Clinical trial results:
Phase 2 Randomized, Double-Blinded, Controlled Study of Tucatinib vs. Placebo in Combination with Capecitabine and Trastuzumab in Patients with Pretreated Unresectable Locally Advanced or Metastatic HER2+ Breast Carcinoma (HER2CLIMB)

Summary

EudraCT number	2015-002801-12
Trial protocol	DE AT CZ BE DK FR PT GB IT
Global end of trial date	11 August 2022

Results information

Result version number	v1 (current)
This version publication date	18 August 2023
First version publication date	18 August 2023

Trial information

Trial identification

Sponsor protocol code	ONT-380-206

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02614794
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Seagen Inc.
Sponsor organisation address	21823 30th Drive S.E., Bothell, United States, 98021
Public contact	Chief Medical Officer, Seagen Inc., 1 8554732436, medinfo@seagen.com
Scientific contact	Chief Medical Officer, Seagen Inc., 1 8554732436, medinfo@seagen.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	15 November 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 August 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

• To assess the effect of tucatinib vs. placebo in combination with capecitabine and trastuzumab on PFS per RECIST 1.1 based on blinded independent central review (BICR)

Protection of trial subjects:

This study was conducted in accordance with applicable Food and Drug Administration (FDA) regulations/guidelines set forth in 21 CFR Parts 11, 50, 54, 56, and 312 and with International Council on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines. Essential documents will be retained in accordance with ICH GCP.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 January 2016
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	United States: 331
Country: Number of subjects enrolled	France: 46
Country: Number of subjects enrolled	United Kingdom: 45
Country: Number of subjects enrolled	Australia: 39
Country: Number of subjects enrolled	Canada: 38
Country: Number of subjects enrolled	Spain: 26
Country: Number of subjects enrolled	Denmark: 20
Country: Number of subjects enrolled	Germany: 17
Country: Number of subjects enrolled	Israel: 16
Country: Number of subjects enrolled	Belgium: 10
Country: Number of subjects enrolled	Italy: 9
Country: Number of subjects enrolled	Austria: 7
Country: Number of subjects enrolled	Portugal: 4
Country: Number of subjects enrolled	Czechia: 3
Country: Number of subjects enrolled	Switzerland: 1
Worldwide total number of subjects	612
EEA total number of subjects	142

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	496
From 65 to 84 years	116
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants were screened for eligibility prior to enrollment.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Tuc+Cap+Tra

Arm description:

Tucatinib in combination with capecitabine & trastuzumab

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

Dosage and administration details:

Tucatinib 300 mg orally twice daily (PO BID) every day (Days 1–21) of each 21-day cycle

Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion, Powder for solution for injection/infusion
Routes of administration	Intravenous use, Subcutaneous use

Dosage and administration details:

Trastuzumab loading dose 8 mg/kg IV on Day 1, followed by 6
mg/kg on Day 1 of a 21-day cycle. In instances of subcutaneous (SC) trastuzumab use, a fixed dose of 600
mg was administered without a loading dose.

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

Dosage and administration details:

Capecitabine 1000 mg/m2 PO BID on Days 1–14 of each 21-day cycle.

Arm title	Pbo+Cap+Tra

Arm description:

Placebo in combination with capecitabine & trastuzumab

Arm type	Placebo-Controlled Active Comparator

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

Dosage and administration details:

Capecitabine 1000 mg/m2 PO BID on Days 1–14 of each 21-day cycle.

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

Dosage and administration details:

Placebo PO BID for Days 1-21 of a 21-day cycle

Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion, Powder for solution for injection/infusion
Routes of administration	Intravenous use, Subcutaneous use

Dosage and administration details:

Trastuzumab loading dose 8 mg/kg IV on Day 1, followed by 6
mg/kg on Day 1 of a 21-day cycle. In instances of subcutaneous (SC) trastuzumab use, a fixed dose of 600
mg was administered without a loading dose.

Number of subjects in period 1	Tuc+Cap+Tra	Pbo+Cap+Tra
Started	410	202
Completed	0	0
Not completed	410	202
Adverse event, serious fatal	258	151
Consent withdrawn by subject	24	5
Physician decision	1	1
Hospital closure	1	-
Lost to follow-up	7	-
Study closure by Sponsor	119	45

Baseline characteristics

Reporting groups	
Reporting group title	Tuc+Cap+Tra
Reporting group description:	
Tucatinib in combination with capecitabine & trastuzumab	
Reporting group title	Pbo+Cap+Tra
Reporting group description:	
Placebo in combination with capecitabine & trastuzumab	

Reporting group values	Tuc+Cap+Tra	Pbo+Cap+Tra	Total
Number of subjects	410	202	612
Age Categorical Units: participants			
<=18 years	0	0	0
Between 18 and 65 years	328	168	496
>=65 years	82	34	116
Age Continuous Units: years			
median	55	54	
full range (min-max)	22 to 80	25 to 82	-
Sex: Female, Male Units: participants			
Female	407	200	607
Male	3	2	5
Region of Enrollment Units: Subjects			
United States	220	111	331
France	29	17	46
United Kingdom	33	12	45
Australia	27	12	39
Canada	26	12	38
Spain	19	7	26
Denmark	13	7	20
Germany	9	8	17
Israel	13	3	16
Belgium	4	6	10
Italy	6	3	9
Austria	6	1	7
Portugal	3	1	4
Czech Republic	2	1	3
Switzerland	0	1	1
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	18	5	23
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	41	14	55

White	287	157	444
More than one race	0	0	0
Unknown or Not Reported	64	26	90
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	37	14	51
Not Hispanic or Latino	362	184	546
Unknown or Not Reported	11	4	15
Eastern Cooperative Oncology Group (ECOG) Performance Status			
0=Normal activity; 1=Symptoms but ambulatory; 2=In bed <50% of the time; 3= In bed >50% of the time; 4=100% bedridden; 5=Dead			
Units: Subjects			
0: Normal activity	204	94	298
1: Symptoms, but ambulatory	206	108	314

End points

End points reporting groups

Reporting group title	Tuc+Cap+Tra
Reporting group description: Tucatinib in combination with capecitabine & trastuzumab	
Reporting group title	Pbo+Cap+Tra
Reporting group description: Placebo in combination with capecitabine & trastuzumab	

Primary: Progression-free survival (PFS) per RECIST 1.1 as determined by blinded independent central review (BICR)

End point title	Progression-free survival (PFS) per RECIST 1.1 as determined by blinded independent central review (BICR)
End point description: Defined as the time from the date of randomization to the date of documented disease progression.	
End point type	Primary
End point timeframe: 34.6 months	

End point values	Tuc+Cap+Tra	Pbo+Cap+Tra		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	320	160		
Units: months				
median (inter-quartile range (Q1-Q3))	7.8 (4.3 to 17.8)	5.6 (3.0 to 9.7)		

Statistical analyses

Statistical analysis title	Progression-Free Survival per BICR
Statistical analysis description: The two treatment arms were compared using a stratified, log-rank test controlling for the randomization stratification factors. P-value for this test was calculated using a re-randomization based procedure to reflect the dynamic, hierarchical allocation scheme used for the study randomization. Median PFS and its 95% confidence interval (CI) was provided for two treatment arms. A Cox proportional-hazards model was used to estimate the hazard ratio (HR) and its 95% CI.	
Comparison groups	Tuc+Cap+Tra v Pbo+Cap+Tra
Number of subjects included in analysis	480
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.00001
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	0.54

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	0.71

Secondary: PFS in patients with brain metastases at baseline using RECIST 1.1 as determined by BICR

End point title	PFS in patients with brain metastases at baseline using RECIST 1.1 as determined by BICR

End point description:

Defined as the time from the date of randomization to the date of documented disease progression.

End point type	Secondary

End point timeframe:

34.6 months

End point values	Tuc+Cap+Tra	Pbo+Cap+Tra		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	198	93		
Units: months				
median (inter-quartile range (Q1-Q3))	7.6 (4.2 to 11.8)	5.4 (3.0 to 7.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) at time of primary analysis

End point title	Overall Survival (OS) at time of primary analysis

End point description:

Defined as time from randomization to death from any cause

End point type	Secondary

End point timeframe:

35.9 months

End point values	Tuc+Cap+Tra	Pbo+Cap+Tra		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	410	202		
Units: months				
median (confidence interval 95%)	21.9 (18.3 to 31.0)	17.4 (13.6 to 19.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Confirmed objective response rate (ORR) per RECIST 1.1 as determined by BICR

End point title	Confirmed objective response rate (ORR) per RECIST 1.1 as determined by BICR

End point description:

Defined as achieving a best overall response of confirmed complete response (CR) or confirmed partial response (PR).

End point type	Secondary

End point timeframe:

34.6 months

End point values	Tuc+Cap+Tra	Pbo+Cap+Tra		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	273	137		
Units: percentage of participants				
number (confidence interval 95%)	40.7 (34.8 to 46.7)	23.4 (16.6 to 31.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: ORR per RECIST 1.1 as determined by investigator assessment

End point title	ORR per RECIST 1.1 as determined by investigator assessment

End point description:

Defined as achieving a best overall response of confirmed CR or confirmed PR.

End point type	Secondary

End point timeframe:

34.6 months

End point values	Tuc+Cap+Tra	Pbo+Cap+Tra		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	280	139		
Units: percentage of participants				
number (confidence interval 95%)	41.4 (35.6 to 47.4)	23.0 (16.3 to 30.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: PFS per RECIST 1.1 as determined by investigator assessment at time of primary analysis

End point title	PFS per RECIST 1.1 as determined by investigator assessment at time of primary analysis

End point description:

Defined as the time from the date of randomization to the date of documented disease progression

End point type	Secondary

End point timeframe:

34.6 months

End point values	Tuc+Cap+Tra	Pbo+Cap+Tra		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	320	160		
Units: months				
median (inter-quartile range (Q1-Q3))	7.5 (4.1 to 13.1)	4.3 (2.7 to 8.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response (DOR) per RECIST 1.1 as determined by BICR

End point title	Duration of response (DOR) per RECIST 1.1 as determined by BICR

End point description:

Defined as the time from the first objective response to documented disease progression or death from any cause, whichever occurred first.

End point type	Secondary

End point timeframe:

24.6 months

End point values	Tuc+Cap+Tra	Pbo+Cap+Tra		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	410	202		
Units: months				
median (inter-quartile range (Q1-Q3))	8.3 (4.3 to 12.8)	6.3 (4.2 to 9.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical benefit rate (CBR) as determined by BICR per RECIST 1.1

End point title	Clinical benefit rate (CBR) as determined by BICR per RECIST 1.1

End point description:

Clinical benefit was defined as achieving stable disease (SD) or non-complete response (CR)/non-progressive disease (PD) for at least 6 months or a best overall response of confirmed CR or confirmed partial response (PR).

End point type	Secondary

End point timeframe:

34.6 months

End point values	Tuc+Cap+Tra	Pbo+Cap+Tra		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	410	202		
Units: percentage of participants				
number (confidence interval 95%)	59.8 (54.8 to 64.5)	38.1 (31.4 to 45.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: DOR per RECIST 1.1 as determined by investigator assessment

End point title	DOR per RECIST 1.1 as determined by investigator assessment

End point description:

Defined as the time from the first objective response to documented disease progression or death from any cause, whichever occurred first.

End point type	Secondary

End point timeframe:

33.2 months

End point values	Tuc+Cap+Tra	Pbo+Cap+Tra		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	410	202		
Units: months				
median (inter-quartile range (Q1-Q3))	7.0 (4.3 to 12.9)	6.9 (4.1 to 9.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: CBR per RECIST 1.1 as determined by investigator assessment

End point title	CBR per RECIST 1.1 as determined by investigator assessment

End point description:

Clinical benefit was defined as achieving stable disease (SD) or non-CR/non-PD for at least 6 months or a best overall response of confirmed CR or confirmed PR.

End point type	Secondary

End point timeframe:

34.6 months

End point values	Tuc+Cap+Tra	Pbo+Cap+Tra		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	410	202		
Units: percentage of participants				
number (confidence interval 95%)	58.0 (53.1 to 62.9)	37.6 (30.9 to 44.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of adverse events (AEs) at time of primary analysis

End point title	Incidence of adverse events (AEs) at time of primary analysis

End point description:

As determined by assessment of AEs, clinical laboratory tests, and vital signs measurements. AEs were classified by system organ class (SOC) and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) Version 22.0 or higher; AE severities were classified using Version 4.03 of the (Common Terminology Criteria for Adverse Events) CTCAE criteria.

End point type	Secondary

End point timeframe:

36.1 months

End point values	Tuc+Cap+Tra	Pbo+Cap+Tra		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	404	197		
Units: Number of Participants				
Any treatment-emergent AE (TEAE)	401	191		
Any Grade 3 or higher TEAE	223	96		
Any treatment-emergent serious AE	104	53		
TEAE leading to death	8	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Frequency of dose modifications

End point title	Frequency of dose modifications

End point description:

End point type	Secondary

End point timeframe:

35.1 months

End point values	Tuc+Cap+Tra	Pbo+Cap+Tra		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	404	197		
Units: Number of Participants				
TEAEs resulting in tuc/pbo dose modification	220	81		
TEAEs resulting in tucatinib/placebo dose hold	216	80		
TEAEs resulting in tuc/pbo dose reduction	84	21		
TEAEs resulting capecitabine dose modification	313	122		
TEAEs resulting in capecitabine dose hold	276	113		
TEAEs resulting in capecitabine dose reduction	243	77		
TEAEs resulting trastuzumab dose modification	104	38		
TEAEs resulting in trastuzumab dose hold	104	38		

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of health resources utilization

End point title	Incidence of health resources utilization

End point description:

Cumulative incidence of health resource utilization, including length of stay, hospitalizations, and ER visits using the EQ-5D-5L questionnaire.

End point type	Secondary

End point timeframe:

36.1 months

End point values	Tuc+Cap+Tra	Pbo+Cap+Tra		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	404	197		
Units: hospitalizations				
Total number of hospitalizations	143	75		
Hospitalization for AE	124	64		
Planned hospitalization (other than AE)	10	6		
Ambulatory Surgery	3	0		
Other	6	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic measure: Ctrough of tucatinib

End point title	Pharmacokinetic measure: Ctrough of tucatinib[1]

End point description:

Individual plasma tucatinib concentrations at each sampling time

End point type	Secondary

End point timeframe:

3.5 months

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: PK outcomes are intended to evaluate the pharmacokinetics of tucatinib and metabolite ONT-993. Participants in the placebo arm are not included in the end point since they did not receive tucatinib.

End point values	Tuc+Cap+Tra			
Subject group type	Reporting group			
Number of subjects analysed	373			
Units: ng/mL				
arithmetic mean (standard deviation)				
Cycle 2, Day 1 (Pre-dose)	246.1 (± 260.9)			
Cycle 3, Day 1 (Pre-dose)	227.6 (± 210.8)			
Cycle 3, Day 1 (Post-dose)	507.1 (± 357.1)			

Cycle 4, Day 1 (Pre-dose)	253.2 (± 236.1)			
Cycle 5, Day 1 (Pre-dose)	257.6 (± 286.9)			
Cycle 6, Day 1 (Pre-dose)	247.8 (± 225.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic measure: ONT-993

End point title	Pharmacokinetic measure: ONT-993[2]

End point description:

Individual plasma primary metabolite concentrations at each sampling time

End point type	Secondary

End point timeframe:

3.5 months

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: PK outcomes are intended to evaluate the pharmacokinetics of tucatinib and metabolite ONT-993. Participants in the placebo arm are not included in the end point since they did not receive tucatinib.

End point values	Tuc+Cap+Tra			
Subject group type	Reporting group			
Number of subjects analysed	373			
Units: ng/mL				
arithmetic mean (standard deviation)				
Cycle 2, Day 1 (Pre-dose)	25.5 (± 24.4)			
Cycle 3, Day 1 (Pre-dose)	22.6 (± 20.6)			
Cycle 3, Day 1 (Post-dose)	47.7 (± 47.2)			
Cycle 4, Day 1 (Pre-dose)	25.2 (± 24.3)			
Cycle 5, Day 1 (Pre-dose)	24.5 (± 30.6)			
Cycle 6, Day 1 (Pre-dose)	20.9 (± 18.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) at time of final analysis

End point title	Overall Survival (OS) at time of final analysis

End point description:

Defined as time from randomization to death from any cause

End point type	Secondary

End point timeframe:

Up to 60.1 months

End point values	Tuc+Cap+Tra	Pbo+Cap+Tra		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	410	202		
Units: months				
median (confidence interval 95%)	24.7 (21.6 to 28.9)	19.2 (16.4 to 21.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: PFS per RECIST 1.1 as determined by investigator assessment at time of final analysis

End point title	PFS per RECIST 1.1 as determined by investigator assessment at time of final analysis

End point description:

Defined as the time from the date of randomization to the date of documented disease progression

End point type	Secondary

End point timeframe:

Up to 58.0 months

End point values	Tuc+Cap+Tra	Pbo+Cap+Tra		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	410	202		
Units: months				
median (inter-quartile range (Q1-Q3))	7.6 (4.1 to 13.8)	4.9 (2.7 to 9.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of adverse events (AEs) at time of final analysis

End point title	Incidence of adverse events (AEs) at time of final analysis

End point description:

As determined by assessment of AEs, clinical laboratory tests, and vital signs measurements. AEs were classified by system organ class (SOC) and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) Version 22.0 or higher; AE severities were classified using Version 4.03 of the (Common Terminology Criteria for Adverse Events) CTCAE criteria.

End point type	Secondary

End point timeframe:
Up to 60.1 months

End point values	Tuc+Cap+Tra	Pbo+Cap+Tra		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	404	197		
Units: Number of Participants				
Any treatment-emergent AE (TEAE)	401	191		
Any Grade 3 or higher TEAE	248	101		
Any treatment-emergent serious AE	123	58		
TEAE leading to death	8	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Frequency of dose modifications at time of final analysis

End point title	Frequency of dose modifications at time of final analysis

End point description:

End point type	Secondary

End point timeframe:
Up to 60.1 months

End point values	Tuc+Cap+Tra	Pbo+Cap+Tra		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	404	197		
Units: Number of Participants				
TEAEs resulting in tuc/pbo dose modification	237	85		
TEAEs resulting in tucatinib/placebo dose hold	232	84		
TEAEs resulting in tuc/pbo dose reduction	92	21		
TEAEs resulting capecitabine dose modification	322	125		
TEAEs resulting in capecitabine dose hold	288	117		
TEAEs resulting in capecitabine dose reduction	251	79		
TEAEs resulting trastuzumab dose modification	117	41		
TEAEs resulting in trastuzumab dose hold	117	41		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Non-serious Adverse Events, Serious Adverse Events, and All-Cause Mortality were followed for up to 60.1 months

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Tuc+Cap+Tra

Reporting group description:

Tucatinib in combination with capecitabine & trastuzumab

Reporting group title	Pbo+Cap+Tra

Reporting group description:

Placebo in combination with capecitabine & trastuzumab

Serious adverse events	Tuc+Cap+Tra	Pbo+Cap+Tra	
Total subjects affected by serious adverse events			
subjects affected / exposed	124 / 404 (30.69%)	62 / 197 (31.47%)	
number of deaths (all causes)	262	152	
number of deaths resulting from adverse events	8	6	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	2 / 404 (0.50%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acral lentiginous melanoma			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 404 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant pleural effusion			
alternative dictionary used: MedDRA 24.1			

subjects affected / exposed	1 / 404 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyogenic granuloma			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 404 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Vena cava thrombosis			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	0 / 404 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphoedema			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 404 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	2 / 404 (0.50%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 404 (0.25%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Abortion induced			
alternative dictionary used: MedDRA 24.1			

subjects affected / exposed	1 / 404 (0.25%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
General physical health deterioration			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 404 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	3 / 404 (0.74%)	2 / 197 (1.02%)	
occurrences causally related to treatment / all	2 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 404 (0.25%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 1	
Non-cardiac chest pain			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 404 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	0 / 404 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
alternative dictionary used: MedDRA 24.1			

subjects affected / exposed	0 / 404 (0.00%)	2 / 197 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 404 (0.25%)	2 / 197 (1.02%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic inflammatory response syndrome			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	0 / 404 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sudden death			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	2 / 404 (0.50%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	4 / 404 (0.99%)	3 / 197 (1.52%)	
occurrences causally related to treatment / all	2 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax spontaneous			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 404 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
alternative dictionary used: MedDRA 24.1			

subjects affected / exposed	2 / 404 (0.50%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	3 / 404 (0.74%)	6 / 197 (3.05%)	
occurrences causally related to treatment / all	0 / 5	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	0 / 404 (0.00%)	2 / 197 (1.02%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	6 / 404 (1.49%)	7 / 197 (3.55%)	
occurrences causally related to treatment / all	0 / 7	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Choking			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 404 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 404 (0.25%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	2 / 404 (0.50%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Psychiatric disorders			
Confusional state			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	2 / 404 (0.50%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 404 (0.25%)	2 / 197 (1.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood bilirubin increased			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 404 (0.25%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ejection fraction decreased			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	6 / 404 (1.49%)	3 / 197 (1.52%)	
occurrences causally related to treatment / all	6 / 6	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram QT prolonged			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	0 / 404 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Troponin I increased			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 404 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased			
alternative dictionary used: MedDRA 24.1			

subjects affected / exposed	1 / 404 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Radius fracture			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	2 / 404 (0.50%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 404 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	2 / 404 (0.50%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 404 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 404 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
alternative dictionary used: MedDRA 24.1			

subjects affected / exposed	1 / 404 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Patella fracture			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 404 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	2 / 404 (0.50%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	2 / 404 (0.50%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sternal fracture			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 404 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 404 (0.25%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic haemothorax			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 404 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pelvic fracture			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	0 / 404 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acetabulum fracture			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	0 / 404 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiovascular disorder			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 404 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 404 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 404 (0.25%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cardiac failure			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	3 / 404 (0.74%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	2 / 3	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure acute			
alternative dictionary used: MedDRA 24.1			

subjects affected / exposed	1 / 404 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	0 / 404 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	0 / 404 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pericardial effusion			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	2 / 404 (0.50%)	2 / 197 (1.02%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 404 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 404 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cauda equina syndrome			
alternative dictionary used: MedDRA 24.1			

subjects affected / exposed	1 / 404 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain oedema			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 404 (0.25%)	2 / 197 (1.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bell's palsy			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	0 / 404 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aphasia			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 404 (0.25%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central nervous system necrosis			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 404 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	0 / 404 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressed level of consciousness			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 404 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Encephalopathy			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 404 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 404 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised tonic-clonic seizure			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	0 / 404 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	3 / 404 (0.74%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic stroke			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 404 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 404 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
alternative dictionary used: MedDRA 24.1			

subjects affected / exposed	11 / 404 (2.72%)	2 / 197 (1.02%)	
occurrences causally related to treatment / all	0 / 11	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocephalus			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 404 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	2 / 404 (0.50%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	2 / 404 (0.50%)	3 / 197 (1.52%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 404 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiplegia			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 404 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
alternative dictionary used: MedDRA 24.1			

subjects affected / exposed	1 / 404 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 404 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	2 / 404 (0.50%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 404 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vestibular disorder			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 404 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Diplopia			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 404 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Optic neuropathy			
alternative dictionary used: MedDRA 24.1			

subjects affected / exposed	1 / 404 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Enteritis			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	0 / 404 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	4 / 404 (0.99%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	2 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain lower			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 404 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	3 / 404 (0.74%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	0 / 404 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
alternative dictionary used: MedDRA 24.1			

subjects affected / exposed	2 / 404 (0.50%)	2 / 197 (1.02%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	17 / 404 (4.21%)	7 / 197 (3.55%)	
occurrences causally related to treatment / all	14 / 18	7 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal distension			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 404 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	0 / 404 (0.00%)	2 / 197 (1.02%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 404 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 404 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 404 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Mechanical ileus alternative dictionary used: MedDRA 24.1				
subjects affected / exposed	0 / 404 (0.00%)	1 / 197 (0.51%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Nausea alternative dictionary used: MedDRA 24.1				
subjects affected / exposed	9 / 404 (2.23%)	4 / 197 (2.03%)		
occurrences causally related to treatment / all	8 / 10	3 / 4		
deaths causally related to treatment / all	0 / 0	0 / 0		
Pancreatitis alternative dictionary used: MedDRA 24.1				
subjects affected / exposed	2 / 404 (0.50%)	0 / 197 (0.00%)		
occurrences causally related to treatment / all	0 / 2	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Small intestinal obstruction alternative dictionary used: MedDRA 24.1				
subjects affected / exposed	1 / 404 (0.25%)	2 / 197 (1.02%)		
occurrences causally related to treatment / all	0 / 1	2 / 2		
deaths causally related to treatment / all	0 / 0	0 / 0		
Stomatitis alternative dictionary used: MedDRA 24.1				
subjects affected / exposed	1 / 404 (0.25%)	0 / 197 (0.00%)		
occurrences causally related to treatment / all	1 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Vomiting alternative dictionary used: MedDRA 24.1				
subjects affected / exposed	11 / 404 (2.72%)	5 / 197 (2.54%)		
occurrences causally related to treatment / all	8 / 12	3 / 5		
deaths causally related to treatment / all	0 / 0	0 / 0		
Oesophageal varices haemorrhage alternative dictionary used: MedDRA 24.1				

subjects affected / exposed	0 / 404 (0.00%)	2 / 197 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Biliary obstruction			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 404 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	3 / 404 (0.74%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 404 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Dermatomyositis			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 404 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Urinary retention			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 404 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureterolithiasis			
alternative dictionary used: MedDRA 24.1			

subjects affected / exposed	1 / 404 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	0 / 404 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 404 (0.25%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	3 / 404 (0.74%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis of jaw			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 404 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	0 / 404 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture nonunion			
alternative dictionary used: MedDRA 24.1			

subjects affected / exposed	1 / 404 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc compression			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	0 / 404 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 404 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	3 / 404 (0.74%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 404 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	0 / 404 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal stenosis			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 404 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Rheumatoid arthritis			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	0 / 404 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 404 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	0 / 404 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bacteraemia			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 404 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 404 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 404 (0.25%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
alternative dictionary used: MedDRA 24.1			

subjects affected / exposed	1 / 404 (0.25%)	2 / 197 (1.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 404 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	3 / 404 (0.74%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	2 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	0 / 404 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected skin ulcer			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 404 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	8 / 404 (1.98%)	3 / 197 (1.52%)	
occurrences causally related to treatment / all	1 / 9	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella sepsis			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	0 / 404 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Large intestine infection				
alternative dictionary used: MedDRA 24.1				
subjects affected / exposed	0 / 404 (0.00%)	1 / 197 (0.51%)		
occurrences causally related to treatment / all	0 / 0	1 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Lower respiratory tract infection viral				
alternative dictionary used: MedDRA 24.1				
subjects affected / exposed	0 / 404 (0.00%)	1 / 197 (0.51%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Oesophageal candidiasis				
alternative dictionary used: MedDRA 24.1				
subjects affected / exposed	1 / 404 (0.25%)	0 / 197 (0.00%)		
occurrences causally related to treatment / all	1 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Oral candidiasis				
alternative dictionary used: MedDRA 24.1				
subjects affected / exposed	1 / 404 (0.25%)	0 / 197 (0.00%)		
occurrences causally related to treatment / all	1 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Peritonitis				
alternative dictionary used: MedDRA 24.1				
subjects affected / exposed	1 / 404 (0.25%)	0 / 197 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Influenza				
alternative dictionary used: MedDRA 24.1				
subjects affected / exposed	1 / 404 (0.25%)	1 / 197 (0.51%)		
occurrences causally related to treatment / all	0 / 1	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Respiratory tract infection viral				
alternative dictionary used: MedDRA 24.1				

subjects affected / exposed	0 / 404 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	4 / 404 (0.99%)	2 / 197 (1.02%)	
occurrences causally related to treatment / all	1 / 4	1 / 2	
deaths causally related to treatment / all	1 / 1	1 / 1	
Septic shock			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 404 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Soft tissue infection			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 404 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 404 (0.25%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 404 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	0 / 404 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Metabolism and nutrition disorders			
Decreased appetite			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 404 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	4 / 404 (0.99%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	3 / 4	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Hypercalcaemia			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 404 (0.25%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypernatraemia			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 404 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 404 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lactic acidosis			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 404 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemia			
alternative dictionary used: MedDRA 24.1			

subjects affected / exposed	0 / 404 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophosphataemia			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 404 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 404 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 404 (0.25%)	4 / 197 (2.03%)	
occurrences causally related to treatment / all	1 / 2	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Tuc+Cap+Tra	Pbo+Cap+Tra	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	399 / 404 (98.76%)	188 / 197 (95.43%)	
Vascular disorders			
Hypertension			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	19 / 404 (4.70%)	10 / 197 (5.08%)	
occurrences (all)	30	14	
General disorders and administration site conditions			
Asthenia			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	34 / 404 (8.42%)	15 / 197 (7.61%)	
occurrences (all)	46	19	

Fatigue			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	193 / 404 (47.77%)	87 / 197 (44.16%)	
occurrences (all)	265	108	
Influenza like illness			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	24 / 404 (5.94%)	6 / 197 (3.05%)	
occurrences (all)	31	6	
Oedema peripheral			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	46 / 404 (11.39%)	19 / 197 (9.64%)	
occurrences (all)	52	25	
Pyrexia			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	25 / 404 (6.19%)	8 / 197 (4.06%)	
occurrences (all)	35	10	
Respiratory, thoracic and mediastinal disorders			
Rhinorrhoea			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	28 / 404 (6.93%)	6 / 197 (3.05%)	
occurrences (all)	32	6	
Oropharyngeal pain			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	31 / 404 (7.67%)	9 / 197 (4.57%)	
occurrences (all)	37	14	
Cough			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	67 / 404 (16.58%)	24 / 197 (12.18%)	
occurrences (all)	85	31	
Dyspnoea			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	53 / 404 (13.12%)	23 / 197 (11.68%)	
occurrences (all)	60	27	
Epistaxis			
alternative dictionary used:			

MedDRA 24.1			
subjects affected / exposed	52 / 404 (12.87%)	10 / 197 (5.08%)	
occurrences (all)	63	10	
Psychiatric disorders			
Insomnia			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	40 / 404 (9.90%)	17 / 197 (8.63%)	
occurrences (all)	45	18	
Investigations			
Alanine aminotransferase increased			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	87 / 404 (21.53%)	13 / 197 (6.60%)	
occurrences (all)	115	15	
Aspartate aminotransferase increased			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	92 / 404 (22.77%)	23 / 197 (11.68%)	
occurrences (all)	137	32	
Blood alkaline phosphatase increased			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	29 / 404 (7.18%)	6 / 197 (3.05%)	
occurrences (all)	47	8	
Blood bilirubin increased			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	81 / 404 (20.05%)	21 / 197 (10.66%)	
occurrences (all)	154	31	
Blood creatinine increased			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	65 / 404 (16.09%)	3 / 197 (1.52%)	
occurrences (all)	108	3	
Neutrophil count decreased			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	21 / 404 (5.20%)	6 / 197 (3.05%)	
occurrences (all)	48	7	
Platelet count decreased			
alternative dictionary used: MedDRA 24.1			

subjects affected / exposed	22 / 404 (5.45%)	5 / 197 (2.54%)	
occurrences (all)	29	6	
Weight decreased			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	62 / 404 (15.35%)	12 / 197 (6.09%)	
occurrences (all)	66	13	
White blood cell count decreased			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	21 / 404 (5.20%)	10 / 197 (5.08%)	
occurrences (all)	57	10	
Injury, poisoning and procedural complications			
Fall			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	28 / 404 (6.93%)	9 / 197 (4.57%)	
occurrences (all)	41	10	
Nervous system disorders			
Dizziness			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	54 / 404 (13.37%)	27 / 197 (13.71%)	
occurrences (all)	68	30	
Dysgeusia			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	33 / 404 (8.17%)	6 / 197 (3.05%)	
occurrences (all)	33	6	
Headache			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	98 / 404 (24.26%)	38 / 197 (19.29%)	
occurrences (all)	150	53	
Paraesthesia			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	26 / 404 (6.44%)	10 / 197 (5.08%)	
occurrences (all)	32	10	
Peripheral sensory neuropathy			
alternative dictionary used: MedDRA 24.1			

subjects affected / exposed	53 / 404 (13.12%)	13 / 197 (6.60%)	
occurrences (all)	65	17	
Blood and lymphatic system disorders			
Anaemia			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	89 / 404 (22.03%)	24 / 197 (12.18%)	
occurrences (all)	146	32	
Thrombocytopenia			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	27 / 404 (6.68%)	11 / 197 (5.58%)	
occurrences (all)	41	15	
Neutropenia			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	37 / 404 (9.16%)	17 / 197 (8.63%)	
occurrences (all)	87	40	
Eye disorders			
Dry eye			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	23 / 404 (5.69%)	10 / 197 (5.08%)	
occurrences (all)	25	10	
Gastrointestinal disorders			
Diarrhoea			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	330 / 404 (81.68%)	106 / 197 (53.81%)	
occurrences (all)	812	181	
Dry mouth			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	22 / 404 (5.45%)	5 / 197 (2.54%)	
occurrences (all)	22	5	
Gastrooesophageal reflux disease			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	25 / 404 (6.19%)	7 / 197 (3.55%)	
occurrences (all)	27	7	
Nausea			
alternative dictionary used: MedDRA 24.1			

subjects affected / exposed	243 / 404 (60.15%)	87 / 197 (44.16%)	
occurrences (all)	382	120	
Stomatitis			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	105 / 404 (25.99%)	28 / 197 (14.21%)	
occurrences (all)	146	35	
Vomiting			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	155 / 404 (38.37%)	49 / 197 (24.87%)	
occurrences (all)	276	80	
Constipation			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	69 / 404 (17.08%)	40 / 197 (20.30%)	
occurrences (all)	90	46	
Abdominal pain upper			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	36 / 404 (8.91%)	17 / 197 (8.63%)	
occurrences (all)	43	20	
Abdominal pain			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	66 / 404 (16.34%)	32 / 197 (16.24%)	
occurrences (all)	98	40	
Abdominal distension			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	27 / 404 (6.68%)	10 / 197 (5.08%)	
occurrences (all)	30	13	
Dyspepsia			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	46 / 404 (11.39%)	19 / 197 (9.64%)	
occurrences (all)	53	22	
Hepatobiliary disorders			
Hyperbilirubinaemia			
alternative dictionary used: MedDRA 24.1			

subjects affected / exposed	29 / 404 (7.18%)	8 / 197 (4.06%)	
occurrences (all)	69	17	
Skin and subcutaneous tissue disorders			
Dry skin			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	43 / 404 (10.64%)	18 / 197 (9.14%)	
occurrences (all)	53	20	
Alopecia			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	25 / 404 (6.19%)	7 / 197 (3.55%)	
occurrences (all)	26	7	
Rash maculo-papular			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	29 / 404 (7.18%)	10 / 197 (5.08%)	
occurrences (all)	43	13	
Pruritus			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	39 / 404 (9.65%)	15 / 197 (7.61%)	
occurrences (all)	48	15	
Palmar-plantar erythrodysaesthesia syndrome			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	265 / 404 (65.59%)	105 / 197 (53.30%)	
occurrences (all)	433	158	
Skin hyperpigmentation			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	34 / 404 (8.42%)	11 / 197 (5.58%)	
occurrences (all)	45	11	
Musculoskeletal and connective tissue disorders			
Arthralgia			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	80 / 404 (19.80%)	17 / 197 (8.63%)	
occurrences (all)	120	25	
Back pain			
alternative dictionary used: MedDRA 24.1			

subjects affected / exposed	58 / 404 (14.36%)	25 / 197 (12.69%)	
occurrences (all)	73	27	
Muscle spasms			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	46 / 404 (11.39%)	6 / 197 (3.05%)	
occurrences (all)	63	7	
Muscular weakness			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	22 / 404 (5.45%)	6 / 197 (3.05%)	
occurrences (all)	25	7	
Myalgia			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	34 / 404 (8.42%)	10 / 197 (5.08%)	
occurrences (all)	43	11	
Pain in extremity			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	51 / 404 (12.62%)	18 / 197 (9.14%)	
occurrences (all)	66	22	
Infections and infestations			
Influenza			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	10 / 404 (2.48%)	10 / 197 (5.08%)	
occurrences (all)	10	10	
Nasopharyngitis			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	21 / 404 (5.20%)	14 / 197 (7.11%)	
occurrences (all)	28	15	
Paronychia			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	23 / 404 (5.69%)	3 / 197 (1.52%)	
occurrences (all)	30	4	
Upper respiratory tract infection			
alternative dictionary used: MedDRA 24.1			

subjects affected / exposed	45 / 404 (11.14%)	15 / 197 (7.61%)	
occurrences (all)	70	18	
Urinary tract infection			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	45 / 404 (11.14%)	16 / 197 (8.12%)	
occurrences (all)	76	24	
Metabolism and nutrition disorders			
Decreased appetite			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	108 / 404 (26.73%)	41 / 197 (20.81%)	
occurrences (all)	130	51	
Dehydration			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	31 / 404 (7.67%)	10 / 197 (5.08%)	
occurrences (all)	40	13	
Hyperglycaemia			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	26 / 404 (6.44%)	3 / 197 (1.52%)	
occurrences (all)	40	5	
Hypokalaemia			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	71 / 404 (17.57%)	24 / 197 (12.18%)	
occurrences (all)	105	32	
Hypomagnesaemia			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	37 / 404 (9.16%)	10 / 197 (5.08%)	
occurrences (all)	61	10	
Hypophosphataemia			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	29 / 404 (7.18%)	10 / 197 (5.08%)	
occurrences (all)	50	10	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 September 2015	A planned interim analysis of PFS as the primary endpoint was removed.
26 January 2016	Inclusion criteria was amended to remove the numerical size limits on certain CNS metastases.
21 March 2016	The unblinding procedure in the event of a concerning drug related safety event was revised.
06 July 2016	The assessment criteria used for the primary endpoint (PFS) was changed from RANO-BM to the validated RECIST 1.1 criteria.
29 November 2016	Increased the number of subjects from approximately 180 to 480. Changed the order of hierarchical testing of the secondary endpoints PFS in subjects with brain metastases and OS. Updated randomization stratification for region. Cardiac failure was added to the safety plan for cardiotoxicity.
30 August 2017	Removed the requirement of prior therapy with a taxane. Added HRQoL and health economics objectives. Removed formal interim analyses of the primary endpoint. Added a list of potential sensitive substrates for UGT1A1.
12 November 2018	Seattle Genetics became the Study Sponsor. Increased the number of subjects from 480 to 600 and the length of enrollment to 48 months. Amended the statistical testing from a hierarchical to parallel structure for key secondary endpoints of PFSBrainMets and OS.
28 February 2019	Amended to reflect the potential interaction of tucatinib with sensitive CYP3A substrates.
25 March 2019	Updated the timing of the PFS primary analysis and second interim analysis of OS and PFSBrainMets. Added details to the timing and scope of sponsor unblinding for the primary analysis. Timing of PFS primary endpoint was revised based on events and complete enrollment for the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported