Clinical trial results:
A Phase 2, Open Label Study of Tucatinib Combined with Trastuzumab in Patients with Human Epidermal Growth Factor Receptor 2 (HER2+) Metastatic Colorectal Cancer

Summary

EudraCT number	2020-000540-60
Trial protocol	FR BE IT
Global end of trial date	02 November 2023

Results information

Result version number	v1 (current)
This version publication date	16 November 2024
First version publication date	16 November 2024

Trial information

Trial identification

Sponsor protocol code	C4251002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03043313
WHO universal trial number (UTN)	-
Other trial identifiers	Seagen Protocol Code: SGNTUC-017

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	22 November 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 November 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the antitumor activity of tucatinib given in combination with trastuzumab, in Cohorts A+B, as measured by confirmed objective response rate (cORR, per response evaluation criteria in solid tumors [RECIST] 1.1 criteria), according to blinded independent central review (BICR) assessment.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Council for Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trials participants were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 June 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 88
Country: Number of subjects enrolled	Italy: 11
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	Belgium: 6
Country: Number of subjects enrolled	Spain: 5
Worldwide total number of subjects	117
EEA total number of subjects	29

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)	94
From 65 to 84 years	23
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 117 participants were enrolled at a total of 56 sites in the United States, Italy, France, Belgium, and Spain. The date of first participant enrollment was 23-Jun-2017. The date of last participant randomisation was 02-Nov-2023.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Tucatinib+Trastuzumab (Cohort A)

Arm description:

Non-randomized cohort. Participants received Tucatinib 300 milligrams (mg) orally (PO) twice daily (BID) on Days 1 to 21 of each 21-day cycle. Trastuzumab 8 milligram/kilogram (mg/kg) by intravenous (IV) infusion on Day 1 of Cycle 1 and 6 mg/kg on Day 1 of each subsequent cycle until progressive disease (PD), death, withdrawal of consent, study closure, or alternative therapy.

Arm type	Experimental
Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received trastuzumab 8 mg/kg by IV infusion on Day 1 of Cycle 1 and 6 mg/kg on Day 1 of each subsequent cycle.

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

Dosage and administration details:

Participants received Tucatinib 300 mg PO BID on Days 1 to 21 of each 21-day cycle.

Arm title	Tucatinib+Trastuzumab (Cohort B)

Arm description:

Randomized cohort. Participants received Tucatinib 300 mg PO BID on Days 1 to 21 of each 21-day cycle. Trastuzumab 8 mg/kg by IV infusion on Day 1 of Cycle 1 and 6 mg/kg on Day 1 of each subsequent cycle until PD, death, withdrawal of consent, study closure, or alternative therapy.

Arm type	Experimental
Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received trastuzumab 8 mg/kg by IV infusion on Day 1 of Cycle 1 and 6 mg/kg on Day 1 of

each subsequent cycle.

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

Dosage and administration details:

Participants received Tucatinib 300 mg PO BID on Days 1 to 21 of each 21-day cycle.

Arm title	Tucatinib Monotherapy (Cohort C)

Arm description:

Participants received Tucatinib 300 mg PO BID on Days 1 to 21 of each 21-day cycle. Participants who did not respond to monotherapy were given the option to receive tucatinib and trastuzumab until PD, death, withdrawal of consent, study closure, or alternative therapy based on radiographic progression (as determined by investigator assessment using response evaluation criteria in solid tumors [RECIST] version [v] 1.1), or if they had not achieved a partial response (PR) or complete response (CR) by the week 12 assessment.

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

Dosage and administration details:

Participants received Tucatinib 300 mg PO BID on Days 1 to 21 of each 21-day cycle.

Number of subjects in period 1	Tucatinib+Trastuzumab (Cohort A)	Tucatinib+Trastuzumab (Cohort B)	Tucatinib Monotherapy (Cohort C)
Started	45	41	31
Completed	0	0	0
Not completed	45	41	31
Consent withdrawn by subject	5	1	1
Death	28	26	17
Lost to follow-up	1	1	-
Participation terminated by sponsor	11	13	13

Baseline characteristics

Reporting groups	
Reporting group title	Tucatinib+Trastuzumab (Cohort A)
Reporting group description:	
Non-randomized cohort. Participants received Tucatinib 300 milligrams (mg) orally (PO) twice daily (BID) on Days 1 to 21 of each 21-day cycle. Trastuzumab 8 milligram/kilogram (mg/kg) by intravenous (IV) infusion on Day 1 of Cycle 1 and 6 mg/kg on Day 1 of each subsequent cycle until progressive disease (PD), death, withdrawal of consent, study closure, or alternative therapy.	
Reporting group title	Tucatinib+Trastuzumab (Cohort B)
Reporting group description:	
Randomized cohort. Participants received Tucatinib 300 mg PO BID on Days 1 to 21 of each 21-day cycle. Trastuzumab 8 mg/kg by IV infusion on Day 1 of Cycle 1 and 6 mg/kg on Day 1 of each subsequent cycle until PD, death, withdrawal of consent, study closure, or alternative therapy.	
Reporting group title	Tucatinib Monotherapy (Cohort C)
Reporting group description:	
Participants received Tucatinib 300 mg PO BID on Days 1 to 21 of each 21-day cycle. Participants who did not respond to monotherapy were given the option to receive tucatinib and trastuzumab until PD, death, withdrawal of consent, study closure, or alternative therapy based on radiographic progression (as determined by investigator assessment using response evaluation criteria in solid tumors [RECIST] version [v] 1.1), or if they had not achieved a partial response (PR) or complete response (CR) by the week 12 assessment.	

Reporting group values	Tucatinib+Trastuzumab (Cohort A)	Tucatinib+Trastuzumab (Cohort B)	Tucatinib Monotherapy (Cohort C)
Number of subjects	45	41	31
Age categorical Units: Participants			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	40	34	20
From 65-84 years	5	7	11
85 years and over	0	0	0
Age Continuous Units: Years			
median	52.0	59.0	60.0
full range (min-max)	24 to 71	31 to 77	29 to 75
Sex: Female, Male Units: Participants			
Female	19	15	16
Male	26	26	15
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	1	0	0
Asian	2	1	0
Native Hawaiian or Other Pacific Islander	0	0	0

Black or African American	1	2	3
White	37	30	24
More than one race	1	0	0
Unknown or Not Reported	3	8	4
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	2	1	1
Not Hispanic or Latino	35	31	26
Unknown or Not Reported	8	9	4
Region of Enrollment Units: Subjects			
North America	45	26	17
Europe	0	15	14
Eastern Cooperative Oncology Group (ECOG) Performance Status			
ECOG performance status was used to assess participants disease progression, and ability to carry out daily living activities. 0=Normal activity; 1=Symptoms but ambulatory; 2=In bed less than (<)50 percent (%) of the time; 3= In bed >50% of the time; 4=100% bedridden; 5=Dead.			
Units: Subjects			
Grade 0	24	28	17
Grade 1	20	11	14
Grade 2	1	2	0

Reporting group values	Total		
Number of subjects	117		
Age categorical Units: Participants			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	94		
From 65-84 years	23		
85 years and over	0		
Age Continuous Units: Years median full range (min-max)	--		
Sex: Female, Male Units: Participants			
Female	50		
Male	67		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	1		
Asian	3		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	6		

White	91		
More than one race	1		
Unknown or Not Reported	15		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	4		
Not Hispanic or Latino	92		
Unknown or Not Reported	21		
Region of Enrollment Units: Subjects			
North America	88		
Europe	29		
Eastern Cooperative Oncology Group (ECOG) Performance Status			
ECOG performance status was used to assess participants disease progression, and ability to carry out daily living activities. 0=Normal activity; 1=Symptoms but ambulatory; 2=In bed less than (<)50 percent (%) of the time; 3= In bed >50% of the time; 4=100% bedridden; 5=Dead.			
Units: Subjects			
Grade 0	69		
Grade 1	45		
Grade 2	3		

End points

End points reporting groups

Reporting group title	Tucatinib+Trastuzumab (Cohort A)

Reporting group description:

Non-randomized cohort. Participants received Tucatinib 300 milligrams (mg) orally (PO) twice daily (BID) on Days 1 to 21 of each 21-day cycle. Trastuzumab 8 milligram/kilogram (mg/kg) by intravenous (IV) infusion on Day 1 of Cycle 1 and 6 mg/kg on Day 1 of each subsequent cycle until progressive disease (PD), death, withdrawal of consent, study closure, or alternative therapy.

Reporting group title	Tucatinib+Trastuzumab (Cohort B)

Reporting group description:

Randomized cohort. Participants received Tucatinib 300 mg PO BID on Days 1 to 21 of each 21-day cycle. Trastuzumab 8 mg/kg by IV infusion on Day 1 of Cycle 1 and 6 mg/kg on Day 1 of each subsequent cycle until PD, death, withdrawal of consent, study closure, or alternative therapy.

Reporting group title	Tucatinib Monotherapy (Cohort C)

Reporting group description:

Participants received Tucatinib 300 mg PO BID on Days 1 to 21 of each 21-day cycle. Participants who did not respond to monotherapy were given the option to receive tucatinib and trastuzumab until PD, death, withdrawal of consent, study closure, or alternative therapy based on radiographic progression (as determined by investigator assessment using response evaluation criteria in solid tumors [RECIST] version [v] 1.1), or if they had not achieved a partial response (PR) or complete response (CR) by the week 12 assessment.

Subject analysis set title	Tucatinib+Trastuzumab (Cohorts A+B)
Subject analysis set type	Per protocol

Subject analysis set description:

Participants received Tucatinib 300 mg PO BID on Days 1 to 21 of each 21-day cycle. Trastuzumab 8 mg/kg by IV infusion on Day 1 of Cycle 1 and 6 mg/kg on Day 1 of each subsequent cycle until PD, death, withdrawal of consent, study closure, or alternative therapy.

Subject analysis set title	Tucatinib Pre-Crossover (Cohort C)
Subject analysis set type	Per protocol

Subject analysis set description:

Participants received Tucatinib 300 mg PO BID on Days 1 to 21 of each 21-day cycle. Participants who did not respond to monotherapy were given the option to receive tucatinib and trastuzumab based on radiographic progression (as determined by investigator assessment using RECIST v1.1), or if they had not achieved a PR or CR by the week 12 assessment.

Subject analysis set title	Tucatinib+Trastuzumab (Cohorts A+B)
Subject analysis set type	Per protocol

Subject analysis set description:

Participants received Tucatinib 300 mg PO BID on Days 1 to 21 of each 21-day cycle. Trastuzumab 8 mg/kg by IV infusion on Day 1 of Cycle 1 and 6 mg/kg on Day 1 of each subsequent cycle until PD, death, withdrawal of consent, study closure, or alternative therapy.

Subject analysis set title	Tucatinib+Trastuzumab (Cohorts A+B)
Subject analysis set type	Per protocol

Subject analysis set description:

Participants received Tucatinib 300 mg PO BID on Days 1 to 21 of each 21-day cycle. Trastuzumab 8 mg/kg by IV infusion on Day 1 of Cycle 1 and 6 mg/kg on Day 1 of each subsequent cycle until PD, death, withdrawal of consent, study closure, or alternative therapy.

Subject analysis set title	Tucatinib Post-Crossover (Cohort C)
Subject analysis set type	Per protocol

Subject analysis set description:

Participants received Tucatinib 300 mg PO BID on Days 1 to 21 of each 21-day cycle. Trastuzumab 8 mg/kg by IV infusion on Day 1 of Cycle 1 and 6 mg/kg on Day 1 of each subsequent cycle until PD, death, withdrawal of consent, study closure, or alternative therapy.

Subject analysis set title	Tucatinib+Trastuzumab (Cohorts A+B)
Subject analysis set type	Per protocol

Subject analysis set description:

Participants received Tucatinib 300 mg PO BID on Days 1 to 21 of each 21-day cycle. Trastuzumab 8

mg/kg by IV infusion on Day 1 of Cycle 1 and 6 mg/kg on Day 1 of each subsequent cycle until PD, death, withdrawal of consent, study closure, or alternative therapy.

Subject analysis set title	Tucatinib Pre-Crossover (Cohort C)
Subject analysis set type	Per protocol

Subject analysis set description:

Participants received Tucatinib 300 mg PO BID on Days 1 to 21 of each 21-day cycle. Participants who did not respond to monotherapy were given the option to receive tucatinib and trastuzumab based on radiographic progression (as determined by investigator assessment using RECIST v1.1), or if they had not achieved a PR or CR by the week 12 assessment.

Primary: Confirmed Objective Response Rate (cORR) per RECIST v1.1 per Blinded Independent Central Review (BICR) in Pooled Cohorts A+B

End point title	Confirmed Objective Response Rate (cORR) per RECIST v1.1 per Blinded Independent Central Review (BICR) in Pooled Cohorts A+B[1]

End point description:

cORR was defined as the percentage (%) of participants with confirmed CR or PR according to RECIST v1.1. CR was defined as the disappearance of all target lesions and each target lymph node must have reduction in short axis to less than (<)1.0 centimetre (cm). PR was defined as at least a 30% decrease in post-baseline sum of the diameters (PBSD) (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the baseline sum of the diameters (BSD). The Full Analysis Set included all participants who were enrolled and received any amount of study treatment and had HER2+ tumors as defined by one or more protocol required local tests. Data for cohort A and B was combined as prespecified in the statistical analysis plan (SAP).

End point type	Primary

End point timeframe:

Up to 46.6 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 for this endpoint.

End point values	Tucatinib+Trastuzumab (Cohorts A+B)			
Subject group type	Subject analysis set			
Number of subjects analysed	84			
Units: Percentage of Participants				
number (confidence interval 95%)	39.3 (28.8 to 50.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: ORR by 12 Weeks of Treatment per RECIST v1.1 According to BICR Assessment

End point title	ORR by 12 Weeks of Treatment per RECIST v1.1 According to BICR Assessment

End point description:

ORR per BICR by 12 Weeks was defined as the percentage of participants with CR or PR by 12 weeks of treatment, and before time of crossover (Cohort C), whichever comes earlier. CR was defined as the disappearance of all target lesions and each target lymph node must have reduction in short axis to more than <1.0 cm. PR was defined as at least a 30% decrease in post-baseline sum of the diameters (PBSD) (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target

lymph nodes at current evaluation) taking as reference the baseline sum of the diameters (BSD). The Full Analysis Set included all participants who were enrolled and received any amount of study treatment and had HER2+ tumors as defined by one or more protocol required local tests. Data for cohort A and B was combined as prespecified in SAP.

End point type	Secondary

End point timeframe:

Up to 3 months

End point values	Tucatinib+Trastuzumab (Cohorts A+B)	Tucatinib Pre-Crossover (Cohort C)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	84	30		
Units: Percentage of Participants				
number (confidence interval 95%)	28.6 (19.2 to 39.5)	3.3 (0.1 to 17.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) per RECIST v1.1 According to BICR Assessment

End point title	Duration of Response (DOR) per RECIST v1.1 According to BICR Assessment

End point description:

DOR: Time from the first objective response (CR or PR) to documented PD per RECIST v1.1 or death from any cause, whichever occurred first. CR: Disappearance of all target lesions and each target lymph node must have reduction in short axis to <1.0 cm. PR: At least 30% decrease in PBSD taking as reference the BSD. PD: At least one new malignant lesion, which also includes any lymph node that was normal at baseline (<1.0 cm short axis) and increased to >=1.0 cm short axis during follow-up or at least 20% increase in PBSD taking as reference the MSD. In addition, PBSD must also demonstrate an absolute increase of at least 0.5 cm from the MSD. Full Analysis Set evaluated. Data for cohort A and B was combined as prespecified in SAP. 'Number of Participants Analyzed' = participants who had CR or PR. '99999' = Data for median and lower or upper limits could not be estimated due to insufficient participants with event.

End point type	Secondary

End point timeframe:

Up to 64.1 months

End point values	Tucatinib Pre-Crossover (Cohort C)	Tucatinib+Trastuzumab (Cohorts A+B)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	30	33		
Units: Months				
median (confidence interval 95%)	99999 (99999 to 99999)	15.2 (8.9 to 20.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS) per RECIST v1.1 According to BICR Assessment for Pooled Cohorts A+B

End point title	Progression-Free Survival (PFS) per RECIST v1.1 According to BICR Assessment for Pooled Cohorts A+B

End point description:

PFS was defined as the time from start of study treatment (Cohort A) or date of randomization (Cohort B) to documented disease progression (as determined by BICR per RECIST v1.1) or death from any cause, whichever occurred first. PD was defined as: at least one new malignant lesion, which also included any lymph node that was normal at baseline (<1.0 cm short axis) and increased to more than or equal to (>=)1.0 cm short axis during follow-up or at least a 20% increase in post-baseline sum of the diameters (PBSD) taking as reference the minimum sum of the diameters (MSD). In addition, the PBSD must also demonstrate an absolute increase of at least 0.5 cm from the MSD. The Full Analysis Set included all participants who were enrolled and received any amount of study treatment and had HER2+ tumors as defined by one or more protocol required local tests. Data for cohort A and B was combined as prespecified in SAP.

End point type	Secondary

End point timeframe:

Up to 64.1 months

End point values	Tucatinib+Trastuzumab (Cohorts A+B)			
Subject group type	Subject analysis set			
Number of subjects analysed	84			
Units: Months				
median (confidence interval 95%)	8.1 (4.2 to 10.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) in Pooled Cohorts A+B

End point title	Overall Survival (OS) in Pooled Cohorts A+B

End point description:

OS was defined as the time from start of study treatment (Cohort A) or randomization (Cohort B) to date of death due to any cause. The Full Analysis Set included all participants who were enrolled and received any amount of study treatment and had HER2+ tumors as defined by one or more protocol required local tests. Data for cohort A and B was combined as prespecified in SAP.

End point type	Secondary

End point timeframe:

Up to 71.8 months

End point values	Tucatinib+Trastuzumab (Cohorts A+B)			
Subject group type	Subject analysis set			
Number of subjects analysed	84			
Units: Months				
median (confidence interval 95%)	23.9 (18.7 to 28.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Adverse Events (AEs): Interim Analysis

End point title	Number of Participants with Adverse Events (AEs): Interim Analysis

End point description:

AE: Any untoward medical occurrence in a participant or clinical investigational participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. TEAEs: Events that were new or worsened on or after receiving the first dose of study treatment and up through 30 days after the last dose of study treatment. SAE: An event that at any dose led to death; life-threatening; required inpatient hospitalization/prolongation of existing hospitalization; persistent/significant disability/incapacity; congenital anomaly/birth defect/ important medical event. Treatment related AEs, SAEs, deaths also included. Relatedness judged by investigator According to NCI CTCAE version 4.03: Grade(G) 3=severe AE, G4=life-threatening, urgent intervention indicated, G5=death related to AE. Safety analysis set evaluated. Data for cohort A and B combined as prespecified in SAP. '99999' indicated tucatinib monotherapy arm.

End point type	Secondary

End point timeframe:

Up to 49.3 months

End point values	Tucatinib Pre-Crossover (Cohort C)	Tucatinib+Trastuzumab (Cohorts A+B)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	30	86		
Units: Participants				
Any TEAE	28	82		
Tucatinib-related TEAE	22	63		
Trastuzumab-related TEAE	99999	58		
Any grade 3-5 TEAE	8	33		
Trastuzumab-related grade 3-5 TEAE	99999	6		
Tucatinib-related grade 3-5 TEAE	2	8		
Any Treatment-Emergent Serious AE (TESAE)	3	19		

Tucatinib-related TESAE	1	3		
Trastuzumab-related TESAE	99999	2		
TEAE leading to death	0	0		
Discontinuation of any study treatment due to TEAE	0	5		
Discontinuation (Disc.) of tucatinib due to TEAE	0	5		
Disc. of tucatinib due to tucatinib-related TEAE	0	2		
Discontinuation of trastuzumab due to TEAE	99999	3		
Disc.of trastuzumab due to trastuzumab-relatedTEAE	99999	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with AEs: Final Analysis

End point title	Number of Participants with AEs: Final Analysis

End point description:

AE: Any untoward medical occurrence in a participant or clinical investigational participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. TEAEs: Events that were new or worsened on or after receiving the first dose of study treatment and up through 30 days after the last dose of study treatment. SAE: An event that at any dose led to death; life-threatening; required inpatient hospitalization/prolongation of existing hospitalization; persistent/significant disability/incapacity; congenital anomaly/birth defect/ important medical event. Treatment related AEs, SAEs, deaths also included. Relatedness judged by investigator according to NCI CTCAE version 4.03: Grade(G) 3=severe AE, G4=life-threatening, urgent intervention indicated, G5=death related to AE. Safety analysis set evaluated. Data for cohort A and B combined as prespecified in SAP.

End point type	Secondary

End point timeframe:

Up to 65.1 months

End point values	Tucatinib+Trastuzumab (Cohorts A+B)	Tucatinib Post-Crossover (Cohort C)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	86	28		
Units: Participants				
Any TEAE	82	23		
Tucatinib-related TEAE	64	15		
Trastuzumab-related TEAE	59	13		
>= Grade 3 TEAE	35	9		
Tucatinib-related >= grade 3 TEAE	8	2		
Trastuzumab-related >= grade 3 TEAE	6	2		
Any TESAE	20	6		
Tucatinib-related TESAE	3	0		
Trastuzumab-related TESAE	2	2		
TEAE leading to death	0	0		

Discontinuation of any study treatment due to TEAE	5	2		
Disc. of tucatinib due to treatment-related TEAE	2	2		
Disc. of tucatinib due to tucatinib-related TEAE	2	2		
Disc. of trastuzumab due to treatment-related TEAE	1	1		
Disc.of trastuzumab due to trastuzumab-relatedTEAE	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with AEs Resulting in Dose Modification: Interim Analysis

End point title	Number of Participants with AEs Resulting in Dose Modification: Interim Analysis

End point description:

Dose modification included dose reduction and dose withheld by investigator due to AEs. Dose holds were defined as any instances where planned administration of the study drug was temporarily withheld or interrupted at the direction of the treating physician. Dose reductions of trastuzumab were not allowed; if trastuzumab could not be restarted after being held for a TEAE, it was discontinued. The safety analysis set included participants who received any amount of study treatment. Data for cohort A and B was combined as prespecified in SAP. '99999' indicated tucatinib monotherapy arm.

End point type	Secondary

End point timeframe:

Up to 49.3 months

End point values	Tucatinib Pre-Crossover (Cohort C)	Tucatinib+Trastuzumab (Cohorts A+B)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	30	86		
Units: Participants				
Tucatinib dose held	3	20		
Tucatinib dose reduced	1	8		
Trastuzumab dose held	99999	24		
Trastuzumab infusion interrupted	99999	6		
Trastuzumab infusion stopped early	99999	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with AEs Resulting in Dose Modification: Final Analysis

End point title	Number of Participants with AEs Resulting in Dose Modification: Final Analysis

End point description:

Dose modification included dose reduction and dose withheld by investigator due to AEs. Dose holds were defined as any instances where planned administration of the study drug was temporarily withheld or interrupted at the direction of the treating physician. Dose reductions of trastuzumab were not allowed; if trastuzumab could not be restarted after being held for a TEAE, it was discontinued. Drug interruption included infusion interrupted (full dose received within 24hrs). The safety analysis set included participants who received any amount of study treatment. Data for cohort A and B was combined as prespecified in SAP.

End point type	Secondary

End point timeframe:

Up to 65.1 months

End point values	Tucatinib+Trastuzumab (Cohorts A+B)	Tucatinib Post-Crossover (Cohort C)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	86	28		
Units: Participants				
Tucatinib dose held	23	7		
Tucatinib dose reduced	9	2		
Trastuzumab dose held	27	2		
Trastuzumab infusion interrupted	6	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Treatment-Emergent Laboratory Abnormalities (Hematology): Interim Analysis

End point title	Number of Participants With Treatment-Emergent Laboratory Abnormalities (Hematology): Interim Analysis

End point description:

The following hematology laboratory parameters were assessed: Hemoglobin decreased; leukocytes decreased; neutrophils decreased and platelets decreased. Treatment emergent laboratory abnormalities were defined as abnormalities that were new or worsened on or after receiving the first dose of study treatment and up through 30 days after the last dose of study treatment. NCI CTCAE v4.03 was used for the laboratory parameters. Grade 1: mild; Grade 2: moderate; Grade 3: severe or clinically significant; Grade 4: life-threatening. The safety analysis set included participants who received any amount of study treatment. Data for cohort A and B was combined as prespecified in SAP. Here, 'Number of Participants Analysed' signifies participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Up to 49.3 months

End point values	Tucatinib+Trastuzumab (Cohorts A+B)	Tucatinib Pre-Crossover (Cohort C)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	85	29		
Units: Participants				
Hemoglobin decreased, Grade 1	28	6		
Hemoglobin decreased, Grade 2	8	2		
Hemoglobin decreased, Grade 3	3	0		
Hemoglobin decreased, Grade 4	0	0		
Leukocytes decreased, Grade 1	14	3		
Leukocytes decreased, Grade 2	5	0		
Leukocytes decreased, Grade 3	0	0		
Leukocytes decreased, Grade 4	0	0		
Neutrophils decreased, Grade 1	6	1		
Neutrophils decreased, Grade 2	2	1		
Neutrophils decreased, Grade 3	0	0		
Neutrophils decreased, Grade 4	0	0		
Platelets decreased, Grade 1	11	1		
Platelets decreased, Grade 2	2	2		
Platelets decreased, Grade 3	0	0		
Platelets decreased, Grade 4	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Treatment-Emergent Laboratory Abnormalities (Hematology): Final Analysis

End point title	Number of Participants With Treatment-Emergent Laboratory Abnormalities (Hematology): Final Analysis

End point description:

The following hematology laboratory parameters were assessed: Hemoglobin decreased; hemoglobin increased; leukocytes decreased; lymphocytes decreased; neutrophils decreased and platelets decreased. Treatment emergent laboratory abnormalities were defined as abnormalities that were new or worsened on or after receiving the first dose of study treatment and up through 30 days after the last dose of study treatment. NCI CTCAE v4.03 was used for the laboratory parameters. Grade 1: mild; Grade 2: moderate; Grade 3: severe or clinically significant; Grade 4: life-threatening. The safety analysis set included participants who received any amount of study treatment. Data for cohort A and B was combined as prespecified in SAP. Here, 'Number of Participants Analysed' signifies participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Up to 65.1 months

End point values	Tucatinib Post-Crossover (Cohort C)	Tucatinib+Trastuzumab (Cohorts A+B)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	28	85		
Units: Participants				
Hemoglobin decreased, All grades	9	42		
Hemoglobin decreased, Grade 3	0	3		
Hemoglobin decreased, Grade 4	0	0		
Hemoglobin increased: All grades	0	3		
Hemoglobin increased: Grade 3	0	0		
Hemoglobin increased: Grade 4	0	0		
Leukocytes decreased, All grades	5	21		
Leukocytes decreased, Grade 3	0	0		
Leukocytes decreased, Grade 4	0	0		
Lymphocytes decreased, All grades	11	25		
Lymphocytes decreased, Grade 3	1	6		
Lymphocytes decreased, Grade 4	0	0		
Neutrophils decreased: All grades	0	10		
Neutrophils decreased: Grade 3	0	0		
Neutrophils decreased: Grade 4	0	0		
Platelets decreased, All grades	4	15		
Platelets decreased, Grade 3	0	0		
Platelets decreased, Grade 4	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Treatment-Emergent Laboratory Abnormalities (Chemistry): Interim Analysis

End point title	Number of Participants With Treatment-Emergent Laboratory Abnormalities (Chemistry): Interim Analysis

End point description:

The following chemistry laboratory parameters were assessed: Potassium increased; potassium decreased; aspartate aminotransferase increased; alanine aminotransferase increased; creatinine increased; alkaline phosphatase increased; total bilirubin increased. Treatment emergent laboratory abnormalities were defined as abnormalities that were new or worsened on or after receiving the first dose of study treatment and up through 30 days after the last dose of study treatment. NCI CTCAE v5.0 was used for creatinine increased. NCI CTCAE v4.03 was used for the other laboratory parameters. Grade 1: mild; Grade 2: moderate; Grade 3: severe or clinically significant; Grade 4: life-threatening. The safety analysis set included participants who received any amount of study treatment. Data for cohort A and B was combined as prespecified in SAP. Here, 'Number of Participants Analysed' signifies participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Up to 49.3 months

End point values	Tucatinib+Trastuzumab (Cohorts A+B)	Tucatinib Pre-Crossover (Cohort C)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	85	29		
Units: Participants				
Potassium increased, Grade 1	5	1		
Potassium increased, Grade 2	1	0		
Potassium increased, Grade 3	0	1		
Potassium increased, Grade 4	0	0		
Potassium decreased, Grade 1	13	3		
Potassium decreased, Grade 2	0	0		
Potassium decreased, Grade 3	1	1		
Potassium decreased, Grade 4	0	0		
Aspartate Aminotransferase increased, Grade 1	20	6		
Aspartate Aminotransferase increased, Grade 2	3	0		
Aspartate Aminotransferase increased, Grade 3	2	2		
Aspartate Aminotransferase increased, Grade 4	3	0		
Alanine Aminotransferase increased, Grade 1	31	4		
Alanine Aminotransferase increased, Grade 2	4	2		
Alanine Aminotransferase increased, Grade 3	2	2		
Alanine Aminotransferase increased, Grade 4	2	0		
Creatinine increased, Grade 1	38	9		
Creatinine increased, Grade 2	11	0		
Creatinine increased, Grade 3	0	0		
Creatinine increased, Grade 4	0	0		
Alkaline Phosphatase increased, Grade 1	16	4		
Alkaline Phosphatase increased, Grade 2	4	2		
Alkaline Phosphatase increased, Grade 3	1	0		
Alkaline Phosphatase increased, Grade 4	0	0		
Total Bilirubin increased, Grade 1	14	6		
Total Bilirubin increased, Grade 2	5	0		
Total Bilirubin increased, Grade 3	3	0		
Total Bilirubin increased, Grade 4	2	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Treatment-Emergent Laboratory Abnormalities (Chemistry): Final Analysis

End point title	Number of Participants With Treatment-Emergent Laboratory Abnormalities (Chemistry): Final Analysis

End point description:

Chemistry laboratory parameters: Potassium increased; potassium decreased; aspartate

aminotransferase increased; alanine aminotransferase increased; creatinine increased; alkaline phosphatase increased; total bilirubin increased; albumin decreased; calcium corrected for albumin decreased; calcium corrected for albumin increased; GFR, estimated decreased; glucose decreased; glucose increased; sodium decreased; sodium increased; calcium & ionized increased. Treatment emergent laboratory abnormalities: Abnormalities that were new or worsened on or after receiving the 1st dose of study treatment & up through 30 days after last dose of treatment. NCI CTCAE v5.0: For creatinine increased & v4.03: For other laboratory parameters. Grade 1: mild; Grade 2: moderate; Grade 3: severe or clinically significant; Grade 4: life-threatening. Safety analysis set evaluated. Data for cohort A & B combined as prespecified in SAP. Number of Participants analysed= Participants evaluable for this endpoint.

End point type	Secondary
End point timeframe:	
Up to 65.1 months	

End point values	Tucatinib Post-Crossover (Cohort C)	Tucatinib+Trastuzumab (Cohorts A+B)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	28	85		
Units: Participants				
Potassium increased, All grades	4	6		
Potassium increased, Grade 3	0	0		
Potassium increased, Grade 4	0	0		
Potassium decreased, All grades	4	15		
Potassium decreased, Grade 3	0	1		
Potassium decreased, Grade 4	0	0		
Aspartate Aminotransferase increased, All grades	9	29		
Aspartate Aminotransferase increased, Grade 3	3	2		
Aspartate Aminotransferase increased, Grade 4	0	3		
Alanine Aminotransferase increased, All grades	7	39		
Alanine Aminotransferase increased, Grade 3	2	2		
Alanine Aminotransferase increased, Grade 4	0	2		
Creatinine increased, All grades	10	50		
Creatinine increased, Grade 3	0	0		
Creatinine increased, Grade 4	0	0		
Alkaline Phosphatase increased, All grades	3	21		
Alkaline Phosphatase increased, Grade 3	0	1		
Alkaline Phosphatase increased, Grade 4	0	0		
Total Bilirubin increased, All grades	4	25		
Total Bilirubin increased, Grade 3	0	3		
Total Bilirubin increased, Grade 4	0	2		
Albumin decreased, All grades	8	23		
Albumin decreased, Grade 3	0	1		
Albumin decreased, Grade 4	0	0		
Calcium Corrected for Albumin decreased,All grades	5	11		
Calcium Corrected for Albumin decreased, Grade 3	0	0		

Calcium Corrected for Albumin decreased, Grade 4	0	0		
Calcium Corrected for Albumin increased,All grades	5	8		
Calcium Corrected for Albumin increased, Grade 3	0	0		
Calcium Corrected for Albumin increased, Grade 4	0	0		
GFR, Estimated decreased, All grades	6	51		
GFR, Estimated decreased, Grade 3	0	6		
GFR, Estimated decreased, Grade 4	0	0		
Glucose decreased, All grades	1	10		
Glucose decreased, Grade 3	0	0		
Glucose decreased, Grade 4	0	0		
Glucose increased, All grades	9	48		
Glucose increased, Grade 3	0	2		
Glucose increased, Grade 4	0	0		
Sodium decreased, All grades	1	18		
Sodium decreased, Grade 3	0	5		
Sodium decreased, Grade 4	0	0		
Sodium increased, All grades	4	7		
Sodium increased, Grade 3	0	0		
Sodium increased, Grade 4	0	0		
Calcium, Ionized increased: All grades	0	2		
Calcium, Ionized increased: Grade 3	0	0		
Calcium, Ionized increased: Grade 4	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Clinically Significant Vital Signs: Final Analysis

End point title	Number of Participants With Clinically Significant Vital Signs: Final Analysis

End point description:

Vital signs included temperature, oxygen saturation, systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate and weight. Vital signs were considered clinically significant: temperature: >= 38 degree Celsius (C); oxygen saturation less than (<)88%; SBP >=120 millimeters of mercury (mmHg) or DBP >=80 mmHg; SBP >=140 mmHg or DBP >=90 mmHg; SBP >=160 mmHg or DBP >=100 mmHg and heart rate >100 beats per minute (bpm) and maximum decrease from baseline in weight in kilograms (kg). The safety analysis set included participants who received any amount of study treatment. Data for cohort A and B was combined as prespecified in SAP.

End point type	Secondary

End point timeframe:

Up to 65.1 months

End point values	Tucatinib+Trastuzumab (Cohorts A+B)	Tucatinib Post-Crossover (Cohort C)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	86	28		
Units: Participants				
Temperature >=38 degree C	1	0		
Oxygen saturation <88%	8	0		
SBP >= 120 mmHg or DBP >= 80 mmHg	80	27		
SBP >= 140 mmHg or DBP >= 90 mmHg	49	13		
SBP >= 160 mmHg or DBP >= 100 mmHg	21	4		
Heart rate > 100 bpm	26	5		
Maximum decrease from baseline in weight (kg)	65	23		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All-cause mortality: From start of study treatment to death by any cause (maximum up to 71.8 months); adverse events were followed during the safety reporting period (from Day 1 through 30 days after last dose of study treatment) maximum up to 65.1 months

Adverse event reporting additional description:

Adverse events (AEs) for Cohorts A and B were analyzed together as prespecified in SAP. All-Cause Mortality is reported for all enrolled participants, regardless of whether or not they received study drug. SAEs and non-serious AEs are reported only for those patients who received at least one dose of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.1

Reporting groups

Reporting group title	Tucatinib+Trastuzumab (Cohorts A+B)

Reporting group description:

Participants received Tucatinib 300 mg PO BID on Days 1 to 21 of each 21-day cycle. Trastuzumab 8 mg/kg by IV infusion on Day 1 of Cycle 1 and 6 mg/kg on Day 1 of each subsequent cycle until PD, death, withdrawal of consent, study closure, or alternative therapy.

Reporting group title	Tucatinib Post-Crossover (Cohort C)

Reporting group description:

Participants received Tucatinib 300 mg PO BID on Days 1 to 21 of each 21-day cycle. Trastuzumab 8 mg/kg by IV infusion on Day 1 of Cycle 1 and 6 mg/kg on Day 1 of each subsequent cycle until PD, death, withdrawal of consent, study closure, or alternative therapy.

Reporting group title	Tucatinib Pre-Crossover (Cohort C)

Reporting group description:

Participants received Tucatinib 300 mg PO BID on Days 1 to 21 of each 21-day cycle. Participants who did not respond to monotherapy were given the option to receive tucatinib and trastuzumab based on radiographic progression (as determined by investigator assessment using RECIST v1.1), or if they had not achieved a PR or CR by the week 12 assessment.

Serious adverse events	Tucatinib+Trastuzumab (Cohorts A+B)	Tucatinib Post-Crossover (Cohort C)	Tucatinib Pre-Crossover (Cohort C)
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 86 (23.26%)	6 / 28 (21.43%)	3 / 30 (10.00%)
number of deaths (all causes)	54	15	2
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	1 / 86 (1.16%)	0 / 28 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			

Hypotension			
subjects affected / exposed	1 / 86 (1.16%)	0 / 28 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 86 (1.16%)	0 / 28 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaise			
subjects affected / exposed	1 / 86 (1.16%)	0 / 28 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 86 (1.16%)	0 / 28 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Ejection fraction decreased			
subjects affected / exposed	0 / 86 (0.00%)	1 / 28 (3.57%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Humerus fracture			
subjects affected / exposed	0 / 86 (0.00%)	1 / 28 (3.57%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			
subjects affected / exposed	0 / 86 (0.00%)	1 / 28 (3.57%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ulna fracture			

subjects affected / exposed	0 / 86 (0.00%)	1 / 28 (3.57%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose			
subjects affected / exposed	0 / 86 (0.00%)	0 / 28 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	0 / 86 (0.00%)	1 / 28 (3.57%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	1 / 86 (1.16%)	0 / 28 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Peripheral sensorimotor neuropathy			
subjects affected / exposed	0 / 86 (0.00%)	1 / 28 (3.57%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebellar haemorrhage			
subjects affected / exposed	1 / 86 (1.16%)	0 / 28 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 86 (2.33%)	0 / 28 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	1 / 86 (1.16%)	0 / 28 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Nausea			
subjects affected / exposed	1 / 86 (1.16%)	0 / 28 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal perforation			
subjects affected / exposed	2 / 86 (2.33%)	0 / 28 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	3 / 86 (3.49%)	0 / 28 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestinal obstruction			
subjects affected / exposed	3 / 86 (3.49%)	0 / 28 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspepsia			
subjects affected / exposed	1 / 86 (1.16%)	0 / 28 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 86 (0.00%)	1 / 28 (3.57%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal obstruction			
subjects affected / exposed	1 / 86 (1.16%)	0 / 28 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal obstruction			
subjects affected / exposed	0 / 86 (0.00%)	0 / 28 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			

Cholecystitis			
subjects affected / exposed	0 / 86 (0.00%)	1 / 28 (3.57%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis			
subjects affected / exposed	1 / 86 (1.16%)	0 / 28 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bile duct stone			
subjects affected / exposed	1 / 86 (1.16%)	0 / 28 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	1 / 86 (1.16%)	0 / 28 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute kidney injury			
subjects affected / exposed	1 / 86 (1.16%)	1 / 28 (3.57%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Flank pain			
subjects affected / exposed	1 / 86 (1.16%)	0 / 28 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	1 / 86 (1.16%)	0 / 28 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
COVID-19 pneumonia			

subjects affected / exposed	2 / 86 (2.33%)	0 / 28 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anorectal infection			
subjects affected / exposed	1 / 86 (1.16%)	0 / 28 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Kidney infection			
subjects affected / exposed	1 / 86 (1.16%)	0 / 28 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection bacterial			
subjects affected / exposed	1 / 86 (1.16%)	0 / 28 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	3 / 86 (3.49%)	0 / 28 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 86 (1.16%)	0 / 28 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 86 (0.00%)	0 / 28 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Tucatinib+Trastuzumab (Cohorts A+B)	Tucatinib Post-Crossover (Cohort C)	Tucatinib Pre-Crossover (Cohort C)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	82 / 86 (95.35%)	23 / 28 (82.14%)	28 / 30 (93.33%)
Vascular disorders			
Hypertension			
subjects affected / exposed	15 / 86 (17.44%)	0 / 28 (0.00%)	0 / 30 (0.00%)
occurrences (all)	20	0	0
Lymphoedema			
subjects affected / exposed	1 / 86 (1.16%)	1 / 28 (3.57%)	0 / 30 (0.00%)
occurrences (all)	1	1	0
Thrombosis			
subjects affected / exposed	0 / 86 (0.00%)	1 / 28 (3.57%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 86 (3.49%)	2 / 28 (7.14%)	5 / 30 (16.67%)
occurrences (all)	4	2	5
Pyrexia			
subjects affected / exposed	18 / 86 (20.93%)	6 / 28 (21.43%)	3 / 30 (10.00%)
occurrences (all)	27	9	4
Oedema peripheral			
subjects affected / exposed	7 / 86 (8.14%)	2 / 28 (7.14%)	2 / 30 (6.67%)
occurrences (all)	8	2	2
Influenza like illness			
subjects affected / exposed	7 / 86 (8.14%)	1 / 28 (3.57%)	0 / 30 (0.00%)
occurrences (all)	8	1	0
Fatigue			
subjects affected / exposed	37 / 86 (43.02%)	3 / 28 (10.71%)	6 / 30 (20.00%)
occurrences (all)	44	3	6
Chills			
subjects affected / exposed	16 / 86 (18.60%)	2 / 28 (7.14%)	0 / 30 (0.00%)
occurrences (all)	17	3	0
Non-cardiac chest pain			
subjects affected / exposed	3 / 86 (3.49%)	0 / 28 (0.00%)	0 / 30 (0.00%)
occurrences (all)	3	0	0
Peripheral swelling			

subjects affected / exposed	2 / 86 (2.33%)	0 / 28 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
Pain			
subjects affected / exposed	2 / 86 (2.33%)	0 / 28 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 86 (0.00%)	1 / 28 (3.57%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Social circumstances			
Pregnancy of partner			
subjects affected / exposed	0 / 86 (0.00%)	0 / 28 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	2 / 86 (2.33%)	0 / 28 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
Vulvovaginal dryness			
subjects affected / exposed	0 / 86 (0.00%)	1 / 28 (3.57%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Nipple pain			
subjects affected / exposed	0 / 86 (0.00%)	0 / 28 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	0	1
Vaginal haemorrhage			
subjects affected / exposed	1 / 86 (1.16%)	0 / 28 (0.00%)	1 / 30 (3.33%)
occurrences (all)	1	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	15 / 86 (17.44%)	4 / 28 (14.29%)	2 / 30 (6.67%)
occurrences (all)	18	4	2
Dyspnoea			
subjects affected / exposed	12 / 86 (13.95%)	2 / 28 (7.14%)	3 / 30 (10.00%)
occurrences (all)	15	2	3
Epistaxis			
subjects affected / exposed	7 / 86 (8.14%)	1 / 28 (3.57%)	0 / 30 (0.00%)
occurrences (all)	7	1	0

Nasal congestion			
subjects affected / exposed	8 / 86 (9.30%)	1 / 28 (3.57%)	0 / 30 (0.00%)
occurrences (all)	13	1	0
Oropharyngeal pain			
subjects affected / exposed	4 / 86 (4.65%)	2 / 28 (7.14%)	0 / 30 (0.00%)
occurrences (all)	9	3	0
Upper-airway cough syndrome			
subjects affected / exposed	6 / 86 (6.98%)	1 / 28 (3.57%)	0 / 30 (0.00%)
occurrences (all)	10	1	0
Rhinitis allergic			
subjects affected / exposed	5 / 86 (5.81%)	1 / 28 (3.57%)	0 / 30 (0.00%)
occurrences (all)	7	1	0
Productive cough			
subjects affected / exposed	6 / 86 (6.98%)	1 / 28 (3.57%)	0 / 30 (0.00%)
occurrences (all)	8	1	0
Rhinorrhoea			
subjects affected / exposed	4 / 86 (4.65%)	0 / 28 (0.00%)	0 / 30 (0.00%)
occurrences (all)	4	0	0
Dysphonia			
subjects affected / exposed	2 / 86 (2.33%)	1 / 28 (3.57%)	0 / 30 (0.00%)
occurrences (all)	2	1	0
Dyspnoea exertional			
subjects affected / exposed	2 / 86 (2.33%)	0 / 28 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
Nasal dryness			
subjects affected / exposed	0 / 86 (0.00%)	1 / 28 (3.57%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Pulmonary embolism			
subjects affected / exposed	2 / 86 (2.33%)	0 / 28 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
Sinus pain			
subjects affected / exposed	2 / 86 (2.33%)	0 / 28 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
Wheezing			
subjects affected / exposed	3 / 86 (3.49%)	0 / 28 (0.00%)	0 / 30 (0.00%)
occurrences (all)	3	0	0

Throat irritation			
subjects affected / exposed	0 / 86 (0.00%)	0 / 28 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	0	1
Psychiatric disorders			
Anxiety			
subjects affected / exposed	9 / 86 (10.47%)	0 / 28 (0.00%)	0 / 30 (0.00%)
occurrences (all)	9	0	0
Insomnia			
subjects affected / exposed	7 / 86 (8.14%)	0 / 28 (0.00%)	1 / 30 (3.33%)
occurrences (all)	8	0	1
Investigations			
Weight decreased			
subjects affected / exposed	8 / 86 (9.30%)	0 / 28 (0.00%)	3 / 30 (10.00%)
occurrences (all)	8	0	3
Ejection fraction decreased			
subjects affected / exposed	5 / 86 (5.81%)	1 / 28 (3.57%)	0 / 30 (0.00%)
occurrences (all)	8	2	0
Aspartate aminotransferase increased			
subjects affected / exposed	5 / 86 (5.81%)	3 / 28 (10.71%)	3 / 30 (10.00%)
occurrences (all)	5	6	3
Alanine aminotransferase increased			
subjects affected / exposed	5 / 86 (5.81%)	2 / 28 (7.14%)	2 / 30 (6.67%)
occurrences (all)	6	5	2
Weight increased			
subjects affected / exposed	3 / 86 (3.49%)	0 / 28 (0.00%)	1 / 30 (3.33%)
occurrences (all)	4	0	1
Blood alkaline phosphatase increased			
subjects affected / exposed	3 / 86 (3.49%)	0 / 28 (0.00%)	0 / 30 (0.00%)
occurrences (all)	3	0	0
Blood creatinine increased			
subjects affected / exposed	4 / 86 (4.65%)	1 / 28 (3.57%)	0 / 30 (0.00%)
occurrences (all)	4	1	0
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	18 / 86 (20.93%)	4 / 28 (14.29%)	0 / 30 (0.00%)
occurrences (all)	19	8	0

Fall			
subjects affected / exposed	4 / 86 (4.65%)	0 / 28 (0.00%)	0 / 30 (0.00%)
occurrences (all)	4	0	0
Procedural pain			
subjects affected / exposed	2 / 86 (2.33%)	0 / 28 (0.00%)	1 / 30 (3.33%)
occurrences (all)	2	0	1
Contusion			
subjects affected / exposed	0 / 86 (0.00%)	0 / 28 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	0	1
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	0 / 86 (0.00%)	1 / 28 (3.57%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	5 / 86 (5.81%)	1 / 28 (3.57%)	2 / 30 (6.67%)
occurrences (all)	7	1	2
Dysgeusia			
subjects affected / exposed	4 / 86 (4.65%)	1 / 28 (3.57%)	1 / 30 (3.33%)
occurrences (all)	4	1	1
Headache			
subjects affected / exposed	9 / 86 (10.47%)	3 / 28 (10.71%)	3 / 30 (10.00%)
occurrences (all)	12	3	3
Peripheral sensory neuropathy			
subjects affected / exposed	7 / 86 (8.14%)	0 / 28 (0.00%)	1 / 30 (3.33%)
occurrences (all)	8	0	1
Neurotoxicity			
subjects affected / exposed	0 / 86 (0.00%)	1 / 28 (3.57%)	1 / 30 (3.33%)
occurrences (all)	0	1	1
Restless legs syndrome			
subjects affected / exposed	2 / 86 (2.33%)	0 / 28 (0.00%)	0 / 30 (0.00%)
occurrences (all)	3	0	0
Syncope			
subjects affected / exposed	2 / 86 (2.33%)	1 / 28 (3.57%)	0 / 30 (0.00%)
occurrences (all)	2	1	0
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	9 / 86 (10.47%)	3 / 28 (10.71%)	1 / 30 (3.33%)
occurrences (all)	10	4	1
Thrombocytopenia			
subjects affected / exposed	2 / 86 (2.33%)	0 / 28 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
Ear and labyrinth disorders			
Meniere's disease			
subjects affected / exposed	0 / 86 (0.00%)	1 / 28 (3.57%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Vertigo			
subjects affected / exposed	2 / 86 (2.33%)	1 / 28 (3.57%)	0 / 30 (0.00%)
occurrences (all)	2	1	0
Eye disorders			
Lacrimation increased			
subjects affected / exposed	1 / 86 (1.16%)	2 / 28 (7.14%)	0 / 30 (0.00%)
occurrences (all)	1	3	0
Blepharospasm			
subjects affected / exposed	2 / 86 (2.33%)	0 / 28 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
Cataract			
subjects affected / exposed	0 / 86 (0.00%)	1 / 28 (3.57%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Dry eye			
subjects affected / exposed	0 / 86 (0.00%)	1 / 28 (3.57%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Eye pruritus			
subjects affected / exposed	0 / 86 (0.00%)	1 / 28 (3.57%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Vision blurred			
subjects affected / exposed	3 / 86 (3.49%)	0 / 28 (0.00%)	0 / 30 (0.00%)
occurrences (all)	8	0	0
Gastrointestinal disorders			
Proctalgia			
subjects affected / exposed	1 / 86 (1.16%)	1 / 28 (3.57%)	1 / 30 (3.33%)
occurrences (all)	1	1	1
Nausea			

subjects affected / exposed	29 / 86 (33.72%)	2 / 28 (7.14%)	5 / 30 (16.67%)
occurrences (all)	35	2	6
Flatulence			
subjects affected / exposed	3 / 86 (3.49%)	2 / 28 (7.14%)	1 / 30 (3.33%)
occurrences (all)	3	2	1
Diarrhoea			
subjects affected / exposed	57 / 86 (66.28%)	11 / 28 (39.29%)	10 / 30 (33.33%)
occurrences (all)	77	19	11
Constipation			
subjects affected / exposed	12 / 86 (13.95%)	2 / 28 (7.14%)	4 / 30 (13.33%)
occurrences (all)	14	2	4
Abdominal pain upper			
subjects affected / exposed	6 / 86 (6.98%)	2 / 28 (7.14%)	2 / 30 (6.67%)
occurrences (all)	9	2	2
Abdominal pain lower			
subjects affected / exposed	0 / 86 (0.00%)	1 / 28 (3.57%)	1 / 30 (3.33%)
occurrences (all)	0	1	1
Abdominal pain			
subjects affected / exposed	11 / 86 (12.79%)	2 / 28 (7.14%)	6 / 30 (20.00%)
occurrences (all)	19	2	7
Abdominal distension			
subjects affected / exposed	2 / 86 (2.33%)	1 / 28 (3.57%)	1 / 30 (3.33%)
occurrences (all)	2	1	1
Abdominal discomfort			
subjects affected / exposed	2 / 86 (2.33%)	2 / 28 (7.14%)	0 / 30 (0.00%)
occurrences (all)	2	2	0
Stomatitis			
subjects affected / exposed	1 / 86 (1.16%)	2 / 28 (7.14%)	3 / 30 (10.00%)
occurrences (all)	1	2	3
Vomiting			
subjects affected / exposed	14 / 86 (16.28%)	4 / 28 (14.29%)	2 / 30 (6.67%)
occurrences (all)	20	4	3
Oral pain			
subjects affected / exposed	0 / 86 (0.00%)	2 / 28 (7.14%)	0 / 30 (0.00%)
occurrences (all)	0	2	0
Dry mouth			

subjects affected / exposed	4 / 86 (4.65%)	0 / 28 (0.00%)	0 / 30 (0.00%)
occurrences (all)	4	0	0
Dyspepsia			
subjects affected / exposed	4 / 86 (4.65%)	0 / 28 (0.00%)	1 / 30 (3.33%)
occurrences (all)	4	0	1
Food poisoning			
subjects affected / exposed	0 / 86 (0.00%)	1 / 28 (3.57%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal pain			
subjects affected / exposed	2 / 86 (2.33%)	0 / 28 (0.00%)	0 / 30 (0.00%)
occurrences (all)	3	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	3 / 86 (3.49%)	1 / 28 (3.57%)	0 / 30 (0.00%)
occurrences (all)	3	1	0
Glossodynia			
subjects affected / exposed	0 / 86 (0.00%)	1 / 28 (3.57%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Noninfective gingivitis			
subjects affected / exposed	0 / 86 (0.00%)	1 / 28 (3.57%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Rectal haemorrhage			
subjects affected / exposed	2 / 86 (2.33%)	0 / 28 (0.00%)	1 / 30 (3.33%)
occurrences (all)	2	0	1
Tooth loss			
subjects affected / exposed	0 / 86 (0.00%)	1 / 28 (3.57%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Haematochezia			
subjects affected / exposed	1 / 86 (1.16%)	0 / 28 (0.00%)	2 / 30 (6.67%)
occurrences (all)	1	0	2
Eructation			
subjects affected / exposed	0 / 86 (0.00%)	0 / 28 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	0	1
Proctitis			
subjects affected / exposed	0 / 86 (0.00%)	0 / 28 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	0	1
Salivary hypersecretion			

subjects affected / exposed	0 / 86 (0.00%)	0 / 28 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	0	1
Toothache			
subjects affected / exposed	0 / 86 (0.00%)	0 / 28 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	0	1
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 86 (0.00%)	0 / 28 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	0	1
Hepatic pain			
subjects affected / exposed	0 / 86 (0.00%)	0 / 28 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	9 / 86 (10.47%)	3 / 28 (10.71%)	1 / 30 (3.33%)
occurrences (all)	12	4	1
Onychoclasis			
subjects affected / exposed	2 / 86 (2.33%)	1 / 28 (3.57%)	1 / 30 (3.33%)
occurrences (all)	2	1	1
Nail disorder			
subjects affected / exposed	2 / 86 (2.33%)	2 / 28 (7.14%)	0 / 30 (0.00%)
occurrences (all)	2	2	0
Dry skin			
subjects affected / exposed	8 / 86 (9.30%)	0 / 28 (0.00%)	0 / 30 (0.00%)
occurrences (all)	9	0	0
Dermatitis acneiform			
subjects affected / exposed	17 / 86 (19.77%)	0 / 28 (0.00%)	2 / 30 (6.67%)
occurrences (all)	21	0	2
Rash maculo-papular			
subjects affected / exposed	7 / 86 (8.14%)	1 / 28 (3.57%)	2 / 30 (6.67%)
occurrences (all)	11	1	2
Ecchymosis			
subjects affected / exposed	2 / 86 (2.33%)	0 / 28 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
Erythema			

subjects affected / exposed	2 / 86 (2.33%)	0 / 28 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
Onychomadesis			
subjects affected / exposed	2 / 86 (2.33%)	0 / 28 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 86 (0.00%)	1 / 28 (3.57%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Rash			
subjects affected / exposed	4 / 86 (4.65%)	0 / 28 (0.00%)	0 / 30 (0.00%)
occurrences (all)	5	0	0
Rash pruritic			
subjects affected / exposed	0 / 86 (0.00%)	1 / 28 (3.57%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Urticaria			
subjects affected / exposed	2 / 86 (2.33%)	0 / 28 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
Alopecia			
subjects affected / exposed	0 / 86 (0.00%)	0 / 28 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	0	1
Pain of skin			
subjects affected / exposed	0 / 86 (0.00%)	0 / 28 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	3 / 86 (3.49%)	2 / 28 (7.14%)	0 / 30 (0.00%)
occurrences (all)	3	2	0
Haematuria			
subjects affected / exposed	4 / 86 (4.65%)	0 / 28 (0.00%)	0 / 30 (0.00%)
occurrences (all)	4	0	0
Nephrolithiasis			
subjects affected / exposed	4 / 86 (4.65%)	0 / 28 (0.00%)	0 / 30 (0.00%)
occurrences (all)	4	0	0
Pollakiuria			

subjects affected / exposed	4 / 86 (4.65%)	0 / 28 (0.00%)	0 / 30 (0.00%)
occurrences (all)	4	0	0
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	5 / 86 (5.81%)	0 / 28 (0.00%)	0 / 30 (0.00%)
occurrences (all)	7	0	0
Muscle spasms			
subjects affected / exposed	7 / 86 (8.14%)	3 / 28 (10.71%)	2 / 30 (6.67%)
occurrences (all)	7	3	2
Hypercreatinaemia			
subjects affected / exposed	3 / 86 (3.49%)	1 / 28 (3.57%)	1 / 30 (3.33%)
occurrences (all)	3	1	1
Back pain			
subjects affected / exposed	16 / 86 (18.60%)	6 / 28 (21.43%)	1 / 30 (3.33%)
occurrences (all)	17	6	1
Arthralgia			
subjects affected / exposed	16 / 86 (18.60%)	4 / 28 (14.29%)	2 / 30 (6.67%)
occurrences (all)	20	5	3
Myalgia			
subjects affected / exposed	11 / 86 (12.79%)	0 / 28 (0.00%)	2 / 30 (6.67%)
occurrences (all)	18	0	3
Pain in extremity			
subjects affected / exposed	8 / 86 (9.30%)	1 / 28 (3.57%)	1 / 30 (3.33%)
occurrences (all)	13	1	2
Flank pain			
subjects affected / exposed	4 / 86 (4.65%)	1 / 28 (3.57%)	0 / 30 (0.00%)
occurrences (all)	4	1	0
Muscular weakness			
subjects affected / exposed	2 / 86 (2.33%)	0 / 28 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
Neck pain			
subjects affected / exposed	1 / 86 (1.16%)	1 / 28 (3.57%)	0 / 30 (0.00%)
occurrences (all)	1	1	0
Arthritis			

subjects affected / exposed	0 / 86 (0.00%)	0 / 28 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	0	1
Musculoskeletal stiffness			
subjects affected / exposed	0 / 86 (0.00%)	0 / 28 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	0	1
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	4 / 86 (4.65%)	4 / 28 (14.29%)	4 / 30 (13.33%)
occurrences (all)	8	7	6
Upper respiratory tract infection			
subjects affected / exposed	2 / 86 (2.33%)	2 / 28 (7.14%)	0 / 30 (0.00%)
occurrences (all)	3	2	0
COVID-19			
subjects affected / exposed	6 / 86 (6.98%)	3 / 28 (10.71%)	0 / 30 (0.00%)
occurrences (all)	6	3	0
Conjunctivitis			
subjects affected / exposed	0 / 86 (0.00%)	1 / 28 (3.57%)	0 / 30 (0.00%)
occurrences (all)	0	2	0
Gastroenteritis			
subjects affected / exposed	0 / 86 (0.00%)	1 / 28 (3.57%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Gingival abscess			
subjects affected / exposed	0 / 86 (0.00%)	1 / 28 (3.57%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Herpes zoster			
subjects affected / exposed	2 / 86 (2.33%)	1 / 28 (3.57%)	0 / 30 (0.00%)
occurrences (all)	2	1	0
Hordeolum			
subjects affected / exposed	1 / 86 (1.16%)	1 / 28 (3.57%)	0 / 30 (0.00%)
occurrences (all)	1	1	0
Influenza			
subjects affected / exposed	2 / 86 (2.33%)	0 / 28 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
Nail infection			
subjects affected / exposed	3 / 86 (3.49%)	1 / 28 (3.57%)	0 / 30 (0.00%)
occurrences (all)	4	1	0

Otitis media			
subjects affected / exposed	2 / 86 (2.33%)	0 / 28 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
Pneumonia			
subjects affected / exposed	2 / 86 (2.33%)	0 / 28 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
Rash pustular			
subjects affected / exposed	1 / 86 (1.16%)	1 / 28 (3.57%)	0 / 30 (0.00%)
occurrences (all)	1	1	0
Rhinitis			
subjects affected / exposed	2 / 86 (2.33%)	0 / 28 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
Kidney infection			
subjects affected / exposed	0 / 86 (0.00%)	0 / 28 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	17 / 86 (19.77%)	2 / 28 (7.14%)	4 / 30 (13.33%)
occurrences (all)	22	2	4
Hypokalaemia			
subjects affected / exposed	5 / 86 (5.81%)	0 / 28 (0.00%)	3 / 30 (10.00%)
occurrences (all)	5	0	3
Dehydration			
subjects affected / exposed	7 / 86 (8.14%)	1 / 28 (3.57%)	0 / 30 (0.00%)
occurrences (all)	11	1	0
Hypoalbuminaemia			
subjects affected / exposed	2 / 86 (2.33%)	0 / 28 (0.00%)	0 / 30 (0.00%)
occurrences (all)	4	0	0
Hyponatraemia			
subjects affected / exposed	3 / 86 (3.49%)	0 / 28 (0.00%)	1 / 30 (3.33%)
occurrences (all)	4	0	1
Hypocalcaemia			
subjects affected / exposed	0 / 86 (0.00%)	0 / 28 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 June 2017	Side effects of Tucatinib updated based on Pharmacy review of investigator's brochure (IB). Side effects of Trastuzumab updated based on Pharmacy review of IB.
20 October 2017	Section 15.14 has been updated with added information regarding the administration of Tucatinib. Section 15.16, additional information was added to the Potential Drug Interactions paragraph. Sections 15.297-98 Nursing Guidelines have been added for Trastuzumab.
21 September 2018	Added language was inserted for clarification regarding Adverse Event-Specific Dose Modifications.
19 April 2019	Trastuzumab reproductive risks; language was added for precautionary measures for pregnant females.
10 September 2019	Removed, information related to suspected unexpected serious adverse reactions (SUSAR), suspected adverse reaction, and expedited and routine reporting were covered by Seattle Genetics SOPs and were outside of the scope of the individual site(s). removed events of interest as ACCRU's definition does not align with Seattle Genetics' definition. Updated the language on death to align with the Seattle Genetics standard language. Added the language on reporting of serious events to align with the Seattle Genetics standard language. Removed the table for reporting timeframes and mechanisms and added the updated information on SAEs (per Seattle Genetics standard SAE reporting language) in section 10.7, on adverse events of special interest (AESI) in section 10.73, and on pregnancies in section 10.83. Updated the information on reporting of pregnancies.
01 November 2019	Addition of 2 cohorts to the study: tucatinib given in combination with trastuzumab (Cohort B) and tucatinib monotherapy (Cohort C). Cohort B was added to assess efficacy (confirmed Objective Response Rate [cORR]) and safety of the dual therapy for metastatic colorectal cancer (mCRC) participants. Cohort C was added to better characterize the antitumor activity of tucatinib when used as a monotherapy. Planned enrollment was increased from 40 to 110 participants. As of Amendment 8, 70 newly enrolled participants will be randomized to either tucatinib given in combination with trastuzumab (40 participants randomized to Cohort B) or tucatinib monotherapy (30 participants randomized to Cohort C).
21 December 2020	Removed requirement to report overdose events or dosing errors following the SAE reporting process.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported