

**Clinical trial results:****Phase II, Multicenter, Open-label, Single Arm Trial to Evaluate the Safety and Efficacy of Oral E7080 in Medullary and Iodine-131 Refractory, Unresectable Differentiated Thyroid Cancers, Stratified by Histology.****Summary**

EudraCT number	2007-005933-12
Trial protocol	FR PL GB IT
Global end of trial date	29 March 2019

**Results information**

Result version number	v2 (current)
This version publication date	16 April 2020
First version publication date	19 December 2018
Version creation reason	• New data added to full data set Full Data Set
Summary attachment (see zip file)	E7080-G000-201 CSR Synopsis (E7080-G000-201-synopsis.pdf)

**Trial information****Trial identification**

Sponsor protocol code	E7080-G000-201
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**Additional study identifiers**

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00784303
WHO universal trial number (UTN)	-

Notes:

**Sponsors**

Sponsor organisation name	Eisai Inc.
Sponsor organisation address	155 Tice Boulevard, Woodcliff Lake, United States, New Jersey 07677
Public contact	Eisai Medical Information, Eisai Inc., 1-888 274-2378, esi_oncmedinfo@eisai.com
Scientific contact	Eisai Medical Information, Eisai Inc., 1-888 274-2378, 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	29 March 2019
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	29 March 2019
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

In subjects with medullary thyroid cancer [MTC] or radioiodine ( $^{131}\text{I}$ ) refractory/resistant differentiated thyroid cancer[DTC]:

- Determine the effect of E7080 on the objective response rate (ORR) based on Response Evaluation Criteria in Solid Tumors (RECIST) by independent imaging review (IIR).

Protection of trial subjects:

This study was conducted in accordance with standard operating procedures (SOPs) 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 (World Medical Association, 2008) - International Council on Harmonisation (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 Registration of Pharmaceuticals for Human Use - Title 21 of the United States (US) Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and Institutional Review Board (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 European Union (EU) country. All suspected unexpected serious adverse reactions were reported, as required, to the Competent Authorities of all involved EU member states. - Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Law (Law No. 145, 1960) for studies conducted in Japan, in addition to Japan's GCP Subject Information and Informed Consent.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 November 2008
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 20
Country: Number of subjects enrolled	United Kingdom: 14
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Italy: 30
Country: Number of subjects enrolled	Australia: 15
Country: Number of subjects enrolled	United States: 78
Worldwide total number of subjects	162
EEA total number of subjects	69

Notes:

<b>Subjects enrolled per age group</b>	
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)	115
From 65 to 84 years	47
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

162 subjects were screened for entry into the study, of which 45 were screening failures and 117 enrolled in the study and were treated.

### Period 1

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

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	DTC Cohort

Arm description:

Subjects with radioiodine (<sup>131</sup>I)-refractory/resistant DTC received 24 milligram (mg) lenvatinib (two 10 mg tablets and one 4 mg tablet) orally, once daily or 10 mg lenvatinib orally twice daily in 28-day treatment cycles. 58 were the total subjects in the DTC cohort: 56 subjects received 24 mg lenvatinib once daily and 2 subjects received 10 mg lenvatinib twice daily (total 20 mg daily), given continuously in 28-day treatment cycles.

Arm type	Experimental
Investigational medicinal product name	Lenvatinib
Investigational medicinal product code	E7080
Other name	LENVIMA
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

24 mg lenvatinib (two 10 mg tablets and one 4 mg tablet) given orally, once daily, or 10 mg lenvatinib orally twice daily (20 mg total). 58 were the total subjects in the DTC cohort: 56 subjects received 24 mg lenvatinib once daily and 2 subjects received 10 mg lenvatinib twice daily (total 20 mg daily), given continuously in 28-day treatment cycles.

<b>Arm title</b>	MTC Cohort
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Arm description:

Subjects with MTC received 24 mg lenvatinib (two 10 mg tablets and one 4 mg tablet) given orally, once daily continuously in 28-day treatment cycles.

Arm type	Experimental
Investigational medicinal product name	Lenvatinib
Investigational medicinal product code	E7080
Other name	LENVIMA
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

24 mg lenvatinib (two 10 mg tablets and one 4 mg tablet) given orally, once daily given continuously in 28-day treatment cycles.

<b>Number of subjects in period 1<sup>[1]</sup></b>	DTC Cohort	MTC Cohort
Started	58	59
Completed	58	59

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Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: The number of subjects in the Baseline period are those who received the study treatment.

## Baseline characteristics

### Reporting groups

Reporting group title	DTC Cohort
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Reporting group description:

Subjects with radioiodine (<sup>131</sup>I)-refractory/resistant DTC received 24 milligram (mg) lenvatinib (two 10 mg tablets and one 4 mg tablet) orally, once daily or 10 mg lenvatinib orally twice daily in 28-day treatment cycles. 58 were the total subjects in the DTC cohort: 56 subjects received 24 mg lenvatinib once daily and 2 subjects received 10 mg lenvatinib twice daily (total 20 mg daily), given continuously in 28-day treatment cycles.

Reporting group title	MTC Cohort
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Reporting group description:

Subjects with MTC received 24 mg lenvatinib (two 10 mg tablets and one 4 mg tablet) given orally, once daily continuously in 28-day treatment cycles.

Reporting group values	DTC Cohort	MTC Cohort	Total
Number of subjects	58	59	117
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	60.9 ± 9.49	51.6 ± 14.11	-
Gender categorical Units: Subjects			
Female	24	22	46
Male	34	37	71

## End points

### End points reporting groups

Reporting group title	DTC Cohort
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Reporting group description:

Subjects with radioiodine (<sup>131</sup>I)-refractory/resistant DTC received 24 milligram (mg) lenvatinib (two 10 mg tablets and one 4 mg tablet) orally, once daily or 10 mg lenvatinib orally twice daily in 28-day treatment cycles. 58 were the total subjects in the DTC cohort: 56 subjects received 24 mg lenvatinib once daily and 2 subjects received 10 mg lenvatinib twice daily (total 20 mg daily), given continuously in 28-day treatment cycles.

Reporting group title	MTC Cohort
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Reporting group description:

Subjects with MTC received 24 mg lenvatinib (two 10 mg tablets and one 4 mg tablet) given orally, once daily continuously in 28-day treatment cycles.

### Primary: ORR

End point title	ORR <sup>[1]</sup>
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End point description:

ORR was the percentage (%) of subjects with best overall response (BOR) of complete response (CR) and partial response (PR) based on modified RECIST 1.0 for target lesions using magnetic resonance imaging/computed tomography (MRI/CT) scans, as determined by IIR. CR was defined as disappearance of all target lesions. PR was defined as at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum of the longest diameter. ORR (CR+PR), was presented with 2-sided 95% confidence interval (CI) by the method of Clopper and Pearson. The Intent to Treat (ITT) Population included all subjects who received at least one dose of the study drug and was the primary analysis set used for efficacy analyses.

End point type	Primary
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End point timeframe:

From date of treatment start until disease progression, development of unacceptable toxicity, withdrawal of consent, subject's choice to stop study treatment, or up to data cutoff date 11 April 2011, for up to approximately 2 years 5 months

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive data was planned to be analyzed for the end point.

End point values	DTC Cohort	MTC Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	59		
Units: Percentage of subjects				
number (confidence interval 90%)	50.0 (36.6 to 63.4)	35.6 (23.6 to 49.1)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Plasma Pharmacokinetics (PK): Steady State Area Under the Plasma Concentration Curve (AUC)

End point title	Plasma Pharmacokinetics (PK): Steady State Area Under the Plasma Concentration Curve (AUC)
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**End point description:**

Up to 9 samples per subject were obtained at specific time points. Plasma concentrations of lenvatinib were analyzed using standard analysis methods. Due to the sparse PK sampling in this study, the data were pooled with data from other Phase 1 studies conducted in subjects with solid tumors for PK model development and covariate analysis. Individual exposure (steady state AUC) to lenvatinib in MTC and DTC subjects in this study was derived based on the individual predicted steady state AUC from the final PK model. Only data for subjects taking 24 mg lenvatinib daily were reported (subjects taking 20 mg lenvatinib daily were not included in this data set). PK population included all subjects who received the 24 mg daily lenvatinib dose and had concentration values above the limit of quantification and non-missing PK sampling/dose time.

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End point type	Secondary
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**End point timeframe:**

Cycle 1 Day 1 (predose and at 0.5 and 2 hours postdose), Cycle 1 Day 8 (predose), Cycle 2 Day 1 (predose and at 0.5 and 2 hours postdose), and Cycle 3 Day 1 (predose and at 2 hours postdose) (Cycle length= 28 days)

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<b>End point values</b>	DTC Cohort	MTC Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	56		
Units: nanogram*hour per milliliter (ng·h/mL)				
median (full range (min-max))	3840 (1610 to 6960)	3350 (1040 to 6840)		

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**Statistical analyses**

No statistical analyses for this end point

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**Secondary: Change From Baseline in Free Thyroxine (T4)**

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End point title	Change From Baseline in Free Thyroxine (T4)
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**End point description:**

Blood samples to measure free T4 were collected at Screening (Baseline), Cycle 1 Day 15 (MTC cohort), Day 1 of Cycles 2 to 20, and Final Visit. Changes in free T4 concentration values from baseline to specific time points were calculated. Only subjects with both baseline and relevant visit values were included. All subjects who received at least 1 dose of study drug. Only subjects with both baseline and relevant visit/time point values were included. Data not reported for DTC cohort at Cycle 1 Day 15 and Cycle 20 Day 1 because no subjects were evaluable at these time points. Here "99999" refers to data not available and, therefore, 99999 is added as a space-filler.

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End point type	Secondary
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**End point timeframe:**

Day 1 or within 72 hours prior to Day 1 of Cycles 2 to 20, and Final Visit, up to data cutoff date 11 April 2011 (Cycle length= 28 days)

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<b>End point values</b>	DTC Cohort	MTC Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	59		
Units: picomole/liter (pmol/L)				
arithmetic mean (standard deviation)				
Cycle 1 Day 15 (n= 0, 1)	0 (± 0)	-3.80 (± 99999)		
Cycle 2 Day 1 (n= 53, 57)	-0.46 (± 5.149)	-0.86 (± 3.913)		
Cycle 3 Day 1 (n= 50, 54)	-0.92 (± 4.985)	-1.00 (± 4.028)		
Cycle 4 Day 1 (n= 48, 50)	-1.05 (± 5.581)	0.34 (± 4.192)		
Cycle 5 Day 1 (n= 46, 47)	-1.03 (± 5.563)	-0.46 (± 3.878)		
Cycle 6 Day 1 (n= 43, 45)	-2.19 (± 5.373)	-0.17 (± 4.719)		
Cycle 7 Day 1 (n= 39, 40)	-2.32 (± 5.098)	-1.07 (± 5.403)		
Cycle 8 Day 1 (n= 37, 37)	-1.74 (± 5.504)	-1.13 (± 5.691)		
Cycle 9 Day 1 (n= 30, 37)	-0.39 (± 5.295)	0.52 (± 5.213)		
Cycle 10 Day 1 (n= 30, 32)	-0.26 (± 6.397)	1.33 (± 6.319)		
Cycle 11 Day 1 (n= 30, 26)	-0.27 (± 6.384)	0.30 (± 5.551)		
Cycle 12 Day 1 (n= 30, 21)	-1.60 (± 6.331)	-0.43 (± 5.380)		
Cycle 13 Day 1 (n= 29, 19)	-0.09 (± 5.416)	0.07 (± 4.347)		
Cycle 14 Day 1 (n= 27, 14)	-0.54 (± 5.772)	-0.82 (± 6.394)		
Cycle 15 Day 1 (n= 26, 10)	0.63 (± 6.703)	-1.01 (± 5.505)		
Cycle 16 Day 1 (n= 24, 9)	-0.98 (± 7.150)	0.60 (± 4.142)		
Cycle 17 Day 1 (n= 17, 6)	1.20 (± 7.075)	0.45 (± 3.528)		
Cycle 18 Day 1 (n= 10, 6)	0.38 (± 4.648)	2.17 (± 4.831)		
Cycle 19 Day 1 (n= 4, 2)	-0.65 (± 4.042)	3.25 (± 4.596)		
Cycle 20 Day 1 (n= 0, 1)	0 (± 0)	5.20 (± 99999)		
Final Visit/Study Termination (n= 21, 22)	-0.36 (± 6.175)	1.27 (± 4.584)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Free Thyroid Stimulating Hormone (TSH)

End point title	Change From Baseline in Free Thyroid Stimulating Hormone (TSH)
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End point description:

Blood samples to measure free TSH were collected at Screening (Baseline), Cycle 1 Day 15 (MTC cohort), Day 1 of Cycles 2 to 20, and Final Visit. Changes in free TSH concentration values from baseline to specific time points were calculated. Only subjects with both baseline and relevant visit values were

included. For any free TSH result that was reported as <0.008 mIU/L, 0.004 mIU/L was used for calculating summary statistics. All subjects who received at least 1 dose of study drug. For each change from baseline assessment time point, only subjects with both baseline and relevant visit/time point values were included. Data not reported for DTC cohort at Cycle 1 Day 15 and Cycle 20 Day 1 because no subjects were evaluable at these time points. Here "99999" refers to data not available and, therefore, 99999 is added as a space-filler.

End point type	Secondary
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End point timeframe:

Day 1 or within 72 hours prior to Day 1 of Cycles 2 to 20, and Final Visit, up to data cutoff date 11 April 2011 (Cycle length= 28 days)

<b>End point values</b>	DTC Cohort	MTC Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	59		
Units: Milli international units per litre				
arithmetic mean (standard deviation)				
Cycle 1 Day 15 (n= 0, 1)	0 (± 0)	2.8030 (± 99999)		
Cycle 2 Day 1 (n= 41, 55)	0.4779 (± 3.07666)	4.1585 (± 7.34946)		
Cycle 3 Day 1 (n= 38, 52)	0.5161 (± 2.79122)	5.5788 (± 13.76600)		
Cycle 4 Day 1 (n= 37, 48)	0.6296 (± 2.29420)	2.8751 (± 6.50098)		
Cycle 5 Day 1 (n= 35, 45)	0.5024 (± 2.22721)	3.7098 (± 6.60386)		
Cycle 6 Day 1 (n= 32, 44)	0.8603 (± 3.09079)	3.9822 (± 10.65477)		
Cycle 7 Day 1 (n= 30, 40)	0.6660 (± 2.08608)	8.4308 (± 22.51715)		
Cycle 8 Day 1 (n= 30, 37)	0.2118 (± 3.16324)	11.4131 (± 32.65896)		
Cycle 9 Day 1 (n= 25, 37)	0.1270 (± 3.53020)	6.6620 (± 18.89412)		
Cycle 10 Day 1 (n= 26, 32)	-0.3277 (± 2.87114)	6.1934 (± 17.99762)		
Cycle 11 Day 1 (n= 25, 26)	-0.2940 (± 3.28192)	2.7928 (± 9.42343)		
Cycle 12 Day 1 (n= 25, 21)	0.3500 (± 5.43946)	5.1879 (± 14.81415)		
Cycle 13 Day 1 (n= 25, 19)	-0.2799 (± 3.31518)	2.0983 (± 7.03903)		
Cycle 14 Day 1 (n= 23, 14)	-0.6232 (± 3.09954)	9.6490 (± 32.48910)		
Cycle 15 Day 1 (n= 22, 10)	-0.5911 (± 3.21447)	0.9955 (± 4.93549)		
Cycle 16 Day 1 (n= 20, 9)	-0.3396 (± 3.68903)	0.2971 (± 3.33103)		
Cycle 17 Day 1 (n= 14, 7)	-1.0352 (± 3.92286)	7.4624 (± 16.18545)		
Cycle 18 Day 1 (n= 8, 6)	0.0331 (± 0.24520)	4.1232 (± 7.01461)		
Cycle 19 Day 1 (n= 4, 2)	0.7805 (± 1.87674)	-0.2080 (± 0.29698)		
Cycle 20 Day 1 (n= 0, 1)	0 (± 0)	0.0000 (± 99999)		

Final Visit/Study Termination (n= 17, 20)	1.0281 ( $\pm$ 2.07161)	3.4905 ( $\pm$ 7.39625)		
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## Statistical analyses

No statistical analyses for this end point

### Secondary: Percent Change From Baseline in Concentrations of Thyroglobulin (DTC Only)

End point title	Percent Change From Baseline in Concentrations of Thyroglobulin (DTC Only) <sup>[2]</sup>
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End point description:

Blood samples to obtain serum were collected at Cycle 1 Day 1 (Baseline), Day 1 of Cycles 2 to 19, Final Visit, and were analyzed for thyroglobulin concentration. Percent changes in thyroglobulin concentration values from baseline to specific time points were calculated. Only subjects with both baseline and relevant visit values were included. All subjects who received at least 1 dose of study drug. For each change from baseline assessment time point, only subjects with both baseline and relevant visit/time point values were included. Here "99999" refers to data not available and, therefore, 99999 is added as a space-filler.

End point type	Secondary
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End point timeframe:

Day 1 or within 72 hours prior to Day 1 of Cycles 2 to 19, and Final Visit, up to data cutoff date 11 April 2011 (Cycle length= 28 days)

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Only descriptive data was planned to be analyzed for the end point.

End point values	DTC Cohort			
Subject group type	Reporting group			
Number of subjects analysed	52			
Units: percent change				
arithmetic mean (standard deviation)				
Cycle 2 Day 1 (n= 47)	-62.21 ( $\pm$ 39.997)			
Cycle 3 Day 1 (n= 44)	-77.80 ( $\pm$ 22.278)			
Cycle 4 Day 1 (n= 41)	-79.25 ( $\pm$ 26.639)			
Cycle 5 Day 1 (n= 40)	-76.00 ( $\pm$ 25.085)			
Cycle 6 Day 1 (n= 40)	-20.36 ( $\pm$ 373.190)			
Cycle 7 Day 1 (n= 30)	-73.38 ( $\pm$ 45.489)			
Cycle 8 Day 1 (n= 29)	-79.96 ( $\pm$ 27.461)			
Cycle 9 Day 1 (n= 21)	-73.98 ( $\pm$ 31.366)			
Cycle 10 Day 1 (n= 26)	-78.26 ( $\pm$ 25.524)			
Cycle 11 Day 1 (n= 28)	-75.54 ( $\pm$ 37.327)			

Cycle 12 Day 1 (n= 26)	-73.51 (± 46.397)			
Cycle 13 Day 1 (n= 26)	-74.05 (± 37.091)			
Cycle 14 Day 1 (n= 24)	-78.70 (± 17.348)			
Cycle 15 Day 1 (n= 23)	-80.28 (± 16.029)			
Cycle 16 Day 1 (n= 22)	-76.38 (± 27.736)			
Cycle 17 Day 1 (n= 15)	-62.99 (± 38.740)			
Cycle 18 Day 1 (n= 9)	-72.67 (± 27.226)			
Cycle 19 Day 1 (n= 4)	-50.65 (± 46.900)			
Final Visit/Study Termination (n= 1)	-68.60 (± 99999)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percent Change From Baseline in Concentrations of Calcitonin (MTC Only)

End point title	Percent Change From Baseline in Concentrations of Calcitonin (MTC Only) <sup>[3]</sup>
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End point description:

Blood samples to obtain serum were collected at Cycle 1 Day 1(Baseline), Day 1 of Cycles 2 to 20, Final Visit, and were analyzed for calcitonin concentration. Percent changes in calcitonin concentration values from baseline to specific time points were calculated. Only subjects with both baseline and relevant visit values were included. All subjects who received at least 1 dose of study drug. For each change from baseline assessment time point, only subjects with both baseline and relevant visit/time point values were included. Here "99999" refers to data not available and, therefore, 99999 is added as a space-filler.

End point type	Secondary
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End point timeframe:

Day 1 or within 72 hours prior to Day 1 of Cycles 2 to 20, and Final Visit, up to data cutoff date 11 April 2011 (Cycle length= 28 days)

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Only descriptive data was planned to be analyzed for the end point.

End point values	MTC Cohort			
Subject group type	Reporting group			
Number of subjects analysed	53			
Units: percent change				
arithmetic mean (standard deviation)				
Cycle 2 Day 1 (n= 51)	-42.27 (± 38.754)			
Cycle 3 Day 1 (n= 47)	-48.11 (± 30.976)			
Cycle 4 Day 1 (n= 44)	-44.54 (± 38.794)			

Cycle 5 Day 1 (n= 40)	-49.97 (± 34.634)			
Cycle 6 Day 1 (n= 39)	-41.73 (± 46.653)			
Cycle 7 Day 1 (n= 34)	-38.18 (± 62.721)			
Cycle 8 Day 1 (n= 33)	-47.29 (± 46.101)			
Cycle 9 Day 1 (n= 29)	-37.52 (± 72.588)			
Cycle 10 Day 1 (n= 29)	-39.57 (± 60.118)			
Cycle 11 Day 1 (n= 24)	-42.68 (± 61.797)			
Cycle 12 Day 1 (n= 19)	-29.25 (± 105.440)			
Cycle 13 Day 1 (n= 17)	-36.26 (± 89.612)			
Cycle 14 Day 1 (n= 12)	-18.16 (± 148.928)			
Cycle 15 Day 1 (n= 9)	-65.26 (± 24.553)			
Cycle 16 Day 1 (n= 8)	-64.24 (± 30.394)			
Cycle 17 Day 1 (n= 7)	-66.03 (± 23.777)			
Cycle 18 Day 1 (n= 6)	-64.57 (± 27.982)			
Cycle 19 Day 1 (n= 2)	-44.30 (± 18.668)			
Cycle 20 Day 1 (n= 1)	-29.40 (± 99999)			
Final Visit/Study Termination (n= 4)	-36.70 (± 28.296)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percent Change From Baseline in Concentrations of Carcinoembryonic Antigen (CEA) (MTC Only)

End point title	Percent Change From Baseline in Concentrations of Carcinoembryonic Antigen (CEA) (MTC Only) <sup>[4]</sup>
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End point description:

Blood samples were collected at Cycle 1 Day 1(Baseline), Day 1 of Cycles 2 to 20, Final Visit, and were analyzed for CEA concentration. Percent changes in CEA concentration values from baseline to specific time points were calculated. Only subjects with both baseline and relevant visit values were included. All subjects who received at least 1 dose of study drug. For each change from baseline assessment time point, only subjects with both baseline and relevant visit/time point values were included. Here "99999" refers to data not available and, therefore, 99999 is added as a space-filler.

End point type	Secondary
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End point timeframe:

Day 1 or within 72 hours prior to Day 1 of Cycles 2 to 20, and Final Visit, up to data cutoff date 11 April 2011 (Cycle length= 28 days)

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Only descriptive data was planned to be analyzed for the end point.

<b>End point values</b>	MTC Cohort			
Subject group type	Reporting group			
Number of subjects analysed	53			
Units: percent change				
arithmetic mean (standard deviation)				
Cycle 2 Day 1 (n= 54)	-26.07 (± 45.864)			
Cycle 3 Day 1 (n= 49)	-37.68 (± 42.236)			
Cycle 4 Day 1 (n= 46)	-41.49 (± 48.035)			
Cycle 5 Day 1 (n= 42)	-44.62 (± 42.138)			
Cycle 6 Day 1 (n= 42)	-41.91 (± 47.388)			
Cycle 7 Day 1 (n= 36)	-41.39 (± 45.677)			
Cycle 8 Day 1 (n= 34)	-42.89 (± 47.818)			
Cycle 9 Day 1 (n= 30)	-49.31 (± 32.185)			
Cycle 10 Day 1 (n= 30)	-47.35 (± 31.621)			
Cycle 11 Day 1 (n= 25)	-51.75 (± 29.671)			
Cycle 12 Day 1 (n= 20)	-49.91 (± 32.597)			
Cycle 13 Day 1 (n= 18)	-46.44 (± 35.967)			
Cycle 14 Day 1 (n= 13)	-47.98 (± 38.324)			
Cycle 15 Day 1 (n= 10)	-56.62 (± 34.051)			
Cycle 16 Day 1 (n= 9)	-59.83 (± 34.762)			
Cycle 17 Day 1 (n= 7)	-53.80 (± 37.981)			
Cycle 18 Day 1 (n= 6)	-46.00 (± 39.905)			
Cycle 19 Day 1 (n= 2)	-45.65 (± 18.738)			
Cycle 20 Day 1 (n= 1)	-61.40 (± 99999)			
Final Visit/Study Termination (n= 4)	-29.43 (± 31.453)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Concentrations of Cytochrome C (CytoC)

End point title	Change From Baseline in Concentrations of Cytochrome C (CytoC)
End point description:	Blood samples to obtain serum were collected at Cycle 1 Day 1(Baseline), Cycle 1 Day 8, Cycle 2 Days 1,8 &15, Cycles 3 to 9,11,13 Day 1, Final Visit, and analyzed for CytoC concentration. Changes in CytoC concentration values from baseline to specific time points were calculated. Only subjects with both baseline and relevant visit values were included. For results reported as below quantifiable level (BQL), zero was used for calculating summary statistics. If more than 50% of the results at a visit were BQL, then only 'n', 'minimum' and 'maximum' were calculated for summary statistics. All subjects who received at least 1 dose of study drug. Only subjects with both baseline and relevant visit/time point values were included. Data not reported for DTC cohort at Cycle 2 Day 1, for MTC cohort at Cycle 2 Day 15, Day 1 of Cycle 11 and 13 because no subject was evaluable at these time points. Here "99999" refers to data not available and, therefore, 99999 is added as a space-filler.
End point type	Secondary
End point timeframe:	Cycle 1 (Day 8), Cycle 2 (Days 1, 8 and 15), Cycles 3, 4, 5, 6, 7, 8, 9, 11, & 13 (Day 1), and Final Visit, up to data cutoff date 11 April 2011 (Cycle length= 28 days)

End point values	DTC Cohort	MTC Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	54		
Units: picogram/milliliter (pg/mL)				
arithmetic mean (standard deviation)				
Cycle 1 Day 8 (n= 52, 52)	155.57 (± 825.091)	502.84 (± 2146.291)		
Cycle 2 Day 1 (n= 0, 1)	0 (± 0)	1679.40 (± 99999)		
Cycle 2 Day 8 (n= 46, 49)	-218.45 (± 591.217)	374.46 (± 2279.207)		
Cycle 2 Day 15 (n= 1, 0)	-215.50 (± 99999)	0 (± 0)		
Cycle 3 Day 1 (n= 44, 47)	-175.43 (± 435.635)	311.85 (± 2363.970)		
Cycle 4 Day 1 (n= 19, 17)	1.38 (± 268.354)	63.01 (± 1738.149)		
Cycle 5 Day 1 (n= 15, 13)	-21.32 (± 85.469)	1078.85 (± 3793.235)		
Cycle 6 Day 1 (n= 14, 10)	721.58 (± 1234.215)	1411.29 (± 3855.502)		
Cycle 7 Day 1 (n= 10, 7)	858.05 (± 1383.962)	2184.30 (± 4689.181)		
Cycle 8 Day 1 (n= 10, 5)	1358.51 (± 1364.706)	451.36 (± 254.305)		
Cycle 9 Day 1 (n= 6, 5)	1356.40 (± 913.685)	459.38 (± 1572.717)		
Cycle 11 Day 1 (n= 1, 0)	139.60 (± 99999)	0 (± 0)		
Cycle 13 Day 1 (n= 1, 0)	129.60 (± 99999)	0 (± 0)		
Final Visit/Study Termination (n= 19, 23)	249.31 (± 765.148)	-45.97 (± 1294.476)		

## Statistical analyses

**Secondary: Change From Baseline in Concentrations of M-30 Neo-Antigen**

End point title	Change From Baseline in Concentrations of M-30 Neo-Antigen
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End point description:

Blood samples to obtain serum were collected at Cycle 1 Day 1(Baseline), Cycle 1 Day 8, Cycle 2 Days 1,8 &15, Cycles 3 to 9,11,13 Day 1, Final Visit, and analyzed for M-30 concentration. Changes in M-30 concentration values from baseline to specific time points were calculated. Only subjects with both baseline and relevant visit values were included. For results reported as BQL, zero was used for calculating summary statistics. If more than 50% of the results at a visit were BQL, then only 'n', 'minimum' and 'maximum' were calculated for summary statistics. All subjects who received at least 1 dose of study drug. Only subjects with both baseline and relevant visit/time point values were included. Data not reported for DTC cohort at Cycle 2 Day 1, for MTC cohort at Cycle 2 Day 15, Day 1 of Cycle 11 and 13 because no subjects were evaluable at these time points. Here "99999" refers to data not available and, therefore, 99999 is added as a space-filler.

End point type	Secondary
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End point timeframe:

Cycle 1 (Day 8), Cycle 2 (Days 1, 8 & 15), Cycles 3, 4, 5, 6, 7, 8, 9, 11 & 13 (Day 1) and Final Visit, up to data cutoff date 11 April 2011 (Cycle length= 28 days)

End point values	DTC Cohort	MTC Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	54		
Units: Units per liter (U/L)				
arithmetic mean (standard deviation)				
Cycle 1 Day 8 (n= 52, 52)	-5.22 (± 108.639)	46.32 (± 197.509)		
Cycle 2 Day 1 (n= 0, 1)	0 (± 0)	-77.80 (± 99999)		
Cycle 2 Day 8 (n= 46, 49)	-26.41 (± 257.723)	-49.33 (± 289.525)		
Cycle 2 Day 15 (n= 1, 0)	35.30 (± 99999)	0 (± 0)		
Cycle 3 Day 1 (n= 44, 47)	19.70 (± 296.010)	90.21 (± 314.343)		
Cycle 4 Day 1 (n= 19, 17)	-7.89 (± 336.124)	-97.53 (± 296.832)		
Cycle 5 Day 1 (n= 15, 13)	-24.83 (± 397.337)	-161.36 (± 265.548)		
Cycle 6 Day 1 (n= 14, 10)	-99.30 (± 321.554)	-161.30 (± 214.299)		
Cycle 7 Day 1 (n= 10, 7)	-168.50 (± 378.071)	-52.79 (± 129.671)		
Cycle 8 Day 1 (n= 10, 5)	-180.22 (± 386.682)	-92.44 (± 57.828)		
Cycle 9 Day 1 (n= 6, 5)	-111.92 (± 189.411)	-85.22 (± 161.751)		
Cycle 11 Day 1 (n= 1, 0)	55.00 (± 99999)	0 (± 0)		
Cycle 13 Day 1 (n= 1, 0)	-263.50 (± 99999)	0 (± 0)		
Final Visit/Study Termination (n= 19, 23)	-151.73 (± 322.159)	-158.99 (± 355.903)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Concentrations of Activated Caspase 3/7 (Casp 3/7)

End point title	Change From Baseline in Concentrations of Activated Caspase 3/7 (Casp 3/7)
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End point description:

Blood samples to obtain serum collected at Cycle 1 Day 1(Baseline), Cycle 1 Day 8, Cycle 2 Days 1, 8, 15, Cycles 3 to 9, 11, 13(Day 1), Final Visit, analyzed for Casp 3/7 concentration. Changes in Casp 3/7 concentration values from baseline were calculated. Only subjects with both baseline and relevant visit values were included. Concentrations of Casp 3/7 were BQL for most subjects at most time points. For results reported as BQL, zero used for calculating summary statistics. If >50% of results at visit were BQL, then only 'n', 'minimum' and 'maximum' were calculated for summary statistics. Subjects received at least 1 dose of study drug. Only subjects with both baseline and relevant visit/time point values included. Data not reported for DTC cohort at Cycle 2 Day 1, MTC cohort at Cycle 2 Day 15, Day 1 of Cycle 11 and 13 as no subjects were evaluable at these time points. Here "99999" refers to data not available and, therefore, 99999 is added as a space filler.

End point type	Secondary
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End point timeframe:

Cycle 1 (Day 8), Cycle 2 (Days 1, 8, & 15), Cycles 3, 4, 5, 6, 7, 8, 9, 11, & 13 (Day 1) and Final Visit, up to data cutoff date 11 April 2011 (Cycle length= 28 days)

End point values	DTC Cohort	MTC Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	59		
Units: U/W				
arithmetic mean (standard deviation)				
Cycle 1 Day 8 (n= 50, 52)	99999 (± 99999)	0.0030 (± 0.00610)		
Cycle 2 Day 1 (n= 0, 1)	0 (± 0)	0.0080 (± 99999)		
Cycle 2 Day 8 (n= 44, 49)	99999 (± 99999)	0.0039 (± 0.00822)		
Cycle 2 Day 15 (n= 1, 0)	0.0110 (± 99999)	0 (± 0)		
Cycle 3 Day 1 (n= 42, 47)	99999 (± 99999)	0.0026 (± 0.00691)		
Cycle 4 Day 1 (n= 18, 17)	99999 (± 99999)	0.0019 (± 0.00743)		
Cycle 5 Day 1 (n= 15, 13)	99999 (± 99999)	0.0042 (± 0.00666)		
Cycle 6 Day 1 (n= 14, 10)	0.0046 (± 0.00605)	99999 (± 99999)		
Cycle 7 Day 1 (n= 10, 7)	0.0058 (± 0.00496)	0.0044 (± 0.00692)		

Cycle 8 Day 1 (n= 10, 5)	0.0078 (± 0.00771)	99999 (± 99999)		
Cycle 9 Day 1 (n= 6, 5)	0.0067 (± 0.00480)	0.0068 (± 0.01329)		
Cycle 11 Day 1 (n= 1, 0)	99999 (± 99999)	0 (± 0)		
Cycle 13 Day 1 (n= 1, 0)	99999 (± 99999)	0 (± 0)		
Final Visit/Study Termination (n= 18, 23)	99999 (± 99999)	99999 (± 99999)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Duration of Response (DoR) Assessed as Per IIR

End point title	Duration of Response (DoR) Assessed as Per IIR
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End point description:

DoR was based on IIR was the time from date of the first CR or PR until the date of first documentation of disease progression or date of death, if death occurred prior to disease progression, for the subjects who had BOR of CR or PR. Subjects without progressive disease or death were censored at the date of last adequate tumor assessment. DoR= End Date - Date of first CR or PR + 1. ITT population. Subjects who were evaluable for this given measure at a given time point were included for this assessment. Here "99999" refers to data not available and, therefore, 99999 is added as a space-filler.

End point type	Secondary
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End point timeframe:

From date of the first CR or PR until the date of first documentation of disease progression or date of death, assessed up to data cutoff date 11 April 2011

End point values	DTC Cohort	MTC Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	21		
Units: Months				
median (confidence interval 95%)	12.7 (8.8 to 99999)	99999 (5.7 to 99999)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Disease Control Rate (DCR) Assessed as Per IIR

End point title	Disease Control Rate (DCR) Assessed as Per IIR
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End point description:

DCR was the percentage of the subjects who had BOR of CR, PR, and stable disease (SD) with the minimum duration of SD lasting greater than or equal to 7 weeks, based on assessments by IIR. DCR = CR+PR+SD greater than or equal to 7 weeks. ITT population. Subjects who were evaluable for this

given measure at a given time point were included for this assessment.

End point type	Secondary
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End point timeframe:

From date of treatment start until disease progression, development of unacceptable toxicity, withdrawal of consent, subject's choice to stop study treatment, or up to data cutoff date 11 April 2011, for up to approximately 2 years 5 months

End point values	DTC Cohort	MTC Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54	47		
Units: Percentage of subjects				
number (confidence interval 95%)	93.1 (83.3 to 98.1)	79.7 (67.2 to 89.0)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Clinical Benefit Rate (CBR) Assessed as Per IIR

End point title	Clinical Benefit Rate (CBR) Assessed as Per IIR
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End point description:

CBR was the percentage of the subjects who had BOR of CR, PR, and SD with the minimum duration of SD lasting greater than or equal to 23 weeks, based on assessments by IIR. CBR = CR+PR+SD greater than or equal to 23 weeks. ITT population. Subjects who were evaluable for this given measure at a given time point were included for this assessment.

End point type	Secondary
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End point timeframe:

From date of treatment start until disease progression, development of unacceptable toxicity, withdrawal of consent, subject's choice to stop study treatment, or up to data cutoff date 11 April 2011, for up to approximately 2 years 5 months

End point values	DTC Cohort	MTC Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	38		
Units: Percentage of subjects				
number (confidence interval 95%)	77.6 (64.7 to 87.5)	64.4 (50.9 to 76.4)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Time to Response (TTR) Assessed as Per IIR

End point title	Time to Response (TTR) Assessed as Per IIR
End point description:	
TTR was defined as "time from start of treatment to the time when a subject first achieves a response of PR/CR" based on assessments by IIR. TTR was only calculated for subjects with confirmed PR or CR. The Efficacy Evaluable Population included all subjects who received at least one dose of the study treatment, had a baseline and at least one posttreatment tumor response evaluation. Subjects who were evaluable for this given measure at a given time point were included for this assessment.	
End point type	Secondary
End point timeframe:	
From date of treatment start until date of first CR or PR, assessed up to data cutoff date 11 April 2011	

End point values	DTC Cohort	MTC Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	29		
Units: Months				
number (confidence interval 95%)	3.6 (1.8 to 3.7)	3.5 (1.9 to 3.7)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Progression Free Survival (PFS) Assessed as Per IIR

End point title	Progression Free Survival (PFS) Assessed as Per IIR
End point description:	
PFS was defined as the time from the date of treatment start until progressive disease or death from any cause in the absence of progressive disease. Disease progression was defined as at least a 20% increase in the sum of the longest diameter of target lesions (taking as reference the smallest sum on study), recorded since the treatment started or the appearance of 1 or more new lesions as assessed by IIR using RECIST 1.0. The duration of PFS was calculated as end date minus date of first drug plus 1, based on assessments by IIR. PFS was calculated using Kaplan-Meier estimate and presented with 2-sided 95% CI. ITT population. Subjects who were evaluable for this given measure at a given time point were included for this assessment. Here "99999" refers to data not available and, therefore, 99999 is added as a space-filler.	
End point type	Secondary
End point timeframe:	
From date of treatment start until date of progressive disease or death from any cause, assessed up to data cutoff date 11 April 2011, for up to approximately 2 years 5 months	

End point values	DTC Cohort	MTC Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	59		
Units: Months				
number (confidence interval 95%)	12.6 (9.9 to 16.1)	9.0 (7.0 to 99999)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)
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End point description:

OS was defined as the time from the date of treatment start until death from any cause. The duration of OS was calculated as 'end date minus date of first drug plus 1', based on assessments by IIR. Subjects without a reported death or those lost to follow-up were censored at their last known alive date at the database cutoff. OS was calculated using Kaplan-Meier estimate and presented with 2- sided 95% CI. ITT population. Subjects who were evaluable for this given measure at a given time point were included for this assessment. Here "99999" refers to data not available and, therefore, 99999 is added as a space-filler.

End point type	Secondary
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End point timeframe:

From date of treatment start until date of death from any cause, assessed up to data cutoff date 11 April 2011, for up to approximately 2 years 5 months

End point values	DTC Cohort	MTC Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	59		
Units: Months				
number (confidence interval 95%)	27.7 (27.7 to 99999)	16.6 (16.4 to 99999)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Subjects With Non-Serious Adverse Events (AEs) and Serious Adverse Events (SAEs) as a Measure of Safety and Tolerability of Lenvatinib

End point title	Number of Subjects With Non-Serious Adverse Events (AEs) and Serious Adverse Events (SAEs) as a Measure of Safety and Tolerability of Lenvatinib
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End point description:

Safety assessments consisted of monitoring and recording all AEs (serious and non-serious) and SAEs; concomitant medications, regular monitoring of hematology, blood chemistry, and urine values; periodic measurement of vital signs, Eastern Cooperative Oncology Group (ECOG) performance status, New York Heart Association (NYHA) assessments, electrocardiograms (ECGs), echocardiograms; and performance of physical examinations. Safety population included all subjects who received at least 1 dose of study drug and had at least 1 posttreatment safety assessment.

End point type	Secondary
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End point timeframe:

For each subject, from the first dose till 30 days after the last dose of study treatment (up to approximately 10 years 4 months)

<b>End point values</b>	DTC Cohort	MTC Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	59		
Units: Subjects				
number (not applicable)				
Non-Serious AEs	58	59		
SAEs	32	42		

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

For each subject, from the first dose until 30 days after the last dose of study treatment (up to approximately 10 years 4 months)

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

### Reporting groups

Reporting group title	DTC Cohort
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Reporting group description:

Subjects with radioiodine (<sup>131</sup>I)-refractory/resistant DTC received 24 mg lenvatinib (two 10 mg tablets and one 4 mg tablet) orally, once daily or 10 mg lenvatinib orally twice daily in 28-day treatment cycles. 58 were the total subjects in the DTC cohort: 56 subjects received 24 mg lenvatinib once daily and 2 subjects received 10 mg lenvatinib twice daily (total 20 mg daily), given continuously in 28-day treatment cycles.

Reporting group title	MTC Cohort
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Reporting group description:

Subjects with MTC received 24 mg lenvatinib (two 10 mg tablets and one 4 mg tablet) given orally, once daily continuously in 28-day treatment cycles.

<b>Serious adverse events</b>	DTC Cohort	MTC Cohort	
Total subjects affected by serious adverse events			
subjects affected / exposed	32 / 58 (55.17%)	42 / 59 (71.19%)	
number of deaths (all causes)	44	37	
number of deaths resulting from adverse events	4	5	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant pleural effusion			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to central nervous system			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic pain			

subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oncologic complication			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Paraneoplastic syndrome			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pharyngeal neoplasm			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour haemorrhage			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial haemorrhage			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Arterial rupture			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			

subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	2 / 58 (3.45%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	4 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	4 / 58 (6.90%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 58 (3.45%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised oedema			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Local swelling			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Reproductive system and breast disorders			
Amenorrhoea			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic pain			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Premature menopause			
subjects affected / exposed	0 / 58 (0.00%)	2 / 59 (3.39%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal haemorrhage			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acquired tracheo-oesophageal fistula			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Aspiration			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			

subjects affected / exposed	0 / 58 (0.00%)	2 / 59 (3.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive airways disorder			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagobronchial fistula			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 58 (1.72%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			

subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Pulmonary embolism</b>			
subjects affected / exposed	4 / 58 (6.90%)	3 / 59 (5.08%)	
occurrences causally related to treatment / all	3 / 4	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Respiratory arrest</b>			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
<b>Respiratory failure</b>			
subjects affected / exposed	0 / 58 (0.00%)	2 / 59 (3.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	1 / 2	
<b>Stridor</b>			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Tracheal fistula</b>			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Investigations</b>			
<b>Echocardiogram abnormal</b>			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Ejection fraction decreased</b>			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Weight decreased</b>			

subjects affected / exposed	1 / 58 (1.72%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Injury, poisoning and procedural complications</b>			
Accidental overdose			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incisional hernia			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pain			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
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	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Cardiac disorders</b>			
Acute myocardial infarction			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Angina pectoris			
subjects affected / exposed	1 / 58 (1.72%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 58 (1.72%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	2 / 58 (3.45%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (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 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure chronic			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular dysfunction			

subjects affected / exposed	1 / 58 (1.72%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Myocardial infarction</b>			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
<b>Myocardial ischaemia</b>			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Sinus node dysfunction</b>			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Tachycardia</b>			
subjects affected / exposed	1 / 58 (1.72%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Nervous system disorders</b>			
<b>Carotid artery stenosis</b>			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Cervical radiculopathy</b>			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Dyskinesia</b>			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Extrapyramidal disorder</b>			

subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Metabolic encephalopathy</b>			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Paraplegia</b>			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Radiculopathy</b>			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Transient ischaemic attack</b>			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Blood and lymphatic system disorders</b>			
<b>Iron deficiency anaemia</b>			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Polycythaemia</b>			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Eye disorders</b>			
<b>Diplopia</b>			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Gastrointestinal disorders</b>			

Abdominal pain			
subjects affected / exposed	0 / 58 (0.00%)	3 / 59 (5.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain lower			
subjects affected / exposed	2 / 58 (3.45%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 58 (1.72%)	2 / 59 (3.39%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	0 / 58 (0.00%)	2 / 59 (3.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised intraabdominal fluid collection			

subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal fistula			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal perforation			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal spasm			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic pseudocyst			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 58 (0.00%)	2 / 59 (3.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 58 (1.72%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			

subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Cholecystitis acute</b>			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Cholelithiasis</b>			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Gallbladder enlargement</b>			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Gallbladder obstruction</b>			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Skin and subcutaneous tissue disorders</b>			
<b>Angioedema</b>			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Skin ulcer</b>			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Renal and urinary disorders</b>			
<b>Acute kidney injury</b>			
subjects affected / exposed	1 / 58 (1.72%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Nephropathy</b>			

subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Proteinuria</b>			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Renal failure</b>			
subjects affected / exposed	2 / 58 (3.45%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Musculoskeletal and connective tissue disorders</b>			
<b>Arthralgia</b>			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Back pain</b>			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Osteolysis</b>			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Pain in extremity</b>			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Spinal osteoarthritis</b>			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Infections and infestations</b>			

Abscess neck			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Candida sepsis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	1 / 58 (1.72%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Implant site infection			

subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Lower respiratory tract infection		
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)
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 / 58 (0.00%)	1 / 59 (1.69%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Lung infection		
subjects affected / exposed	0 / 58 (0.00%)	3 / 59 (5.08%)
occurrences causally related to treatment / all	0 / 0	2 / 4
deaths causally related to treatment / all	0 / 0	0 / 0
Lung infection pseudomonal		
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Periorbital cellulitis		
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pneumonia		
subjects affected / exposed	2 / 58 (3.45%)	4 / 59 (6.78%)
occurrences causally related to treatment / all	0 / 2	2 / 5
deaths causally related to treatment / all	0 / 0	0 / 0
Pneumonia staphylococcal		
subjects affected / exposed	0 / 58 (0.00%)	2 / 59 (3.39%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Pseudomonas infection		

subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sinusitis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tuberculosis			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 58 (1.72%)	3 / 59 (5.08%)	
occurrences causally related to treatment / all	1 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	4 / 58 (6.90%)	3 / 59 (5.08%)	
occurrences causally related to treatment / all	5 / 7	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcitonaemia			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	DTC Cohort	MTC Cohort	
Total subjects affected by non-serious adverse events subjects affected / exposed	58 / 58 (100.00%)	59 / 59 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps) Basal cell carcinoma subjects affected / exposed occurrences (all)	3 / 58 (5.17%) 3	0 / 59 (0.00%) 0	
Vascular disorders Deep vein thrombosis subjects affected / exposed occurrences (all)  Hypertension subjects affected / exposed occurrences (all)  Hypotension subjects affected / exposed occurrences (all)	3 / 58 (5.17%) 3  45 / 58 (77.59%) 108  14 / 58 (24.14%) 19	1 / 59 (1.69%) 1  31 / 59 (52.54%) 74  10 / 59 (16.95%) 19	
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all)  Chest discomfort subjects affected / exposed occurrences (all)  Chills subjects affected / exposed occurrences (all)  Fatigue subjects affected / exposed occurrences (all)  Influenza like illness subjects affected / exposed occurrences (all)  Local swelling	14 / 58 (24.14%) 36  0 / 58 (0.00%) 0  3 / 58 (5.17%) 4  35 / 58 (60.34%) 97  4 / 58 (6.90%) 4	6 / 59 (10.17%) 32  3 / 59 (5.08%) 3  3 / 59 (5.08%) 5  33 / 59 (55.93%) 84  6 / 59 (10.17%) 8	

subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0	3 / 59 (5.08%) 4	
Malaise subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0	5 / 59 (8.47%) 6	
Mucosal inflammation subjects affected / exposed occurrences (all)	6 / 58 (10.34%) 7	7 / 59 (11.86%) 8	
Oedema peripheral subjects affected / exposed occurrences (all)	14 / 58 (24.14%) 20	8 / 59 (13.56%) 8	
Pain subjects affected / exposed occurrences (all)	6 / 58 (10.34%) 6	3 / 59 (5.08%) 3	
Peripheral swelling subjects affected / exposed occurrences (all)	5 / 58 (8.62%) 11	4 / 59 (6.78%) 4	
Pyrexia subjects affected / exposed occurrences (all)	15 / 58 (25.86%) 21	12 / 59 (20.34%) 17	
Temperature intolerance subjects affected / exposed occurrences (all)	4 / 58 (6.90%) 4	4 / 59 (6.78%) 4	
Immune system disorders Seasonal allergy subjects affected / exposed occurrences (all)	2 / 58 (3.45%) 2	4 / 59 (6.78%) 4	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	28 / 58 (48.28%) 46	24 / 59 (40.68%) 38	
Dysphonia subjects affected / exposed occurrences (all)	25 / 58 (43.10%) 39	20 / 59 (33.90%) 38	
Dyspnoea			

subjects affected / exposed occurrences (all)	20 / 58 (34.48%) 32	16 / 59 (27.12%) 25	
Epistaxis			
subjects affected / exposed occurrences (all)	18 / 58 (31.03%) 28	13 / 59 (22.03%) 21	
Haemoptysis			
subjects affected / exposed occurrences (all)	6 / 58 (10.34%) 10	8 / 59 (13.56%) 13	
Nasal congestion			
subjects affected / exposed occurrences (all)	4 / 58 (6.90%) 6	2 / 59 (3.39%) 2	
Nasal dryness			
subjects affected / exposed occurrences (all)	3 / 58 (5.17%) 4	0 / 59 (0.00%) 0	
Oropharyngeal pain			
subjects affected / exposed occurrences (all)	16 / 58 (27.59%) 35	13 / 59 (22.03%) 25	
Pleural effusion			
subjects affected / exposed occurrences (all)	5 / 58 (8.62%) 9	4 / 59 (6.78%) 4	
Productive cough			
subjects affected / exposed occurrences (all)	4 / 58 (6.90%) 6	3 / 59 (5.08%) 3	
Rhinorrhoea			
subjects affected / exposed occurrences (all)	4 / 58 (6.90%) 4	3 / 59 (5.08%) 3	
Psychiatric disorders			
Anxiety			
subjects affected / exposed occurrences (all)	6 / 58 (10.34%) 7	8 / 59 (13.56%) 9	
Confusional state			
subjects affected / exposed occurrences (all)	1 / 58 (1.72%) 1	3 / 59 (5.08%) 4	
Depression			
subjects affected / exposed occurrences (all)	11 / 58 (18.97%) 11	5 / 59 (8.47%) 6	

Insomnia			
subjects affected / exposed	13 / 58 (22.41%)	7 / 59 (11.86%)	
occurrences (all)	14	9	
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	6 / 58 (10.34%)	5 / 59 (8.47%)	
occurrences (all)	6	5	
Alanine aminotransferase increased			
subjects affected / exposed	7 / 58 (12.07%)	9 / 59 (15.25%)	
occurrences (all)	17	21	
Aspartate aminotransferase increased			
subjects affected / exposed	9 / 58 (15.52%)	9 / 59 (15.25%)	
occurrences (all)	15	18	
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 58 (3.45%)	5 / 59 (8.47%)	
occurrences (all)	5	12	
Blood bilirubin increased			
subjects affected / exposed	1 / 58 (1.72%)	3 / 59 (5.08%)	
occurrences (all)	1	4	
Blood creatine phosphokinase increased			
subjects affected / exposed	4 / 58 (6.90%)	2 / 59 (3.39%)	
occurrences (all)	6	3	
Blood creatinine increased			
subjects affected / exposed	3 / 58 (5.17%)	4 / 59 (6.78%)	
occurrences (all)	4	11	
Blood lactate dehydrogenase increased			
subjects affected / exposed	3 / 58 (5.17%)	1 / 59 (1.69%)	
occurrences (all)	3	1	
Blood pressure increased			
subjects affected / exposed	3 / 58 (5.17%)	4 / 59 (6.78%)	
occurrences (all)	9	4	
Blood thyroid stimulating hormone decreased			
subjects affected / exposed	0 / 58 (0.00%)	3 / 59 (5.08%)	
occurrences (all)	0	4	

Blood thyroid stimulating hormone increased			
subjects affected / exposed	4 / 58 (6.90%)	13 / 59 (22.03%)	
occurrences (all)	4	16	
Blood triglycerides increased			
subjects affected / exposed	1 / 58 (1.72%)	3 / 59 (5.08%)	
occurrences (all)	3	5	
Blood urea increased			
subjects affected / exposed	5 / 58 (8.62%)	2 / 59 (3.39%)	
occurrences (all)	9	2	
Blood urine present			
subjects affected / exposed	3 / 58 (5.17%)	0 / 59 (0.00%)	
occurrences (all)	4	0	
Electrocardiogram QT prolonged			
subjects affected / exposed	4 / 58 (6.90%)	4 / 59 (6.78%)	
occurrences (all)	5	7	
Haemoglobin decreased			
subjects affected / exposed	5 / 58 (8.62%)	2 / 59 (3.39%)	
occurrences (all)	5	3	
Platelet count decreased			
subjects affected / exposed	2 / 58 (3.45%)	3 / 59 (5.08%)	
occurrences (all)	7	3	
Prothrombin time prolonged			
subjects affected / exposed	3 / 58 (5.17%)	0 / 59 (0.00%)	
occurrences (all)	3	0	
Weight decreased			
subjects affected / exposed	39 / 58 (67.24%)	29 / 59 (49.15%)	
occurrences (all)	125	81	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 58 (0.00%)	3 / 59 (5.08%)	
occurrences (all)	0	7	
Fall			
subjects affected / exposed	2 / 58 (3.45%)	3 / 59 (5.08%)	
occurrences (all)	2	5	
Thermal burn			

subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0	3 / 59 (5.08%) 3	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	3 / 58 (5.17%)	0 / 59 (0.00%)	
occurrences (all)	3	0	
Bradycardia			
subjects affected / exposed	5 / 58 (8.62%)	0 / 59 (0.00%)	
occurrences (all)	6	0	
Sinus tachycardia			
subjects affected / exposed	0 / 58 (0.00%)	3 / 59 (5.08%)	
occurrences (all)	0	4	
Tachycardia			
subjects affected / exposed	7 / 58 (12.07%)	7 / 59 (11.86%)	
occurrences (all)	7	9	
Nervous system disorders			
Burning sensation			
subjects affected / exposed	1 / 58 (1.72%)	3 / 59 (5.08%)	
occurrences (all)	1	4	
Dizziness			
subjects affected / exposed	10 / 58 (17.24%)	13 / 59 (22.03%)	
occurrences (all)	14	15	
Dysgeusia			
subjects affected / exposed	12 / 58 (20.69%)	9 / 59 (15.25%)	
occurrences (all)	14	13	
Headache			
subjects affected / exposed	27 / 58 (46.55%)	27 / 59 (45.76%)	
occurrences (all)	49	59	
Hyperaesthesia			
subjects affected / exposed	1 / 58 (1.72%)	11 / 59 (18.64%)	
occurrences (all)	1	15	
Hypoaesthesia			
subjects affected / exposed	3 / 58 (5.17%)	4 / 59 (6.78%)	
occurrences (all)	5	4	
Paraesthesia			

subjects affected / exposed occurrences (all)	7 / 58 (12.07%) 8	1 / 59 (1.69%) 1	
Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	3 / 58 (5.17%) 8	3 / 59 (5.08%) 4	
Sinus headache subjects affected / exposed occurrences (all)	3 / 58 (5.17%) 3	1 / 59 (1.69%) 2	
Somnolence subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0	5 / 59 (8.47%) 8	
Tremor subjects affected / exposed occurrences (all)	3 / 58 (5.17%) 3	2 / 59 (3.39%) 2	
<b>Blood and lymphatic system disorders</b>			
Anaemia subjects affected / exposed occurrences (all)	2 / 58 (3.45%) 2	3 / 59 (5.08%) 9	
Leukopenia subjects affected / exposed occurrences (all)	3 / 58 (5.17%) 4	2 / 59 (3.39%) 2	
Lymphadenopathy subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0	3 / 59 (5.08%) 3	
Lymphopenia subjects affected / exposed occurrences (all)	2 / 58 (3.45%) 3	6 / 59 (10.17%) 6	
Neutropenia subjects affected / exposed occurrences (all)	5 / 58 (8.62%) 7	2 / 59 (3.39%) 3	
Thrombocytopenia subjects affected / exposed occurrences (all)	2 / 58 (3.45%) 3	5 / 59 (8.47%) 8	
<b>Ear and labyrinth disorders</b>			
Ear discomfort			

subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0	4 / 59 (6.78%) 4	
Ear pain subjects affected / exposed occurrences (all)	3 / 58 (5.17%) 5	0 / 59 (0.00%) 0	
Eye disorders Cataract subjects affected / exposed occurrences (all)	3 / 58 (5.17%) 3	0 / 59 (0.00%) 0	
Lacrimation increased subjects affected / exposed occurrences (all)	4 / 58 (6.90%) 4	1 / 59 (1.69%) 1	
Vision blurred subjects affected / exposed occurrences (all)	4 / 58 (6.90%) 4	2 / 59 (3.39%) 2	
Visual impairment subjects affected / exposed occurrences (all)	3 / 58 (5.17%) 4	1 / 59 (1.69%) 1	
Gastrointestinal disorders Abdominal distension subjects affected / exposed occurrences (all)	8 / 58 (13.79%) 12	2 / 59 (3.39%) 2	
Abdominal pain subjects affected / exposed occurrences (all)	20 / 58 (34.48%) 31	19 / 59 (32.20%) 38	
Abdominal pain lower subjects affected / exposed occurrences (all)	2 / 58 (3.45%) 2	4 / 59 (6.78%) 5	
Abdominal pain upper subjects affected / exposed occurrences (all)	18 / 58 (31.03%) 33	18 / 59 (30.51%) 28	
Cheilitis subjects affected / exposed occurrences (all)	3 / 58 (5.17%) 5	3 / 59 (5.08%) 3	
Constipation			

subjects affected / exposed	16 / 58 (27.59%)	17 / 59 (28.81%)
occurrences (all)	23	37
Diarrhoea		
subjects affected / exposed	40 / 58 (68.97%)	45 / 59 (76.27%)
occurrences (all)	146	242
Dry mouth		
subjects affected / exposed	21 / 58 (36.21%)	10 / 59 (16.95%)
occurrences (all)	25	11
Dyspepsia		
subjects affected / exposed	6 / 58 (10.34%)	8 / 59 (13.56%)
occurrences (all)	8	10
Dysphagia		
subjects affected / exposed	14 / 58 (24.14%)	12 / 59 (20.34%)
occurrences (all)	17	16
Faeces pale		
subjects affected / exposed	3 / 58 (5.17%)	0 / 59 (0.00%)
occurrences (all)	6	0
Flatulence		
subjects affected / exposed	5 / 58 (8.62%)	2 / 59 (3.39%)
occurrences (all)	5	3
Gastrooesophageal reflux disease		
subjects affected / exposed	5 / 58 (8.62%)	7 / 59 (11.86%)
occurrences (all)	9	11
Gingival bleeding		
subjects affected / exposed	0 / 58 (0.00%)	4 / 59 (6.78%)
occurrences (all)	0	7
Gingival pain		
subjects affected / exposed	1 / 58 (1.72%)	4 / 59 (6.78%)
occurrences (all)	1	7
Glossitis		
subjects affected / exposed	5 / 58 (8.62%)	1 / 59 (1.69%)
occurrences (all)	5	1
Glossodynia		
subjects affected / exposed	9 / 58 (15.52%)	12 / 59 (20.34%)
occurrences (all)	14	17
Haematochezia		

subjects affected / exposed occurrences (all)	2 / 58 (3.45%) 2	4 / 59 (6.78%) 4	
Haemorrhoids			
subjects affected / exposed occurrences (all)	5 / 58 (8.62%) 5	2 / 59 (3.39%) 2	
Mouth ulceration			
subjects affected / exposed occurrences (all)	3 / 58 (5.17%) 3	5 / 59 (8.47%) 5	
Nausea			
subjects affected / exposed occurrences (all)	30 / 58 (51.72%) 70	30 / 59 (50.85%) 82	
Oesophagitis			
subjects affected / exposed occurrences (all)	4 / 58 (6.90%) 5	0 / 59 (0.00%) 0	
Oral discomfort			
subjects affected / exposed occurrences (all)	3 / 58 (5.17%) 3	8 / 59 (13.56%) 10	
Oral pain			
subjects affected / exposed occurrences (all)	7 / 58 (12.07%) 14	8 / 59 (13.56%) 11	
Stomatitis			
subjects affected / exposed occurrences (all)	19 / 58 (32.76%) 55	15 / 59 (25.42%) 22	
Tongue disorder			
subjects affected / exposed occurrences (all)	3 / 58 (5.17%) 3	0 / 59 (0.00%) 0	
Toothache			
subjects affected / exposed occurrences (all)	5 / 58 (8.62%) 5	6 / 59 (10.17%) 7	
Vomiting			
subjects affected / exposed occurrences (all)	23 / 58 (39.66%) 83	25 / 59 (42.37%) 91	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed occurrences (all)	7 / 58 (12.07%) 7	7 / 59 (11.86%) 7	

Blister		
subjects affected / exposed	2 / 58 (3.45%)	3 / 59 (5.08%)
occurrences (all)	2	6
Dermatitis		
subjects affected / exposed	2 / 58 (3.45%)	3 / 59 (5.08%)
occurrences (all)	2	3
Dermatitis acneiform		
subjects affected / exposed	1 / 58 (1.72%)	3 / 59 (5.08%)
occurrences (all)	1	3
Dermatitis allergic		
subjects affected / exposed	3 / 58 (5.17%)	2 / 59 (3.39%)
occurrences (all)	4	2
Dry skin		
subjects affected / exposed	10 / 58 (17.24%)	11 / 59 (18.64%)
occurrences (all)	14	17
Erythema		
subjects affected / exposed	4 / 58 (6.90%)	4 / 59 (6.78%)
occurrences (all)	4	4
Exfoliative rash		
subjects affected / exposed	2 / 58 (3.45%)	3 / 59 (5.08%)
occurrences (all)	2	8
Hair texture abnormal		
subjects affected / exposed	3 / 58 (5.17%)	0 / 59 (0.00%)
occurrences (all)	3	0
Hyperhidrosis		
subjects affected / exposed	2 / 58 (3.45%)	3 / 59 (5.08%)
occurrences (all)	2	3
Hyperkeratosis		
subjects affected / exposed	4 / 58 (6.90%)	7 / 59 (11.86%)
occurrences (all)	4	10
Night sweats		
subjects affected / exposed	0 / 58 (0.00%)	3 / 59 (5.08%)
occurrences (all)	0	3
Palmar-plantar erythrodysesthesia syndrome		

subjects affected / exposed occurrences (all)	15 / 58 (25.86%) 37	15 / 59 (25.42%) 45
Pruritus		
subjects affected / exposed occurrences (all)	5 / 58 (8.62%) 7	5 / 59 (8.47%) 6
Rash		
subjects affected / exposed occurrences (all)	10 / 58 (17.24%) 12	16 / 59 (27.12%) 28
Rash macular		
subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0	3 / 59 (5.08%) 3
Rash papular		
subjects affected / exposed occurrences (all)	3 / 58 (5.17%) 3	6 / 59 (10.17%) 7
Rash pruritic		
subjects affected / exposed occurrences (all)	3 / 58 (5.17%) 4	2 / 59 (3.39%) 2
Skin exfoliation		
subjects affected / exposed occurrences (all)	2 / 58 (3.45%) 5	6 / 59 (10.17%) 16
Skin fissures		
subjects affected / exposed occurrences (all)	3 / 58 (5.17%) 6	1 / 59 (1.69%) 1
Skin induration		
subjects affected / exposed occurrences (all)	3 / 58 (5.17%) 6	3 / 59 (5.08%) 6
Skin lesion		
subjects affected / exposed occurrences (all)	7 / 58 (12.07%) 11	4 / 59 (6.78%) 6
Skin ulcer		
subjects affected / exposed occurrences (all)	5 / 58 (8.62%) 5	1 / 59 (1.69%) 2
Swelling face		
subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0	5 / 59 (8.47%) 7
Renal and urinary disorders		

Dysuria			
subjects affected / exposed	3 / 58 (5.17%)	3 / 59 (5.08%)	
occurrences (all)	3	3	
Haematuria			
subjects affected / exposed	5 / 58 (8.62%)	1 / 59 (1.69%)	
occurrences (all)	7	2	
Pollakiuria			
subjects affected / exposed	4 / 58 (6.90%)	2 / 59 (3.39%)	
occurrences (all)	4	3	
Proteinuria			
subjects affected / exposed	41 / 58 (70.69%)	38 / 59 (64.41%)	
occurrences (all)	195	160	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 58 (0.00%)	3 / 59 (5.08%)	
occurrences (all)	0	3	
Hypothyroidism			
subjects affected / exposed	2 / 58 (3.45%)	3 / 59 (5.08%)	
occurrences (all)	2	4	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	22 / 58 (37.93%)	21 / 59 (35.59%)	
occurrences (all)	51	51	
Arthritis			
subjects affected / exposed	3 / 58 (5.17%)	0 / 59 (0.00%)	
occurrences (all)	4	0	
Back pain			
subjects affected / exposed	23 / 58 (39.66%)	14 / 59 (23.73%)	
occurrences (all)	34	31	
Bone pain			
subjects affected / exposed	5 / 58 (8.62%)	3 / 59 (5.08%)	
occurrences (all)	5	15	
Joint stiffness			
subjects affected / exposed	2 / 58 (3.45%)	3 / 59 (5.08%)	
occurrences (all)	3	4	
Joint swelling			

subjects affected / exposed	2 / 58 (3.45%)	3 / 59 (5.08%)
occurrences (all)	2	3
Muscle spasms		
subjects affected / exposed	13 / 58 (22.41%)	7 / 59 (11.86%)
occurrences (all)	27	11
Muscle tightness		
subjects affected / exposed	1 / 58 (1.72%)	4 / 59 (6.78%)
occurrences (all)	1	5
Muscular weakness		
subjects affected / exposed	3 / 58 (5.17%)	4 / 59 (6.78%)
occurrences (all)	6	5
Musculoskeletal chest pain		
subjects affected / exposed	14 / 58 (24.14%)	14 / 59 (23.73%)
occurrences (all)	14	19
Musculoskeletal pain		
subjects affected / exposed	19 / 58 (32.76%)	17 / 59 (28.81%)
occurrences (all)	33	24
Musculoskeletal stiffness		
subjects affected / exposed	2 / 58 (3.45%)	3 / 59 (5.08%)
occurrences (all)	2	4
Myalgia		
subjects affected / exposed	14 / 58 (24.14%)	14 / 59 (23.73%)
occurrences (all)	29	27
Neck pain		
subjects affected / exposed	8 / 58 (13.79%)	9 / 59 (15.25%)
occurrences (all)	11	10
Pain in extremity		
subjects affected / exposed	19 / 58 (32.76%)	17 / 59 (28.81%)
occurrences (all)	46	43
Pain in jaw		
subjects affected / exposed	2 / 58 (3.45%)	5 / 59 (8.47%)
occurrences (all)	2	12
Periarthritis		
subjects affected / exposed	3 / 58 (5.17%)	0 / 59 (0.00%)
occurrences (all)	4	0
Flank pain		

subjects affected / exposed occurrences (all)	2 / 58 (3.45%) 4	3 / 59 (5.08%) 5	
<b>Infections and infestations</b>			
<b>Bronchitis</b>			
subjects affected / exposed occurrences (all)	2 / 58 (3.45%) 2	5 / 59 (8.47%) 5	
<b>Gastroenteritis viral</b>			
subjects affected / exposed occurrences (all)	4 / 58 (6.90%) 5	3 / 59 (5.08%) 5	
<b>Gingivitis</b>			
subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0	3 / 59 (5.08%) 7	
<b>Influenza</b>			
subjects affected / exposed occurrences (all)	6 / 58 (10.34%) 10	7 / 59 (11.86%) 9	
<b>Laryngitis</b>			
subjects affected / exposed occurrences (all)	1 / 58 (1.72%) 1	3 / 59 (5.08%) 4	
<b>Localised infection</b>			
subjects affected / exposed occurrences (all)	2 / 58 (3.45%) 2	4 / 59 (6.78%) 8	
<b>Lower respiratory tract infection</b>			
subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0	5 / 59 (8.47%) 10	
<b>Nasopharyngitis</b>			
subjects affected / exposed occurrences (all)	2 / 58 (3.45%) 3	7 / 59 (11.86%) 21	
<b>Oral candidiasis</b>			
subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0	4 / 59 (6.78%) 5	
<b>Pharyngitis</b>			
subjects affected / exposed occurrences (all)	4 / 58 (6.90%) 5	4 / 59 (6.78%) 7	
<b>Pneumonia</b>			
subjects affected / exposed occurrences (all)	4 / 58 (6.90%) 6	1 / 59 (1.69%) 1	

Rash pustular			
subjects affected / exposed	0 / 58 (0.00%)	3 / 59 (5.08%)	
occurrences (all)	0	4	
Rhinitis			
subjects affected / exposed	3 / 58 (5.17%)	3 / 59 (5.08%)	
occurrences (all)	4	3	
Sinusitis			
subjects affected / exposed	3 / 58 (5.17%)	6 / 59 (10.17%)	
occurrences (all)	5	12	
Tooth abscess			
subjects affected / exposed	4 / 58 (6.90%)	4 / 59 (6.78%)	
occurrences (all)	4	5	
Upper respiratory tract infection			
subjects affected / exposed	12 / 58 (20.69%)	12 / 59 (20.34%)	
occurrences (all)	13	19	
Urinary tract infection			
subjects affected / exposed	11 / 58 (18.97%)	8 / 59 (13.56%)	
occurrences (all)	15	17	
Vaginal infection			
subjects affected / exposed	3 / 58 (5.17%)	1 / 59 (1.69%)	
occurrences (all)	3	1	
Viral infection			
subjects affected / exposed	0 / 58 (0.00%)	3 / 59 (5.08%)	
occurrences (all)	0	4	
Gastroenteritis			
subjects affected / exposed	2 / 58 (3.45%)	5 / 59 (8.47%)	
occurrences (all)	2	5	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	32 / 58 (55.17%)	32 / 59 (54.24%)	
occurrences (all)	61	74	
Dehydration			
subjects affected / exposed	9 / 58 (15.52%)	6 / 59 (10.17%)	
occurrences (all)	10	10	
Dyslipidaemia			

subjects affected / exposed	2 / 58 (3.45%)	3 / 59 (5.08%)
occurrences (all)	3	3
<b>Hypercalcaemia</b>		
subjects affected / exposed	1 / 58 (1.72%)	4 / 59 (6.78%)
occurrences (all)	1	5
<b>Hypercholesterolaemia</b>		
subjects affected / exposed	6 / 58 (10.34%)	2 / 59 (3.39%)
occurrences (all)	15	5
<b>Hyperglycaemia</b>		
subjects affected / exposed	4 / 58 (6.90%)	6 / 59 (10.17%)
occurrences (all)	13	9
<b>Hyperkalaemia</b>		
subjects affected / exposed	2 / 58 (3.45%)	3 / 59 (5.08%)
occurrences (all)	4	3
<b>Hypertriglyceridaemia</b>		
subjects affected / exposed	6 / 58 (10.34%)	2 / 59 (3.39%)
occurrences (all)	22	2
<b>Hypoalbuminaemia</b>		
subjects affected / exposed	1 / 58 (1.72%)	3 / 59 (5.08%)
occurrences (all)	1	5
<b>Hypocalcaemia</b>		
subjects affected / exposed	9 / 58 (15.52%)	12 / 59 (20.34%)
occurrences (all)	21	20
<b>Hypoglycaemia</b>		
subjects affected / exposed	2 / 58 (3.45%)	4 / 59 (6.78%)
occurrences (all)	2	4
<b>Hypokalaemia</b>		
subjects affected / exposed	6 / 58 (10.34%)	7 / 59 (11.86%)
occurrences (all)	8	12
<b>Hypomagnesaemia</b>		
subjects affected / exposed	0 / 58 (0.00%)	3 / 59 (5.08%)
occurrences (all)	0	3
<b>Hyponatraemia</b>		
subjects affected / exposed	3 / 58 (5.17%)	5 / 59 (8.47%)
occurrences (all)	3	6



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 April 2009	Amendment 01: The protocol was amended to remove the dose limiting toxicity component of study and changed to once daily dosing of 24 mg instead of twice daily 10 mg dosing, change the study design to Simon's optimal two-stage design, which would have allowed for early termination of the study if the response was not sufficient, add simplified electrocardiogram (ECG) monitoring scheme, increased the timing of disease progression window to 12 months from 6 months for inclusion criteria, include proteinuria as a toxicity.
12 April 2010	Amendment 02: The protocol was amended to clarify that subjects with classical papillary thyroid cancer and minimally or widely invasive follicular thyroid cancer could have been included in the subject population, remove renal function with serum creatinine greater than (>) 1.5 upper limit normal (ULN) as an exclusion criteria, exclude subjects with greater than or equal to (>=) 1 gram (g) per (/)24 hour proteinuria, include a section on reporting overdose of study drug and include the reporting of significant treatment-emergent laboratory abnormalities as adverse events.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported