171,162)	87.91 (± 15.764)	89.51 (± 15.529)		
Cognitive Functioning; Cycle 2 Day 1(n=157,151)	87.15 (± 15.661)	88.85 (± 18.025)		
Cognitive Functioning; Cycle 3 Day 1(n=149,141)	84.45 (± 19.049)	87.47 (± 17.946)		
Cognitive Functioning; Cycle 4 Day 1(n=133,136)	83.58 (± 19.461)	90.32 (± 13.692)		
Cognitive Functioning; Cycle 5 Day 1(n=127,126)	83.99 (± 17.239)	87.43 (± 17.086)		
Cognitive Functioning; Cycle 6 Day 1(n=121,119)	84.71 (± 16.886)	87.68 (± 18.470)		
Cognitive Functioning; Cycle 7 Day 1(n=107,105)	82.40 (± 18.855)	87.94 (± 14.708)		
Cognitive Functioning; Cycle 8 Day 1(n=98,97)	81.97 (± 21.227)	88.49 (± 16.380)		
Cognitive Functioning; Cycle 9 Day 1(n=91,92)	83.70 (± 18.084)	87.68 (± 17.095)		
Cognitive Functioning; Cycle 10 Day 1(n=81,75)	85.39 (± 17.947)	90.44 (± 13.747)		
Cognitive Functioning; Cycle 11 Day 1(n=69,72)	84.06 (± 18.176)	88.89 (± 15.824)		
Cognitive Functioning; Cycle 12 Day 1(n=64,60)	85.42 (± 16.400)	88.61 (± 17.758)		
Cognitive Functioning; Cycle 13 Day 1(n=56,55)	83.93 (± 17.685)	89.70 (± 12.624)		
Cognitive Functioning; Cycle 14 Day 1(n=49,52)	85.71 (± 18.634)	87.18 (± 16.375)		
Cognitive Functioning; Cycle 15 Day 1(n=44,51)	84.85 (± 18.264)	83.99 (± 17.308)		
Cognitive Functioning; Cycle 16 Day 1(n=41,47)	83.74 (± 18.062)	89.36 (± 13.649)		
Cognitive Functioning; Cycle 17 Day 1(n=36,40)	82.87 (± 18.033)	89.58 (± 14.465)		
Cognitive Functioning; Cycle 18 Day 1(n=31,34)	83.87 (± 17.994)	90.20 (± 15.417)		
Cognitive Functioning; Cycle 19 Day 1(n=27,34)	80.25 (± 18.511)	89.22 (± 14.727)		
Cognitive Functioning; Cycle 20 Day 1(n=27,31)	82.10 (± 17.250)	91.94 (± 12.073)		
Cognitive Functioning; Cycle 21 Day 1(n=26,28)	81.41 (± 19.623)	88.10 (± 12.715)		
Cognitive Functioning; Cycle 22 Day 1(n=19,27)	88.60 (± 14.754)	90.12 (± 12.454)		

Cognitive Functioning; Cycle 23 Day 1(n=15,24)	83.33 (± 16.667)	88.19 (± 14.311)		
Cognitive Functioning; Cycle 24 Day 1(n=15,19)	84.44 (± 16.019)	92.11 (± 8.550)		
Cognitive Functioning; Cycle 25 Day 1(n=12,16)	84.72 (± 15.006)	98.96 (± 4.167)		
Cognitive Functioning; Cycle 26 Day 1(n=8,13)	89.58 (± 12.400)	92.31 (± 11.004)		
Cognitive Functioning; Cycle 27 Day 1(n=6,7)	83.33 (± 14.907)	95.24 (± 12.599)		
Cognitive Functioning; Cycle 28 Day 1(n=4,6)	91.67 (± 9.623)	100 (± 0)		
Cognitive Functioning; Cycle 29 Day 1(n=4,5)	91.67 (± 9.623)	100 (± 0)		
Cognitive Functioning; Cycle 30 Day 1(n=4,1)	87.50 (± 15.957)	100 (± 99999)		
Cognitive Functioning; Cycle 31 Day 1(n=1,0)	83.33 (± 99999)	99999 (± 99999)		
Cognitive Functioning; Off-treatment(n=80,74)	75.21 (± 25.846)	80.41 (± 23.304)		
Social Functioning; Baseline(n=171,162)	77.29 (± 25.678)	78.29 (± 27.243)		
Social Functioning; Cycle 2 Day 1(n=157,151)	73.46 (± 25.386)	77.15 (± 27.190)		
Social Functioning; Cycle 3 Day 1(n=149,141)	72.04 (± 26.229)	77.19 (± 25.309)		
Social Functioning; Cycle 4 Day 1(n=133,136)	71.43 (± 24.837)	77.33 (± 25.311)		
Social Functioning; Cycle 5 Day 1(n=127,126)	71.78 (± 25.589)	79.63 (± 23.934)		
Social Functioning; Cycle 6 Day 1(n=121,119)	70.80 (± 26.812)	78.71 (± 25.758)		
Social Functioning; Cycle 7 Day 1(n=106,105)	71.70 (± 26.544)	77.30 (± 24.691)		
Social Functioning; Cycle 8 Day 1(n=98,97)	70.24 (± 28.139)	79.04 (± 24.565)		
Social Functioning; Cycle 9 Day 1(n=91,92)	72.16 (± 25.946)	78.62 (± 20.573)		
Social Functioning; Cycle 10 Day 1(n=81,74)	72.43 (± 28.156)	85.14 (± 19.422)		
Social Functioning; Cycle 11 Day 1(n=69,72)	73.91 (± 25.801)	85.19 (± 19.086)		
Social Functioning; Cycle 12 Day 1(n=64,60)	76.56 (± 24.073)	83.89 (± 23.161)		
Social Functioning; Cycle 13 Day 1(n=56,55)	72.92 (± 23.476)	83.94 (± 21.508)		
Social Functioning; Cycle 14 Day 1(n=49,52)	72.79 (± 22.997)	83.97 (± 19.792)		
Social Functioning; Cycle 15 Day 1(n=44,51)	72.73 (± 25.942)	81.37 (± 22.273)		
Social Functioning; Cycle 16 Day 1(n=41,46)	73.17 (± 24.403)	80.80 (± 22.489)		
Social Functioning; Cycle 17 Day 1(n=36,40)	70.37 (± 22.222)	80.42 (± 24.134)		
Social Functioning; Cycle 18 Day 1(n=31,34)	76.88 (± 20.493)	82.84 (± 21.116)		
Social Functioning; Cycle 19 Day 1(n=27,34)	74.07 (± 22.329)	80.88 (± 25.667)		
Social Functioning; Cycle 20 Day 1(n=27,31)	75.31 (± 24.183)	81.72 (± 22.092)		
Social Functioning; Cycle 21 Day 1(n=26,28)	73.72 (± 18.362)	82.14 (± 24.398)		

Social Functioning; Cycle 22 Day 1(n=19,27)	79.82 (± 17.194)	82.10 (± 20.634)		
Social Functioning; Cycle 23 Day 1(n=15,24)	82.22 (± 18.330)	83.33 (± 22.522)		
Social Functioning; Cycle 24 Day 1(n=15,19)	83.33 (± 17.817)	84.21 (± 19.621)		
Social Functioning; Cycle 25 Day 1(n=12,16)	87.50 (± 12.563)	84.38 (± 18.727)		
Social Functioning; Cycle 26 Day 1(n=8,13)	83.33 (± 15.430)	76.92 (± 31.578)		
Social Functioning; Cycle 27 Day 1(n=6,7)	80.56 (± 12.546)	95.24 (± 12.599)		
Social Functioning; Cycle 28 Day 1(n=4,6)	83.33 (± 19.245)	100 (± 0)		
Social Functioning; Cycle 29 Day 1(n=4,5)	79.17 (± 15.957)	100 (± 0)		
Social Functioning; Cycle 30 Day 1(n=4,1)	70.83 (± 8.333)	100 (± 99999)		
Social Functioning; Cycle 31 Day 1(n=1,0)	100 (± 99999)	99999 (± 99999)		
Social Functioning; Off-treatment(n=80,73)	64.58 (± 31.419)	66.89 (± 32.453)		
Fatigue Score; Baseline(n=171,162)	31.32 (± 21.379)	31.76 (± 25.224)		
Fatigue Score; Cycle 2 Day 1(n=158,150)	39.21 (± 22.171)	36.74 (± 23.665)		
Fatigue Score; Cycle 3 Day 1(n=148,142)	40.09 (± 24.095)	36.62 (± 24.031)		
Fatigue Score; Cycle 4 Day 1(n=135,137)	40.21 (± 23.504)	32.68 (± 23.829)		
Fatigue Score; Cycle 5 Day 1(n=128,127)	37.54 (± 23.329)	35.17 (± 22.431)		
Fatigue Score; Cycle 6 Day 1(n=123,120)	38.80 (± 23.246)	33.19 (± 23.696)		
Fatigue Score; Cycle 7 Day 1(n=107,105)	38.06 (± 21.850)	30.79 (± 21.859)		
Fatigue Score; Cycle 8 Day 1(n=97,97)	36.14 (± 22.852)	30.81 (± 23.268)		
Fatigue Score; Cycle 9 Day 1(n=91,92)	35.90 (± 21.281)	30.80 (± 21.293)		
Fatigue Score; Cycle 10 Day 1(n=81,75)	34.57 (± 22.635)	27.11 (± 20.278)		
Fatigue Score; Cycle 11 Day 1(n=69,71)	32.37 (± 20.851)	27.46 (± 22.788)		
Fatigue Score; Cycle 12 Day 1(n=65,62)	32.82 (± 20.264)	23.48 (± 21.302)		
Fatigue Score; Cycle 13 Day 1(n=56,55)	35.52 (± 18.882)	25.05 (± 21.300)		
Fatigue Score; Cycle 14 Day 1(n=49,53)	30.84 (± 21.429)	25.58 (± 20.276)		
Fatigue Score; Cycle 15 Day 1(n=44,51)	28.03 (± 20.682)	28.98 (± 23.315)		
Fatigue Score; Cycle 16 Day 1(n=41,47)	33.33 (± 22.361)	25.53 (± 20.581)		
Fatigue Score; Cycle 17 Day 1(n=36,40)	33.33 (± 21.902)	25 (± 20.090)		
Fatigue Score; Cycle 18 Day 1(n=31,34)	34.05 (± 22.024)	24.84 (± 19.546)		
Fatigue Score; Cycle 19 Day 1(n=27,34)	37.04 (± 23.061)	27.45 (± 22.595)		
Fatigue Score; Cycle 20 Day 1(n=27,31)	34.57 (± 19.812)	27.24 (± 22.192)		

Fatigue Score; Cycle 21 Day 1(n=26,28)	34.19 (± 20.828)	23.02 (± 17.088)		
Fatigue Score; Cycle 22 Day 1(n=19,27)	26.32 (± 18.596)	26.75 (± 20.033)		
Fatigue Score; Cycle 23 Day 1(n=15,24)	26.67 (± 20.053)	29.17 (± 21.934)		
Fatigue Score; Cycle 24 Day 1(n=15,19)	28.15 (± 20.082)	26.90 (± 17.496)		
Fatigue Score; Cycle 25 Day 1(n=12,16)	33.33 (± 19.534)	25.69 (± 19.338)		
Fatigue Score; Cycle 26 Day 1(n=8,13)	26.39 (± 17.755)	37.61 (± 28.160)		
Fatigue Score; Cycle 27 Day 1(n=6,7)	27.78 (± 16.851)	20.63 (± 20.716)		
Fatigue Score; Cycle 28 Day 1(n=4,6)	22.22 (± 15.713)	16.67 (± 19.563)		
Fatigue Score; Cycle 29 Day 1(n=4,5)	22.22 (± 15.713)	15.56 (± 14.907)		
Fatigue Score; Cycle 30 Day 1(n=4,1)	25 (± 16.667)	11.11 (± 99999)		
Fatigue Score; Cycle 31 Day 1(n=1,0)	33.33 (± 99999)	99999 (± 99999)		
Fatigue Score; Off-treatment Visit(n=80,74)	43.47 (± 28.173)	38.89 (± 28.977)		
Nausea and Vomiting; Baseline(n=171,162)	7.60 (± 17.265)	6.28 (± 14.510)		
Nausea and Vomiting; Cycle 2 Day 1(n=158,150)	11.50 (± 18.229)	9.56 (± 17.943)		
Nausea and Vomiting; Cycle 3 Day 1(n=148,142)	14.86 (± 24.057)	9.74 (± 18.219)		
Nausea and Vomiting; Cycle 4 Day 1(n=135,137)	15.80 (± 21.386)	12.17 (± 18.906)		
Nausea and Vomiting; Cycle 5 Day 1(n=127,127)	12.07 (± 17.017)	11.42 (± 18.270)		
Nausea and Vomiting; Cycle 6 Day 1(n=123,120)	12.74 (± 19.215)	10.14 (± 18.996)		
Nausea and Vomiting; Cycle 7 Day 1(n=107,105)	12.46 (± 18.612)	8.57 (± 13.696)		
Nausea and Vomiting; Cycle 8 Day 1(n=98,97)	13.10 (± 21.836)	10.14 (± 15.508)		
Nausea and Vomiting; Cycle 9 Day 1(n=91,92)	12.27 (± 20.005)	9.96 (± 17.306)		
Nausea and Vomiting; Cycle 10 Day 1(n=81,75)	15.02 (± 22.299)	7.78 (± 16.287)		
Nausea and Vomiting; Cycle 11 Day 1(n=69,71)	11.11 (± 18.002)	8.69 (± 15.394)		
Nausea and Vomiting; Cycle 12 Day 1(n=65,62)	12.82 (± 19.042)	6.99 (± 14.645)		
Nausea and Vomiting; Cycle 13 Day 1(n=56,55)	12.20 (± 18.934)	6.97 (± 13.867)		
Nausea and Vomiting; Cycle 14 Day 1(n=49,53)	14.97 (± 21.849)	7.55 (± 16.527)		
Nausea and Vomiting; Cycle 15 Day 1(n=44,51)	14.02 (± 20.631)	8.82 (± 15.038)		
Nausea and Vomiting; Cycle 16 Day 1(n=41,47)	11.38 (± 19.874)	9.22 (± 15.467)		
Nausea and Vomiting; Cycle 17 Day 1(n=36,40)	14.35 (± 22.940)	5 (± 13.183)		
Nausea and Vomiting; Cycle 18 Day 1(n=31,34)	10.75 (± 22.587)	9.31 (± 15.457)		
Nausea and Vomiting; Cycle 19 Day 1(n=27,34)	16.67 (± 27.347)	7.35 (± 15.457)		

Nausea and Vomiting; Cycle 20 Day 1(n=27,31)	16.67 (± 23.113)	10.22 (± 15.915)		
Nausea and Vomiting; Cycle 21 Day 1(n=26,28)	12.82 (± 20.714)	7.74 (± 12.408)		
Nausea and Vomiting; Cycle 22 Day 1(n=19,27)	7.02 (± 11.541)	8.64 (± 13.374)		
Nausea and Vomiting; Cycle 23 Day 1(n=15,24)	5.56 (± 12.062)	6.25 (± 11.849)		
Nausea and Vomiting; Cycle 24 Day 1(n=15,19)	6.67 (± 13.801)	7.89 (± 17.004)		
Nausea and Vomiting; Cycle 25 Day 1(n=12,16)	13.89 (± 21.122)	2.08 (± 8.333)		
Nausea and Vomiting; Cycle 26 Day 1(n=8,13)	4.17 (± 7.715)	14.10 (± 24.387)		
Nausea and Vomiting; Cycle 27 Day 1(n=6,7)	5.56 (± 13.608)	16.67 (± 28.868)		
Nausea and Vomiting; Cycle 28 Day 1(n=4,6)	12.50 (± 15.957)	8.33 (± 20.412)		
Nausea and Vomiting; Cycle 29 Day 1(n=4,5)	16.67 (± 13.608)	0 (± 0)		
Nausea and Vomiting; Cycle 30 Day 1(n=4,1)	8.33 (± 16.667)	0 (± 99999)		
Nausea and Vomiting; Cycle 31 Day 1(n=1,0)	16.67 (± 99999)	99999 (± 99999)		
Nausea and Vomiting; Off-treatment(n=80,74)	13.33 (± 22.564)	6.76 (± 13.207)		
Pain Score; Baseline(n=171,162)	23.39 (± 25.410)	23.77 (± 26.323)		
Pain Score; Cycle 2 Day 1(n=158,151)	26.79 (± 25.850)	27.04 (± 23.862)		
Pain Score; Cycle 3 Day 1(n=149,142)	27.63 (± 24.103)	25 (± 24.046)		
Pain Score; Cycle 4 Day 1(n=135,137)	26.67 (± 24.788)	22.87 (± 21.486)		
Pain Score; Cycle 5 Day 1(n=128,127)	29.04 (± 26.805)	22.97 (± 22.314)		
Pain Score; Cycle 6 Day 1(n=123,120)	26.29 (± 24.887)	22.50 (± 25.716)		
Pain Score; Cycle 7 Day 1(n=107,105)	28.04 (± 23.189)	23.65 (± 22.142)		
Pain Score; Cycle 8 Day 1(n=98,97)	27.38 (± 23.722)	23.20 (± 24.949)		
Pain Score; Cycle 9 Day 1(n=91,92)	27.11 (± 23.393)	21.01 (± 20.053)		
Pain Score; Cycle 10 Day 1(n=81,75)	26.95 (± 22.603)	19.33 (± 18.792)		
Pain Score; Cycle 11 Day 1(n=69,72)	27.29 (± 22.319)	18.06 (± 20.508)		
Pain Score; Cycle 12 Day 1(n=65,62)	26.41 (± 21.018)	18.55 (± 19.814)		
Pain Score; Cycle 13 Day 1(n=56,55)	24.40 (± 20.092)	18.48 (± 20.203)		
Pain Score; Cycle 14 Day 1(n=49,53)	22.11 (± 22.666)	16.04 (± 19.601)		
Pain Score; Cycle 15 Day 1(n=44,53)	24.24 (± 23.966)	17.65 (± 18.078)		
Pain Score; Cycle 16 Day 1(n=41,47)	29.67 (± 25.417)	18.44 (± 20.628)		
Pain Score; Cycle 17 Day 1(n=36,40)	27.78 (± 25.198)	17.50 (± 19.954)		
Pain Score; Cycle 18 Day 1(n=31,34)	25.27 (± 20.125)	16.67 (± 18.803)		

Pain Score; Cycle 19 Day 1(n=27,34)	31.48 (± 23.266)	19.61 (± 22.274)		
Pain Score; Cycle 20 Day 1(n=27,31)	29.63 (± 23.266)	19.35 (± 21.558)		
Pain Score; Cycle 21 Day 1(n=26,28)	26.92 (± 23.131)	17.86 (± 21.721)		
Pain Score; Cycle 22 Day 1(n=19,27)	23.68 (± 17.843)	22.84 (± 24.085)		
Pain Score; Cycle 23 Day 1(n=15,24)	21.11 (± 14.729)	18.06 (± 23.527)		
Pain Score; Cycle 24 Day 1(n=15,19)	22.22 (± 20.574)	14.91 (± 19.160)		
Pain Score; Cycle 25 Day 1(n=12,16)	27.78 (± 23.925)	15.63 (± 19.691)		
Pain Score; Cycle 26 Day 1(n=8,13)	27.08 (± 21.708)	21.79 (± 27.542)		
Pain Score; Cycle 27 Day 1(n=6,7)	25 (± 20.412)	11.90 (± 24.934)		
Pain Score; Cycle 28 Day 1(n=4,6)	25 (± 21.517)	2.78 (± 6.804)		
Pain Score; Cycle 29 Day 1(n=4,5)	25 (± 21.517)	6.67 (± 14.907)		
Pain Score; Cycle 30 Day 1(n=4,1)	25 (± 16.667)	0 (± 99999)		
Pain Score; Cycle 31 Day 1(n=1,0)	33.33 (± 99999)	99999 (± 99999)		
Pain Score; Off-treatment Visit(n=80,74)	28.33 (± 27.354)	27.70 (± 28.171)		
Dyspnea; Baseline(n=170,162)	21.18 (± 25.562)	22.22 (± 26.006)		
Dyspnea; Cycle 2 Day 1(n=157,150)	18.90 (± 24.248)	19.56 (± 23.865)		
Dyspnea; Cycle 3 Day 1(n=147,142)	20.63 (± 24.155)	19.72 (± 23.871)		
Dyspnea; Cycle 4 Day 1(n=134,137)	19.90 (± 24.224)	17.52 (± 20.643)		
Dyspnea; Cycle 5 Day 1(n=127,127)	19.16 (± 23.201)	15.75 (± 20.925)		
Dyspnea; Cycle 6 Day 1(n=122,120)	16.67 (± 21.104)	18.89 (± 23.957)		
Dyspnea; Cycle 7 Day 1(n=105,105)	19.37 (± 23.922)	15.87 (± 21.728)		
Dyspnea; Cycle 8 Day 1(n=97,97)	19.24 (± 23.489)	14.09 (± 20.319)		
Dyspnea; Cycle 9 Day 1(n=90,92)	15.93 (± 20.740)	14.49 (± 21.712)		
Dyspnea; Cycle 10 Day 1(n=80,75)	17.92 (± 21.832)	11.56 (± 19.369)		
Dyspnea; Cycle 11 Day 1(n=68,71)	18.63 (± 23.310)	15.02 (± 23.764)		
Dyspnea; Cycle 12 Day 1(n=64,62)	13.54 (± 21.998)	12.90 (± 22.057)		
Dyspnea; Cycle 13 Day 1(n=56,55)	13.69 (± 20.867)	10.91 (± 20.341)		
Dyspnea; Cycle 14 Day 1(n=49,53)	15.65 (± 21.626)	10.69 (± 20.437)		
Dyspnea; Cycle 15 Day 1(n=44,51)	15.15 (± 19.628)	12.42 (± 21.040)		
Dyspnea; Cycle 16 Day 1(n=41,47)	16.26 (± 22.512)	9.93 (± 16.904)		
Dyspnea; Cycle 17 Day 1(n=36,40)	15.74 (± 20.293)	10 (± 20.255)		
Dyspnea; Cycle 18 Day 1(n=31,34)	16.13 (± 20.854)	10.78 (± 17.829)		

Dyspnea; Cycle 19 Day 1(n=26,34)	15.38 (± 21.563)	9.80 (± 17.465)		
Dyspnea; Cycle 20 Day 1(n=27,31)	23.46 (± 20.286)	11.83 (± 16.212)		
Dyspnea; Cycle 21 Day 1(n=26,28)	15.38 (± 16.946)	7.14 (± 13.929)		
Dyspnea; Cycle 22 Day 1(n=19,27)	17.54 (± 20.393)	12.35 (± 18.829)		
Dyspnea; Cycle 23 Day 1(n=15,24)	13.33 (± 21.082)	11.11 (± 18.822)		
Dyspnea; Cycle 24 Day 1(n=15,19)	20 (± 21.082)	12.28 (± 16.520)		
Dyspnea; Cycle 25 Day 1(n=12,16)	22.22 (± 29.588)	8.33 (± 14.907)		
Dyspnea; Cycle 26 Day 1(n=8,13)	16.67 (± 17.817)	15.38 (± 22.008)		
Dyspnea; Cycle 27 Day 1(n=6,7)	11.11 (± 17.213)	14.29 (± 17.817)		
Dyspnea; Cycle 28 Day 1(n=4,6)	16.67 (± 19.245)	16.67 (± 18.257)		
Dyspnea; Cycle 29 Day 1(n=4,5)	25 (± 16.667)	20 (± 18.257)		
Dyspnea; Cycle 30 Day 1(n=4,1)	16.67 (± 19.245)	0 (± 99999)		
Dyspnea; Cycle 31 Day 1(n=1,0)	33.33 (± 99999)	99999 (± 99999)		
Dyspnea; Off-treatment Visit(n=77,74)	24.68 (± 27.254)	21.62 (± 28.898)		
Insomnia; Baseline (n=169,162)	23.08 (± 26.972)	22.84 (± 27.671)		
Insomnia; Cycle 2 Day 1(n=157,149)	26.11 (± 27.038)	19.91 (± 25.386)		
Insomnia; Cycle 3 Day 1(n=147,142)	30.39 (± 29.435)	23 (± 25.477)		
Insomnia; Cycle 4 Day 1(n=133,137)	26.57 (± 28.057)	20.19 (± 24.036)		
Insomnia; Cycle 5 Day 1(n=126,127)	23.02 (± 26.487)	22.05 (± 24.205)		
Insomnia; Cycle 6 Day 1(n=122,120)	24.86 (± 26.955)	17.50 (± 22.019)		
Insomnia; Cycle 7 Day 1(n=105,105)	25.08 (± 27.651)	20 (± 25.149)		
Insomnia; Cycle 8 Day 1(n=97,97)	26.46 (± 28.843)	19.59 (± 25.346)		
Insomnia; Cycle 9 Day 1(n=90,92)	25.56 (± 27.392)	16.67 (± 21.255)		
Insomnia; Cycle 10 Day 1(n=80,75)	24.58 (± 25.844)	18.22 (± 22.789)		
Insomnia; Cycle 11 Day 1(n=68,71)	24.02 (± 26.918)	17.37 (± 24.468)		
Insomnia; Cycle 12 Day 1(n=64,62)	23.44 (± 23.518)	13.98 (± 22.216)		
Insomnia; Cycle 13 Day 1(n=56,55)	21.43 (± 21.489)	13.33 (± 21.849)		
Insomnia; Cycle 14 Day 1(n=48,53)	18.06 (± 23.778)	11.95 (± 21.774)		
Insomnia; Cycle 15 Day 1(n=44,50)	18.94 (± 20.832)	16 (± 23.561)		
Insomnia; Cycle 16 Day 1(n=41,47)	20.33 (± 20.921)	14.89 (± 21.768)		
Insomnia; Cycle 17 Day 1(n=36,40)	17.59 (± 16.877)	13.33 (± 21.082)		

Insomnia; Cycle 18 Day 1(n=31,34)	27.96 (± 25.958)	11.76 (± 19.903)		
Insomnia; Cycle 19 Day 1(n=27,34)	24.69 (± 25.474)	13.73 (± 21.893)		
Insomnia; Cycle 20 Day 1(n=27,31)	25.93 (± 25.036)	12.90 (± 20.507)		
Insomnia; Cycle 21 Day 1(n=26,28)	23.08 (± 27.919)	10.71 (± 18.265)		
Insomnia; Cycle 22 Day 1(n=19,27)	21.05 (± 19.909)	6.17 (± 16.111)		
Insomnia; Cycle 23 Day 1(n=15,24)	26.67 (± 22.537)	11.11 (± 23.399)		
Insomnia; Cycle 24 Day 1(n=15,19)	24.44 (± 26.627)	12.28 (± 19.909)		
Insomnia; Cycle 25 Day 1(n=12,16)	16.67 (± 17.408)	12.50 (± 20.638)		
Insomnia; Cycle 26 Day 1(n=8,13)	16.67 (± 17.817)	20.51 (± 32.026)		
Insomnia; Cycle 27 Day 1(n=6,7)	22.22 (± 17.213)	9.52 (± 16.265)		
Insomnia; Cycle 28 Day 1(n=4,6)	25 (± 16.667)	11.11 (± 17.213)		
Insomnia; Cycle 29 Day 1(n=4,5)	25 (± 16.667)	13.33 (± 18.257)		
Insomnia; Cycle 30 Day 1(n=4,1)	25 (± 16.667)	0 (± 99999)		
Insomnia; Cycle 31 Day 1(n=1,0)	33.33 (± 99999)	99999 (± 99999)		
Insomnia; Off-treatment Visit(n=78,74)	32.05 (± 32.430)	28.83 (± 31.850)		
Appetite Loss; Baseline(n=171,162)	15.79 (± 24.606)	18.31 (± 27.060)		
Appetite Loss; Cycle 2 Day 1(n=158,150)	26.79 (± 31.129)	27.56 (± 32.020)		
Appetite Loss; Cycle 3 Day 1(n=147,142)	31.97 (± 31.905)	29.81 (± 31.687)		
Appetite Loss; Cycle 4 Day 1(n=134,137)	32.09 (± 31.239)	30.90 (± 32.749)		
Appetite Loss; Cycle 5 Day 1(n=128,125)	30.47 (± 29.881)	30.67 (± 32.129)		
Appetite Loss; Cycle 6 Day 1(n=123,120)	30.35 (± 31.365)	26.11 (± 29.996)		
Appetite Loss; Cycle 7 Day 1(n=107,105)	29.28 (± 31.956)	26.98 (± 28.154)		
Appetite Loss; Cycle 8 Day 1(n=98,96)	29.25 (± 31.483)	25.00 (± 26.491)		
Appetite Loss; Cycle 9 Day 1(n=91,92)	29.30 (± 30.565)	25.36 (± 27.678)		
Appetite Loss; Cycle 10 Day 1(n=81,75)	27.57 (± 29.716)	22.22 (± 22.815)		
Appetite Loss; Cycle 11 Day 1(n=69,71)	24.15 (± 27.938)	22.07 (± 26.988)		
Appetite Loss; Cycle 12 Day 1(n=65,62)	22.05 (± 24.493)	18.82 (± 25.336)		
Appetite Loss; Cycle 13 Day 1(n=56,54)	23.21 (± 25.362)	17.28 (± 21.221)		
Appetite Loss; Cycle 14 Day 1(n=49,53)	19.73 (± 24.456)	17.61 (± 24.111)		
Appetite Loss; Cycle 15 Day 1(n=44,51)	17.42 (± 23.282)	24.18 (± 30.608)		
Appetite Loss; Cycle 16 Day 1(n=41,47)	23.58 (± 27.125)	22.70 (± 27.014)		

Appetite Loss; Cycle 17 Day 1(n=36,40)	20.37 (± 21.496)	22.50 (± 25.473)		
Appetite Loss; Cycle 18 Day 1(n=31,33)	19.35 (± 22.401)	22.22 (± 24.533)		
Appetite Loss; Cycle 19 Day 1(n=27,34)	19.75 (± 23.130)	20.59 (± 25.969)		
Appetite Loss; Cycle 20 Day 1(n=27,31)	23.46 (± 25.844)	21.51 (± 30.488)		
Appetite Loss; Cycle 21 Day 1(n=26,28)	23.08 (± 20.590)	15.48 (± 21.242)		
Appetite Loss; Cycle 22 Day 1(n=19,27)	17.54 (± 20.393)	17.28 (± 25.099)		
Appetite Loss; Cycle 23 Day 1(n=15,24)	17.78 (± 24.774)	20.83 (± 27.474)		
Appetite Loss; Cycle 24 Day 1(n=15,19)	13.33 (± 24.560)	15.79 (± 25.744)		
Appetite Loss; Cycle 25 Day 1(n=12,16)	19.44 (± 22.285)	18.75 (± 29.736)		
Appetite Loss; Cycle 26 Day 1(n=8,13)	29.17 (± 27.817)	23.08 (± 34.385)		
Appetite Loss; Cycle 27 Day 1(n=6,7)	16.67 (± 18.257)	9.52 (± 16.265)		
Appetite Loss; Cycle 28 Day 1(n=4,6)	8.33 (± 16.667)	11.11 (± 17.213)		
Appetite Loss; Cycle 29 Day 1(n=4,5)	16.67 (± 19.245)	0 (± 0)		
Appetite Loss; Cycle 30 Day 1(n=4,1)	8.33 (± 16.667)	0 (± 99999)		
Appetite Loss; Cycle 31 Day 1(n=1,0)	0 (± 99999)	99999 (± 99999)		
Appetite Loss Score; Off-treatment(n=80,74)	29.58 (± 31.820)	25.23 (± 32.082)		
Constipation; Baseline(n=171,162)	15.98 (± 24.876)	12.55 (± 23.501)		
Constipation; Cycle 2 Day 1(n=157,150)	10.40 (± 20.274)	11.11 (± 21.035)		
Constipation; Cycle 3 Day 1(n=147,142)	9.52 (± 20.644)	10.80 (± 20.456)		
Constipation; Cycle 4 Day 1(n=135,136)	11.11 (± 21.930)	9.80 (± 19.081)		
Constipation; Cycle 5 Day 1(n=128,125)	12.24 (± 20.438)	9.87 (± 19.411)		
Constipation; Cycle 6 Day 1(n=122,118)	8.47 (± 16.905)	8.47 (± 19.090)		
Constipation; Cycle 7 Day 1(n=106,103)	11.01 (± 22.874)	7.44 (± 16.785)		
Constipation; Cycle 8 Day 1(n=97,97)	9.62 (± 18.608)	7.22 (± 14.614)		
Constipation; Cycle 9 Day 1(n=91,92)	6.23 (± 15.644)	9.42 (± 19.967)		
Constipation; Cycle 10 Day 1(n=81,75)	6.58 (± 13.354)	8.00 (± 18.042)		
Constipation; Cycle 11 Day 1(n=69,71)	6.76 (± 15.739)	7.98 (± 18.227)		
Constipation; Cycle 12 Day 1(n=65,62)	5.64 (± 13.906)	9.68 (± 18.492)		
Constipation; Cycle 13 Day 1(n=55,55)	3.64 (± 12.294)	9.09 (± 18.653)		
Constipation; Cycle 14 Day 1(n=49,52)	5.44 (± 14.186)	7.69 (± 16.978)		
Constipation; Cycle 15 Day 1(n=43,50)	5.43 (± 17.714)	9.33 (± 19.095)		

Constipation; Cycle 16 Day 1(n=39,47)	5.98 (± 16.879)	9.93 (± 18.277)		
Constipation; Cycle 17 Day 1(n=36,40)	11.11 (± 22.537)	5.00 (± 12.054)		
Constipation; Cycle 18 Day 1(n=31,34)	7.53 (± 14.167)	7.84 (± 16.532)		
Constipation; Cycle 19 Day 1(n=27,34)	9.88 (± 18.057)	9.80 (± 20.969)		
Constipation; Cycle 20 Day 1(n=27,31)	8.64 (± 17.523)	8.60 (± 22.718)		
Constipation; Cycle 21 Day 1(n=26,28)	8.97 (± 17.783)	7.14 (± 16.623)		
Constipation; Cycle 22 Day 1(n=19,27)	7.02 (± 13.962)	7.41 (± 19.245)		
Constipation; Cycle 23 Day 1(n=15,24)	6.67 (± 13.801)	11.11 (± 21.234)		
Constipation; Cycle 24 Day 1(n=15,19)	4.44 (± 17.213)	8.77 (± 21.779)		
Constipation; Cycle 25 Day 1(n=12,16)	5.56 (± 12.975)	18.75 (± 29.736)		
Constipation; Cycle 26 Day 1(n=8,13)	8.33 (± 15.430)	15.38 (± 25.875)		
Constipation; Cycle 27 Day 1(n=6,7)	16.67 (± 27.889)	0 (± 0)		
Constipation; Cycle 28 Day 1(n=4,6)	25.00 (± 31.914)	0 (± 0)		
Constipation; Cycle 29 Day 1(n=4,5)	25.00 (± 31.914)	0 (± 0)		
Constipation; Cycle 30 Day 1(n=4,1)	16.67 (± 33.333)	0 (± 99999)		
Constipation; Cycle 31 Day 1(n=1,0)	33.33 (± 99999)	99999 (± 99999)		
Constipation; Off-treatment(n=80,74)	13.33 (± 23.481)	12.61 (± 21.863)		
Diarrhea; Baseline(n=171,162)	6.43 (± 15.045)	6.79 (± 15.823)		
Diarrhea; Cycle 2 Day 1(n=157,151)	22.29 (± 29.572)	17.66 (± 26.333)		
Diarrhea; Cycle 3 Day 1(n=149,141)	32.21 (± 30.858)	27.19 (± 32.023)		
Diarrhea; Cycle 4 Day 1(n=133,136)	35.59 (± 33.634)	29.41 (± 28.991)		
Diarrhea; Cycle 5 Day 1(n=127,125)	28.61 (± 28.085)	29.33 (± 29.207)		
Diarrhea; Cycle 6 Day 1(n=121,119)	31.96 (± 30.550)	26.89 (± 27.541)		
Diarrhea; Cycle 7 Day 1(n=107,105)	33.64 (± 31.885)	31.75 (± 27.881)		
Diarrhea; Cycle 8 Day 1(n=97,97)	29.55 (± 28.818)	31.27 (± 28.793)		
Diarrhea; Cycle 9 Day 1(n=91,92)	34.43 (± 33.129)	28.62 (± 28.637)		
Diarrhea; Cycle 10 Day 1(n=81,75)	29.22 (± 29.992)	29.33 (± 25.088)		
Diarrhea; Cycle 11 Day 1(n=69,72)	28.02 (± 28.367)	26.85 (± 26.619)		
Diarrhea; Cycle 12 Day 1(n=62,60)	28.49 (± 31.273)	22.78 (± 23.363)		
Diarrhea; Cycle 13 Day 1(n=56,55)	26.19 (± 28.223)	23.03 (± 25.558)		
Diarrhea; Cycle 14 Day 1(n=49,52)	26.53 (± 25.440)	24.36 (± 22.008)		

Diarrhea; Cycle 15 Day 1(n=44,51)	29.55 (± 29.828)	30.07 (± 26.038)		
Diarrhea; Cycle 16 Day 1(n=41,47)	20.33 (± 27.767)	23.40 (± 21.886)		
Diarrhea; Cycle 17 Day 1(n=36,40)	21.30 (± 24.107)	29.17 (± 28.432)		
Diarrhea; Cycle 18 Day 1(n=31,34)	21.51 (± 25.164)	25.49 (± 23.296)		
Diarrhea; Cycle 19 Day 1(n=27,34)	23.46 (± 28.963)	21.57 (± 21.528)		
Diarrhea; Cycle 20 Day 1(n=27,31)	19.75 (± 23.130)	22.58 (± 23.392)		
Diarrhea; Cycle 21 Day 1(n=26,28)	20.51 (± 26.795)	21.43 (± 18.624)		
Diarrhea; Cycle 22 Day 1(n=19,27)	17.54 (± 20.393)	24.69 (± 19.812)		
Diarrhea; Cycle 23 Day 1(n=15,24)	15.56 (± 17.213)	22.22 (± 16.051)		
Diarrhea; Cycle 24 Day 1(n=15,19)	11.11 (± 16.265)	19.30 (± 16.909)		
Diarrhea; Cycle 25 Day 1(n=12,16)	19.44 (± 22.285)	18.75 (± 17.078)		
Diarrhea; Cycle 26 Day 1(n=8,13)	25.00 (± 29.547)	17.95 (± 17.296)		
Diarrhea; Cycle 27 Day 1(n=6,7)	33.33 (± 21.082)	33.33 (± 19.245)		
Diarrhea; Cycle 28 Day 1(n=4,6)	16.67 (± 19.245)	22.22 (± 17.213)		
Diarrhea; Cycle 29 Day 1(n=4,5)	8.33 (± 16.667)	20.00 (± 18.257)		
Diarrhea; Cycle 30 Day 1(n=4,1)	16.67 (± 19.245)	0 (± 99999)		
Diarrhea; Cycle 31 Day 1(n=1,0)	33.33 (± 99999)	99999 (± 99999)		
Diarrhea; Off-treatment(n=80,74)	18.33 (± 25.380)	12.16 (± 19.565)		
Financial Difficulties; Baseline(n=170,162)	21.76 (± 28.382)	20.37 (± 29.076)		
Financial Difficulties; Cycle 2 Day 1(n=155,151)	21.08 (± 28.177)	15.01 (± 24.852)		
Financial Difficulties; Cycle 3 Day 1(n=147,141)	23.13 (± 27.201)	18.20 (± 27.451)		
Financial Difficulties; Cycle 4 Day 1(n=131,134)	22.90 (± 27.761)	16.42 (± 25.113)		
Financial Difficulties; Cycle 5 Day 1(n=125,126)	22.93 (± 28.213)	18.78 (± 29.058)		
Financial Difficulties; Cycle 6 Day 1(n=120,118)	25.00 (± 27.416)	17.80 (± 25.666)		
Financial Difficulties; Cycle 7 Day 1(n=105,105)	30.16 (± 31.866)	15.87 (± 24.062)		
Financial Difficulties; Cycle 8 Day 1(n=97,97)	25.43 (± 29.176)	17.53 (± 24.576)		
Financial Difficulties; Cycle 9 Day 1(n=90,90)	25.56 (± 30.002)	16.67 (± 23.440)		
Financial Difficulties; Cycle 10 Day 1(n=80,73)	22.50 (± 27.952)	17.35 (± 24.913)		
Financial Difficulties; Cycle 11 Day 1(n=66,72)	26.26 (± 30.108)	16.20 (± 24.382)		
Financial Difficulties; Cycle 12 Day 1(n=63,60)	24.87 (± 28.061)	16.11 (± 24.156)		
Financial Difficulties; Cycle 13 Day 1(n=55,54)	23.03 (± 26.351)	19.14 (± 25.577)		

Financial Difficulties; Cycle 14 Day 1(n=48,52)	20.83 (± 22.413)	17.31 (± 25.127)		
Financial Difficulties; Cycle 15 Day 1(n=43,51)	21.71 (± 27.103)	19.61 (± 26.813)		
Financial Difficulties; Cycle 16 Day 1(n=40,47)	21.67 (± 25.654)	17.02 (± 24.937)		
Financial Difficulties; Cycle 17 Day 1(n=35,40)	23.81 (± 27.501)	19.17 (± 27.099)		
Financial Difficulties; Cycle 18 Day 1(n=31,34)	17.20 (± 18.995)	19.61 (± 28.566)		
Financial Difficulties; Cycle 19 Day 1(n=27,34)	18.52 (± 19.245)	20.59 (± 28.444)		
Financial Difficulties; Cycle 20 Day 1(n=27,31)	16.05 (± 21.424)	20.43 (± 30.644)		
Financial Difficulties; Cycle 21 Day 1(n=26,28)	19.23 (± 21.444)	20.24 (± 27.725)		
Financial Difficulties; Cycle 22 Day 1(n=19,27)	24.56 (± 24.450)	20.99 (± 29.451)		
Financial Difficulties; Cycle 23 Day 1(n=15,24)	17.78 (± 17.213)	23.61 (± 31.819)		
Financial Difficulties; Cycle 24 Day 1(n=15,19)	17.78 (± 21.331)	19.30 (± 25.618)		
Financial Difficulties; Cycle 25 Day 1(n=12,16)	16.67 (± 22.473)	16.67 (± 24.343)		
Financial Difficulties; Cycle 26 Day 1(n=8,13)	20.83 (± 24.801)	20.51 (± 32.026)		
Financial Difficulties; Cycle 27 Day 1(n=6,7)	16.67 (± 18.257)	0 (± 0)		
Financial Difficulties; Cycle 28 Day 1(n=4,6)	25.00 (± 16.667)	0 (± 0)		
Financial Difficulties; Cycle 29 Day 1(n=4,5)	25.00 (± 16.667)	0 (± 0)		
Financial Difficulties; Cycle 30 Day 1(n=4,1)	25.00 (± 16.667)	0 (± 99999)		
Financial Difficulties; Cycle 31 Day 1(n=1,0)	0 (± 99999)	99999 (± 99999)		
Financial Difficulties; Off-treatment(n=79,73)	31.65 (± 32.423)	25.11 (± 30.318)		

Statistical analyses

No statistical analyses for this end point

Secondary: HRQoL Assessed by European Quality of Life (EuroQol) Five-Dimensional, 3-Level (EQ-5D-3L) Index Score and Visual Analogue Scale (VAS)

End point title	HRQoL Assessed by European Quality of Life (EuroQol) Five-Dimensional, 3-Level (EQ-5D-3L) Index Score and Visual Analogue Scale (VAS)

End point description:

In EQ-5D-3L, subjects rate 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) by choosing from 3 answering options (1=no problems; 2=some problems; 3=extreme problems). Summed score ranges from 5-15, "5" =no problems "15" =severe problems in 5 dimensions. EQ-5D index calculated by applying preference-based weights (tariffs) to scores of 5 health state dimensions. Index values range from -1 to 1, 0 =health state equivalent to death and 1=perfect health. EQ-5D-3L also included EQVAS ranges between 100 (best imaginable health) and 0 (worst imaginable health). Decrease in EQ-5D-3L =improvement. Total index EQ-5D-3L score was weighted with range of -0.594 (worst) to 1.0 (best). QoL analysis set. "N"=subjects evaluable for endpoint; "n”=subjects evaluable at given time points and 99999=no data was calculated due to less subjects. As pre-specified in protocol, data for this endpoint was collected and analyzed till primary analysis only.

End point type	Secondary

End point timeframe:

At baseline (prior to first dose of study drug), on Day 1 of each subsequent cycle (cycle length =28 days), and at the Off-treatment visit (up to 29 months)

End point values	Lenvatinib 14 mg + Everolimus 5 mg	Lenvatinib 18 mg + Everolimus 5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	168	161		
Units: score on a scale				
arithmetic mean (standard deviation)				
EQ-5D Index Score; Baseline(n=168,161)	0.76 (± 0.216)	0.78 (± 0.232)		
EQ-5D Index Score; Cycle 2 Day 1(n=151,147)	0.76 (± 0.178)	0.76 (± 0.230)		
EQ-5D Index Score; Cycle 3 Day 1(n=144,134)	0.73 (± 0.232)	0.78 (± 0.239)		
EQ-5D Index Score; Cycle 4 Day 1(n=131,131)	0.73 (± 0.213)	0.78 (± 0.236)		
EQ-5D Index Score; Cycle 5 Day 1(n=124,124)	0.73 (± 0.212)	0.78 (± 0.199)		
EQ-5D Index Score; Cycle 6 Day 1(n=121,114)	0.73 (± 0.220)	0.77 (± 0.225)		
EQ-5D Index Score; Cycle 7 Day 1(n=103,102)	0.71 (± 0.219)	0.78 (± 0.196)		
EQ-5D Index Score; Cycle 8 Day 1(n=95,95)	0.75 (± 0.187)	0.80 (± 0.187)		
EQ-5D Index Score; Cycle 9 Day 1(n=87,89)	0.73 (± 0.192)	0.79 (± 0.192)		
EQ-5D Index Score; Cycle 10 Day 1(n=77,71)	0.76 (± 0.186)	0.81 (± 0.177)		
EQ-5D Index Score; Cycle 11 Day 1(n=67,70)	0.77 (± 0.185)	0.82 (± 0.82)		
EQ-5D Index Score; Cycle 12 Day 1(n=64,59)	0.77 (± 0.173)	0.83 (± 0.161)		
EQ-5D Index Score; Cycle 13 Day 1(n=56,54)	0.76 (± 0.157)	0.82 (± 0.179)		
EQ-5D Index Score; Cycle 14 Day 1(n=49,51)	0.77 (± 0.186)	0.83 (± 0.163)		
EQ-5D Index Score; Cycle 15 Day 1(n=43,49)	0.76 (± 0.191)	0.81 (± 0.165)		
EQ-5D Index Score; Cycle 16 Day 1(n=40,46)	0.73 (± 0.179)	0.81 (± 0.212)		
EQ-5D Index Score; Cycle 17 Day 1(n=37,39)	0.73 (± 0.211)	0.83 (± 0.158)		
EQ-5D Index Score; Cycle 18 Day 1(n=31,33)	0.76 (± 0.148)	0.84 (± 0.177)		
EQ-5D Index Score; Cycle 19 Day 1(n=26,33)	0.69 (± 0.266)	0.79 (± 0.205)		
EQ-5D Index Score; Cycle 20 Day 1(n=27,30)	0.70 (± 0.259)	0.82 (± 0.167)		
EQ-5D Index Score; Cycle 21 Day 1(n=26,28)	0.73 (± 0.223)	0.83 (± 0.180)		
EQ-5D Index Score; Cycle 22 Day 1(n=19,27)	0.74 (± 0.157)	0.85 (± 0.173)		

EQ-5D Index Score; Cycle 23 Day 1(n=14,24)	0.74 (± 0.149)	0.82 (± 0.242)		
EQ-5D Index Score; Cycle 24 Day 1(n=15,18)	0.75 (± 0.172)	0.84 (± 0.156)		
EQ-5D Index Score; Cycle 25 Day 1(n=12,16)	0.70 (± 0.245)	0.83 (± 0.175)		
EQ-5D Index Score; Cycle 26 Day 1(n=8,13)	0.72 (± 0.170)	0.73 (± 0.438)		
EQ-5D Index Score; Cycle 27 Day 1(n=6,6)	0.77 (± 0.135)	0.93 (± 0.117)		
EQ-5D Index Score; Cycle 28 Day 1(n=4,5)	0.73 (± 0.112)	0.97 (± 0.067)		
EQ-5D Index Score; Cycle 29 Day 1(n=4,4)	0.74 (± 0.120)	0.96 (± 0.075)		
EQ-5D Index Score; Cycle 30 Day 1(n=4,1)	0.61 (± 0.391)	1 (± 99999)		
EQ-5D Index Score; Cycle 31 Day 1(n=1,0)	0.87 (± 99999)	99999 (± 99999)		
EQ-5D Index Score; Off-treatment Visit(n=77,72)	0.61 (± 0.331)	0.68 (± 0.314)		
EQ-VAS Score; Baseline(n=167,161)	68.57 (± 18.348)	70.01 (± 20.552)		
EQ-VAS Score; Cycle 2 Day 1(n=149,147)	66.05 (± 18.531)	69.52 (± 19.155)		
EQ-VAS Score; Cycle 3 Day 1(n=145,137)	66.22 (± 17.804)	70.71 (± 17.648)		
EQ-VAS Score; Cycle 4 Day 1(n=130,133)	65.69 (± 18.265)	69.66 (± 17.784)		
EQ-VAS Score; Cycle 5 Day 1(n=122,125)	65.86 (± 18.908)	70.30 (± 19.492)		
EQ-VAS Score; Cycle 6 Day 1(n=118,116)	65.53 (± 20.027)	71.73 (± 17.366)		
EQ-VAS Score; Cycle 7 Day 1(n=102,104)	65.74 (± 18.063)	70.39 (± 19.387)		
EQ-VAS Score; Cycle 8 Day 1(n=97,95)	64.16 (± 18.969)	70.40 (± 20.130)		
EQ-VAS Score; Cycle 9 Day 1(n=90,90)	65.51 (± 17.670)	69.92 (± 19.452)		
EQ-VAS Score; Cycle 10 Day 1(n=77,73)	66.92 (± 17.747)	73.18 (± 20.167)		
EQ-VAS Score; Cycle 11 Day 1(n=69,71)	67.74 (± 16.850)	73.21 (± 19.310)		
EQ-VAS Score; Cycle 12 Day 1(n=65,61)	66.46 (± 18.680)	74.46 (± 17.139)		
EQ-VAS Score; Cycle 13 Day 1(n=56,55)	65.64 (± 19.690)	74.35 (± 17.766)		
EQ-VAS Score; Cycle 14 Day 1(n=49,53)	66.41 (± 17.839)	74.40 (± 17.678)		
EQ-VAS Score; Cycle 15 Day 1(n=44,50)	67.05 (± 17.847)	72.58 (± 19.060)		
EQ-VAS Score; Cycle 16 Day 1(n=41,46)	66.54 (± 18.118)	72.80 (± 17.733)		
EQ-VAS Score; Cycle 17 Day 1(n=37,40)	65.78 (± 17.755)	73.80 (± 17.593)		
EQ-VAS Score; Cycle 18 Day 1(n=30,34)	64.70 (± 18.170)	73.71 (± 16.665)		
EQ-VAS Score; Cycle 19 Day 1(n=26,34)	62.15 (± 20.676)	71.76 (± 19.272)		
EQ-VAS Score; Cycle 20 Day 1(n=27,30)	62.70 (± 19.779)	72.07 (± 19.293)		
EQ-VAS Score; Cycle 21 Day 1(n=26,28)	62.12 (± 17.974)	76.46 (± 16.836)		

EQ-VAS Score; Cycle 22 Day 1(n=19,27)	65.21 (± 14.722)	74.44 (± 16.860)		
EQ-VAS Score; Cycle 23 Day 1(n=15,24)	67.73 (± 15.650)	73.67 (± 17.704)		
EQ-VAS Score; Cycle 24 Day 1(n=15,19)	65.27 (± 19.381)	71.21 (± 21.212)		
EQ-VAS Score; Cycle 25 Day 1(n=12,16)	60.58 (± 19.313)	72.81 (± 16.897)		
EQ-VAS Score; Cycle 26 Day 1(n=8,13)	64.13 (± 16.313)	65.23 (± 25.652)		
EQ-VAS Score; Cycle 27 Day 1(n=6,7)	61.83 (± 18.357)	77.43 (± 16.762)		
EQ-VAS Score; Cycle 28 Day 1(n=4,6)	54.25 (± 8.694)	77.50 (± 20.907)		
EQ-VAS Score; Cycle 29 Day 1(n=4,5)	52.75 (± 12.093)	74 (± 21.036)		
EQ-VAS Score; Cycle 30 Day 1(n=4,1)	51.75 (± 11.295)	50 (± 99999)		
EQ-VAS Score; Cycle 31 Day 1(n=1,0)	35 (± 99999)	99999 (± 99999)		
EQ-VAS Score; Off-treatment Visit(n=77,73)	58.48 (± 23.516)	62.66 (± 22.252)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival After Next Line of Therapy (PFS2)

End point title	Progression-free Survival After Next Line of Therapy (PFS2)

End point description:

PFS2, defined as the time from randomization to the date of PD after next line of therapy or death from any cause, whichever occurred first based on investigator assessment according to RECIST v1.1. PD: at least 20% increase (including an absolute increase of at least 5 mm) in the SOD of target lesions, taking as reference the smallest sum and/or unequivocal progression of existing non-target lesions and/or appearance of 1 or more new lesions. Median PFS2 was analyzed using the Kaplan-Meier product-limit estimates for each treatment group and presented with 2-sided 95% CI. PPAS1 included all randomized subjects minus the 32 subjects who had received >=2 incorrect lenvatinib doses due to IxRS issues. As pre-specified in protocol, data for this secondary endpoint was collected and analyzed till the primary analysis only.

End point type	Secondary

End point timeframe:

From the time of randomization to the date of PD after next line of therapy or death from any cause or the date of data cutoff for the primary analysis, whichever occurs first (up to 29 months)

End point values	Lenvatinib 14 mg + Everolimus 5 mg	Lenvatinib 18 mg + Everolimus 5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	156	155		
Units: months				
median (confidence interval 95%)	18.2 (13.1 to 22.5)	19.5 (14.1 to 23.8)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From date of first dose of study drug up to 28 days after last dose of study drug (up to 71 months)	
Adverse event reporting additional description:	
Reported deaths included all anticipated and unanticipated deaths due to any cause in the study.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups	
Reporting group title	Lenvatinib 18 mg + Everolimus 5 mg
Reporting group description:	
Subjects received lenvatinib 18 mg, capsule, orally, once daily along with everolimus 5 mg, tablet, orally, once daily as the starting dose for in a 28-day treatment cycle until PD, development of unacceptable toxicity, subject requested to discontinue treatment, withdrew consent or lost to follow-up, until the end of the study, or until study termination by the sponsor, whichever occurred first.	
Reporting group title	Lenvatinib 14 mg + Everolimus 5 mg
Reporting group description:	
Subjects received lenvatinib 14 mg, capsule, orally, once daily along with everolimus 5 mg, tablet, orally, once daily as the starting dose for in a 28-day treatment cycle until progressive disease (PD), development of unacceptable toxicity, subject requested to discontinue treatment, withdrew consent or lost to follow-up, until the end of the study, or until study termination by the sponsor, whichever occurred first. If there were no intolerable Grade 2 or any >= Grade 3 TEAEs that required dose reduction in the first 28-day cycle (that is, the first 4 weeks of treatment), lenvatinib dose was escalated to 18 mg once daily (along with everolimus 5 mg) beginning in Cycle 2 or later (cycle length = 28 days) during randomization phase.	

Serious adverse events	Lenvatinib 18 mg + Everolimus 5 mg	Lenvatinib 14 mg + Everolimus 5 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	87 / 168 (51.79%)	92 / 173 (53.18%)	
number of deaths (all causes)	60	71	
number of deaths resulting from adverse events	17	24	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute leukaemia			
subjects affected / exposed	0 / 168 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cancer pain			
subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Tumour pain			
subjects affected / exposed	2 / 168 (1.19%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour obstruction			
subjects affected / exposed	0 / 168 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour necrosis			
subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion malignant			
subjects affected / exposed	0 / 168 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to lung			
subjects affected / exposed	1 / 168 (0.60%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Malignant pleural effusion			
subjects affected / exposed	0 / 168 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm progression			
subjects affected / exposed	5 / 168 (2.98%)	5 / 173 (2.89%)	
occurrences causally related to treatment / all	0 / 5	0 / 6	
deaths causally related to treatment / all	0 / 5	0 / 5	
Cholangiocarcinoma			
subjects affected / exposed	0 / 168 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cancer fatigue			

subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic renal cell carcinoma			
subjects affected / exposed	0 / 168 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oncologic complication			
subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic thrombosis			
subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	2 / 168 (1.19%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	2 / 168 (1.19%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	2 / 168 (1.19%)	3 / 173 (1.73%)	
occurrences causally related to treatment / all	1 / 2	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemic shock			
subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral venous disease			

subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock			
subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery occlusion			
subjects affected / exposed	0 / 168 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			
subjects affected / exposed	0 / 168 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 168 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	2 / 168 (1.19%)	2 / 173 (1.16%)	
occurrences causally related to treatment / all	0 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 168 (0.60%)	2 / 173 (1.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	
Fatigue			
subjects affected / exposed	0 / 168 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			

subjects affected / exposed	2 / 168 (1.19%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Localised oedema			
subjects affected / exposed	0 / 168 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 168 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	2 / 168 (1.19%)	2 / 173 (1.16%)	
occurrences causally related to treatment / all	1 / 2	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pyrexia			
subjects affected / exposed	1 / 168 (0.60%)	4 / 173 (2.31%)	
occurrences causally related to treatment / all	1 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			

Acute respiratory distress syndrome			
subjects affected / exposed	0 / 168 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dyspnoea			
subjects affected / exposed	3 / 168 (1.79%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cough			
subjects affected / exposed	0 / 168 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrothorax			
subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oropharyngeal pain			
subjects affected / exposed	0 / 168 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	3 / 168 (1.79%)	2 / 173 (1.16%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Pneumonitis			
subjects affected / exposed	2 / 168 (1.19%)	2 / 173 (1.16%)	
occurrences causally related to treatment / all	3 / 3	2 / 4	
deaths causally related to treatment / all	0 / 0	1 / 2	
Pneumothorax			
subjects affected / exposed	1 / 168 (0.60%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumothorax spontaneous			

subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary cavitation			
subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	0 / 168 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	3 / 168 (1.79%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	3 / 168 (1.79%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 168 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary haemorrhage			
subjects affected / exposed	0 / 168 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	0 / 168 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			

subjects affected / exposed	0 / 168 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Troponin increased			
subjects affected / exposed	1 / 168 (0.60%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lipase increased			
subjects affected / exposed	0 / 168 (0.00%)	2 / 173 (1.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	4 / 168 (2.38%)	2 / 173 (1.16%)	
occurrences causally related to treatment / all	3 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Amylase increased			
subjects affected / exposed	0 / 168 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Hip fracture			
subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pain			
subjects affected / exposed	0 / 168 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Wound dehiscence			
subjects affected / exposed	0 / 168 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulna fracture			
subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haemorrhage			
subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	2 / 168 (1.19%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 168 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiovascular disorder			
subjects affected / exposed	0 / 168 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Coronary artery disease			

subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 168 (0.60%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiopulmonary failure			
subjects affected / exposed	0 / 168 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Myocardial ischaemia			
subjects affected / exposed	0 / 168 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Partial seizures			
subjects affected / exposed	0 / 168 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuralgia			

subjects affected / exposed	0 / 168 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intraventricular haemorrhage			
subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	0 / 168 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ataxia			
subjects affected / exposed	0 / 168 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 168 (0.00%)	2 / 173 (1.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	2 / 168 (1.19%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	2 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic vein thrombosis			

subjects affected / exposed	0 / 168 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Blindness			
subjects affected / exposed	0 / 168 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 168 (1.19%)	3 / 173 (1.73%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 168 (0.60%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fistula			
subjects affected / exposed	1 / 168 (0.60%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aphthous ulcer			
subjects affected / exposed	0 / 168 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 168 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Constipation			
subjects affected / exposed	2 / 168 (1.19%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	6 / 168 (3.57%)	11 / 173 (6.36%)	
occurrences causally related to treatment / all	3 / 6	10 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	0 / 168 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	0 / 168 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer perforation			
subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 168 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	0 / 168 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			

subjects affected / exposed	0 / 168 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Large intestinal obstruction			
subjects affected / exposed	0 / 168 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Large intestine perforation			
subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 168 (0.60%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal perforation			
subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Vomiting			

subjects affected / exposed	2 / 168 (1.19%)	6 / 173 (3.47%)	
occurrences causally related to treatment / all	1 / 3	7 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 168 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faeces hard			
subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	2 / 168 (1.19%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stenosis			
subjects affected / exposed	0 / 168 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			

subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	2 / 168 (1.19%)	2 / 173 (1.16%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	0 / 168 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallbladder obstruction			
subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatitis			
subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant biliary obstruction			
subjects affected / exposed	0 / 168 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis acute			
subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Acute febrile neutrophilic dermatosis			

subjects affected / exposed	0 / 168 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angioedema			
subjects affected / exposed	0 / 168 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis acneiform			
subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Livedo reticularis			
subjects affected / exposed	0 / 168 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Tubulointerstitial nephritis			
subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 168 (0.60%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proteinuria			
subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephropathy toxic			
subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			

subjects affected / exposed	1 / 168 (0.60%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus bladder			
subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	6 / 168 (3.57%)	3 / 173 (1.73%)	
occurrences causally related to treatment / all	7 / 10	2 / 4	
deaths causally related to treatment / all	1 / 1	0 / 0	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Rhabdomyolysis			
subjects affected / exposed	0 / 168 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	1 / 168 (0.60%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Osteonecrosis of jaw			
subjects affected / exposed	1 / 168 (0.60%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	0 / 168 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture pain			
subjects affected / exposed	0 / 168 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	1 / 168 (0.60%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			
subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma muscle			
subjects affected / exposed	0 / 168 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib deformity			
subjects affected / exposed	0 / 168 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			

Cholecystitis infective			
subjects affected / exposed	1 / 168 (0.60%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
subjects affected / exposed	0 / 168 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendiceal abscess			
subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 168 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis perforated			
subjects affected / exposed	1 / 168 (0.60%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bacteraemia			
subjects affected / exposed	2 / 168 (1.19%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paracancerous pneumonia			
subjects affected / exposed	0 / 168 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphangitis			

subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Empyema			
subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis			
subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 168 (0.60%)	4 / 173 (2.31%)	
occurrences causally related to treatment / all	0 / 1	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	0 / 168 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes virus infection			
subjects affected / exposed	0 / 168 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	0 / 168 (0.00%)	2 / 173 (1.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			

subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal sepsis			
subjects affected / exposed	0 / 168 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Large intestine infection			
subjects affected / exposed	0 / 168 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver abscess			
subjects affected / exposed	0 / 168 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 168 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung abscess			
subjects affected / exposed	0 / 168 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic sinusitis			
subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perihepatic abscess			
subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perineal abscess			

subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	2 / 168 (1.19%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	7 / 168 (4.17%)	13 / 173 (7.51%)	
occurrences causally related to treatment / all	2 / 9	1 / 17	
deaths causally related to treatment / all	0 / 1	0 / 3	
Pneumonia fungal			
subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 168 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 168 (0.00%)	2 / 173 (1.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	2 / 168 (1.19%)	3 / 173 (1.73%)	
occurrences causally related to treatment / all	1 / 2	3 / 5	
deaths causally related to treatment / all	0 / 0	1 / 2	
Septic shock			
subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			

subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	2 / 168 (1.19%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 168 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral diarrhoea			
subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis			
subjects affected / exposed	0 / 168 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	0 / 168 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	0 / 168 (0.00%)	2 / 173 (1.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			

subjects affected / exposed	1 / 168 (0.60%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid overload			
subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrolyte imbalance			
subjects affected / exposed	0 / 168 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	1 / 168 (0.60%)	2 / 173 (1.16%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	2 / 168 (1.19%)	2 / 173 (1.16%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertriglyceridaemia			
subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gout			
subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 168 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			

subjects affected / exposed	2 / 168 (1.19%)	2 / 173 (1.16%)	
occurrences causally related to treatment / all	0 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	2 / 168 (1.19%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	0 / 168 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoalbuminaemia			
subjects affected / exposed	1 / 168 (0.60%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Lenvatinib 18 mg + Everolimus 5 mg	Lenvatinib 14 mg + Everolimus 5 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	166 / 168 (98.81%)	172 / 173 (99.42%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	10 / 168 (5.95%)	7 / 173 (4.05%)	
occurrences (all)	16	7	
Hypertension			
subjects affected / exposed	59 / 168 (35.12%)	54 / 173 (31.21%)	
occurrences (all)	101	113	
General disorders and administration site conditions			

Pyrexia			
subjects affected / exposed	16 / 168 (9.52%)	17 / 173 (9.83%)	
occurrences (all)	21	22	
Oedema peripheral			
subjects affected / exposed	23 / 168 (13.69%)	21 / 173 (12.14%)	
occurrences (all)	44	31	
Fatigue			
subjects affected / exposed	50 / 168 (29.76%)	51 / 173 (29.48%)	
occurrences (all)	104	93	
Asthenia			
subjects affected / exposed	39 / 168 (23.21%)	42 / 173 (24.28%)	
occurrences (all)	100	104	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	24 / 168 (14.29%)	26 / 173 (15.03%)	
occurrences (all)	28	36	
Cough			
subjects affected / exposed	30 / 168 (17.86%)	13 / 173 (7.51%)	
occurrences (all)	47	16	
Dysphonia			
subjects affected / exposed	24 / 168 (14.29%)	20 / 173 (11.56%)	
occurrences (all)	25	28	
Dyspnoea			
subjects affected / exposed	25 / 168 (14.88%)	15 / 173 (8.67%)	
occurrences (all)	33	23	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	16 / 168 (9.52%)	12 / 173 (6.94%)	
occurrences (all)	19	14	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	14 / 168 (8.33%)	11 / 173 (6.36%)	
occurrences (all)	21	21	
Amylase increased			
subjects affected / exposed	8 / 168 (4.76%)	9 / 173 (5.20%)	
occurrences (all)	12	15	

Aspartate aminotransferase increased			
subjects affected / exposed	12 / 168 (7.14%)	13 / 173 (7.51%)	
occurrences (all)	16	17	
Blood alkaline phosphatase increased			
subjects affected / exposed	9 / 168 (5.36%)	11 / 173 (6.36%)	
occurrences (all)	12	11	
Blood cholesterol increased			
subjects affected / exposed	22 / 168 (13.10%)	13 / 173 (7.51%)	
occurrences (all)	37	19	
Blood creatinine increased			
subjects affected / exposed	25 / 168 (14.88%)	23 / 173 (13.29%)	
occurrences (all)	42	30	
Blood thyroid stimulating hormone increased			
subjects affected / exposed	5 / 168 (2.98%)	11 / 173 (6.36%)	
occurrences (all)	6	17	
Blood triglycerides increased			
subjects affected / exposed	13 / 168 (7.74%)	7 / 173 (4.05%)	
occurrences (all)	36	19	
Lipase increased			
subjects affected / exposed	16 / 168 (9.52%)	18 / 173 (10.40%)	
occurrences (all)	26	33	
Platelet count decreased			
subjects affected / exposed	12 / 168 (7.14%)	9 / 173 (5.20%)	
occurrences (all)	20	22	
Weight decreased			
subjects affected / exposed	41 / 168 (24.40%)	36 / 173 (20.81%)	
occurrences (all)	73	63	
Nervous system disorders			
Headache			
subjects affected / exposed	20 / 168 (11.90%)	24 / 173 (13.87%)	
occurrences (all)	28	34	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	10 / 168 (5.95%)	10 / 173 (5.78%)	
occurrences (all)	29	13	
Anaemia			

subjects affected / exposed	29 / 168 (17.26%)	37 / 173 (21.39%)	
occurrences (all)	74	56	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	123 / 168 (73.21%)	117 / 173 (67.63%)	
occurrences (all)	394	352	
Constipation			
subjects affected / exposed	25 / 168 (14.88%)	22 / 173 (12.72%)	
occurrences (all)	32	25	
Abdominal pain upper			
subjects affected / exposed	13 / 168 (7.74%)	15 / 173 (8.67%)	
occurrences (all)	21	20	
Abdominal pain			
subjects affected / exposed	28 / 168 (16.67%)	29 / 173 (16.76%)	
occurrences (all)	40	46	
Vomiting			
subjects affected / exposed	43 / 168 (25.60%)	41 / 173 (23.70%)	
occurrences (all)	85	85	
Toothache			
subjects affected / exposed	11 / 168 (6.55%)	8 / 173 (4.62%)	
occurrences (all)	11	10	
Stomatitis			
subjects affected / exposed	49 / 168 (29.17%)	61 / 173 (35.26%)	
occurrences (all)	92	120	
Nausea			
subjects affected / exposed	52 / 168 (30.95%)	54 / 173 (31.21%)	
occurrences (all)	103	104	
Dyspepsia			
subjects affected / exposed	15 / 168 (8.93%)	14 / 173 (8.09%)	
occurrences (all)	23	21	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	29 / 168 (17.26%)	28 / 173 (16.18%)	
occurrences (all)	43	41	
Pruritus			

subjects affected / exposed	12 / 168 (7.14%)	6 / 173 (3.47%)	
occurrences (all)	12	9	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	26 / 168 (15.48%)	24 / 173 (13.87%)	
occurrences (all)	26	36	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	66 / 168 (39.29%)	40 / 173 (23.12%)	
occurrences (all)	186	133	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	9 / 168 (5.36%)	5 / 173 (2.89%)	
occurrences (all)	11	6	
Hypothyroidism			
subjects affected / exposed	35 / 168 (20.83%)	30 / 173 (17.34%)	
occurrences (all)	42	38	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	17 / 168 (10.12%)	23 / 173 (13.29%)	
occurrences (all)	31	29	
Back pain			
subjects affected / exposed	17 / 168 (10.12%)	18 / 173 (10.40%)	
occurrences (all)	26	23	
Musculoskeletal chest pain			
subjects affected / exposed	12 / 168 (7.14%)	9 / 173 (5.20%)	
occurrences (all)	16	9	
Musculoskeletal pain			
subjects affected / exposed	5 / 168 (2.98%)	12 / 173 (6.94%)	
occurrences (all)	8	20	
Pain in extremity			
subjects affected / exposed	13 / 168 (7.74%)	8 / 173 (4.62%)	
occurrences (all)	19	9	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	9 / 168 (5.36%)	4 / 173 (2.31%)	
occurrences (all)	12	4	

Urinary tract infection			
subjects affected / exposed	9 / 168 (5.36%)	11 / 173 (6.36%)	
occurrences (all)	14	16	
Pneumonia			
subjects affected / exposed	6 / 168 (3.57%)	9 / 173 (5.20%)	
occurrences (all)	6	9	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	57 / 168 (33.93%)	64 / 173 (36.99%)	
occurrences (all)	137	130	
Hypercholesterolaemia			
subjects affected / exposed	26 / 168 (15.48%)	31 / 173 (17.92%)	
occurrences (all)	49	64	
Hyperglycaemia			
subjects affected / exposed	12 / 168 (7.14%)	13 / 173 (7.51%)	
occurrences (all)	36	20	
Hypertriglyceridaemia			
subjects affected / exposed	38 / 168 (22.62%)	37 / 173 (21.39%)	
occurrences (all)	136	112	
Hypoalbuminaemia			
subjects affected / exposed	10 / 168 (5.95%)	8 / 173 (4.62%)	
occurrences (all)	18	10	
Hypocalcaemia			
subjects affected / exposed	13 / 168 (7.74%)	7 / 173 (4.05%)	
occurrences (all)	21	11	
Hypokalaemia			
subjects affected / exposed	19 / 168 (11.31%)	10 / 173 (5.78%)	
occurrences (all)	31	12	
Hypomagnesaemia			
subjects affected / exposed	11 / 168 (6.55%)	11 / 173 (6.36%)	
occurrences (all)	23	11	
Hyponatraemia			
subjects affected / exposed	13 / 168 (7.74%)	11 / 173 (6.36%)	
occurrences (all)	26	18	
Hypophosphataemia			

subjects affected / exposed	11 / 168 (6.55%)	16 / 173 (9.25%)	
occurrences (all)	19	24	
Dehydration			
subjects affected / exposed	5 / 168 (2.98%)	9 / 173 (5.20%)	
occurrences (all)	9	12	
Hyperkalaemia			
subjects affected / exposed	10 / 168 (5.95%)	9 / 173 (5.20%)	
occurrences (all)	12	14	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 April 2017	Protocol amendment 1: Changes included: added safety results regarding dose modifications and reasons for treatment discontinuation due to toxicity. Added details on sensitivity analysis to be performed for primary endpoints to explore homogeneity of treatment effect across study centers/regions. Added details/explanation on estimation of non-inferiority margin.
12 July 2017	Protocol amendment 2: Changes included: removed all references related to central imaging from synopsis and protocol. Revised following statement in the Synopsis and Protocol: "The analysis will be detailed in the biomarker analysis plan (BAP) and reported separately".
23 May 2018	Protocol amendment 3: Changes included: removed all references related to pharmacogenetic (PG) sampling and testing from synopsis and protocol. New paragraph was added for consistency of prior anticancer regimens. Made clarifications to footnotes in the Schedule of Procedures/Assessments.
23 July 2018	Protocol amendment 4: Changes included: revised text to reflect change from double-blind to open-label study design. Revised text regarding lenvatinib dispensing instructions.
18 October 2018	Protocol amendment 5: Changes included: clarified that lenvatinib in plasma and everolimus in blood will be used for PK assessments, and that PK assessments will be done using the population PK approach. Updated total sample size to approximately 338 subjects (169 subjects in each arm). Full Analysis set changed from primary analysis set to a secondary analysis set.
04 January 2019	Protocol amendment 6: Changes included: added an exploratory objective: to explore tumor response parameters (ORR24W, ORR, PFS) based on blinded independent imaging review (IIR) for efficacy assessment. Added exploratory endpoints: tumor response endpoints ORR24W, ORR, and PFS based on IIR assessment. These endpoints were defined in the same way as those based on the investigator assessments. Added statistical analyses for the IIR assessments: exploratory efficacy response endpoints ORR24W, ORR, and PFS based on IIR assessment were summarized using the same statistical methods as those used for the same response parameters based on the investigator assessments.
07 February 2020	Protocol amendment 7: Changes included: clarified that the data cutoff for the primary analysis refers to the statistical end of the study for analysis purposes (end of the Randomization Phase) and that the End of Study refers to the last subject last visit after which all subjects will have completed their off-treatment visits.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported