Clinical trial results:
An open-label, two-arm, randomized, single-stage phase II study of ATezolizumab in combination with dual HER2 blockade plus epirubicin as NEoadjuvant therapy for HER2-positive early breast cancer

Summary

EudraCT number	2019-002364-27
Trial protocol	AT
Global end of trial date	23 November 2022

Results information

Result version number	v1
This version publication date	29 September 2023
First version publication date	29 September 2023

Trial information

Trial identification

Sponsor protocol code	ABCSG_52

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Roche ID: ML40391

Notes:

Sponsors

Sponsor organisation name	ABCSG (Austrian Breast & Colorectal Cancer Study Group)
Sponsor organisation address	Nussdorfer Platz 8/12, Wien, Austria, 1190
Public contact	Trial Office, ABCSG (Austrian Breast & Colorectal Cancer Study Group), +43 14089230, christian.fesl@abcsg.at
Scientific contact	Trial Office, ABCSG (Austrian Breast & Colorectal Cancer Study Group), +43 14089230, christian.fesl@abcsg.at

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	30 May 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 May 2022
Global end of trial reached?	Yes
Global end of trial date	23 November 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of a neoadjuvant immunochemotherapy regimen consisting of atezolizumab, trastuzumab, pertuzumab and epirubicin in regards to pathologic complete response (pCR = ypT0/is, ypN0) which is assessed in the overall study population at the time of surgery

Protection of trial subjects:

The investigators ensured that patients were given comprehensive oral and written information about the nature, significance, and scope of the study prior to enrolment. The study specific patient information and informed consent form included language to encourage study participants to reach out to the Study Doctor / Study Team in case they had any questions, concerns or doubts. Section 16 specifically referenced a 24/7 contact person to reach out to, the ICF furthermore contained a reference to the local ombudsman / patient advocacy / data privacy officer and the trial sites had the opportunity to hand out Patient Cards to the recruited patients for use in case of emergency which includes the trial site’s contact details, information of the study drug(s) and the EudraCT-number. A dedicated DMC was established to ensure patient safety throughout the trial.

Background therapy:

Background therapy of trastuzumab, pertuzumab and epirubicin only in treatment part 2 (in treatment arm A and arm B)

Evidence for comparator:

No

Actual start date of recruitment	03 July 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 58
Worldwide total number of subjects	58
EEA total number of subjects	58

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	46
From 65 to 84 years	12
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment phase for this study was 1.4 years. No follow up was done for this study.

Pre-assignment

Screening details:

A careful check of inclusion and exclusion criteria had to be performed by the Investigators / Site Teams and a centralized web based screeening and randomization system was subsequently used which assigned treatment arms electronically, i.e. randomized the participants into the previously described treatment arms.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Atezolizumab+Pertuzumab+Trastuzumab+Epirubicin (Arm A)

Arm description:

For treatment part 1, arm A patients received 2 3-week cycles of pertuzumab (starting with 840 mg iv on cycle 1, followed by 420 mg iv for the subsequent cycle), 2 3-week cycles of trastuzumab (starting with 600 mg sc or 8 mg/kg iv on cycle 1, followed by 600 mg sc or 6 mg/kg iv for the subsequent cycle) and 2 3-week cycles of atezolizumab (1200 mg iv per cycle).
For treatment part 2, arm A patients received 4 3-week cycles of atezolizumab (1200 mg iv per cycle), 4 3-week cycles pertuzumab (420 mg iv per cycle), 4 3-week cycles trastuzumab (600 mg sc or 6 mg/kg iv per cycle) as well as 4 3-week cycles of epirubicin (90 mg/m² per cycle).

Arm type	Experimental
Investigational medicinal product name	Atezolizumab
Investigational medicinal product code	RO5541267/F03
Other name	Tecentriq
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intraventricular use

Dosage and administration details:

60 mg/ml

Investigational medicinal product name	Pertuzumab
Investigational medicinal product code	RO4368451
Other name	Perjeta
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

30 mg/ml

Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	180288-69-1
Other name	Herceptin
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

120 mg/ml

Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	180288-69-1
Other name	Herceptin
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

150 mg/ml

Arm title	Pertuzumab+Trastuzumab+Epirubicin (Arm B)

Arm description:

For treatment part 1, arm B patients received 2 3-week cycles of pertuzumab (starting with 840 mg iv on cycle 1, followed by 420 mg iv for the subsequent cycle) and 2 3-week cycles of trastuzumab (starting with 600 mg sc or 8 mg/kg iv on cycle 1, followed by 600 mg sc or 6 mg/kg iv for the subsequent cycle).
For treatment part 2, arm B patients received 4 3-week cycles of atezolizumab (1200 mg iv per cycle), 4 3-week cycles pertuzumab (420 mg iv per cycle), 4 3-week cycles trastuzumab (600 mg sc or 6 mg/kg iv per cycle) as well as 4 3-week cycles of epirubicin (90 mg/m² per cycle).

Arm type	Experimental
Investigational medicinal product name	Pertuzumab
Investigational medicinal product code	RO4368451
Other name	Perjeta
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

30 mg/ml

Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	180288-69-1
Other name	Herceptin
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

120 mg/ml

Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	180288-69-1
Other name	Herceptin
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

150 mg/ml

Number of subjects in period 1	Atezolizumab+Pertuzumab+Trastuzumab+Epirubicin (Arm A)	Pertuzumab+Trastuzumab+Epirubicin (Arm B)
Started	29	29
Completed	28	28
Not completed	1	1
Consent withdrawn by subject	1	-
Lost to follow-up	-	1

Baseline characteristics

Reporting groups

Reporting group title	Atezolizumab+Pertuzumab+Trastuzumab+Epirubicin (Arm A)

Reporting group description:

For treatment part 1, arm A patients received 2 3-week cycles of pertuzumab (starting with 840 mg iv on cycle 1, followed by 420 mg iv for the subsequent cycle), 2 3-week cycles of trastuzumab (starting with 600 mg sc or 8 mg/kg iv on cycle 1, followed by 600 mg sc or 6 mg/kg iv for the subsequent cycle) and 2 3-week cycles of atezolizumab (1200 mg iv per cycle).
For treatment part 2, arm A patients received 4 3-week cycles of atezolizumab (1200 mg iv per cycle), 4 3-week cycles pertuzumab (420 mg iv per cycle), 4 3-week cycles trastuzumab (600 mg sc or 6 mg/kg iv per cycle) as well as 4 3-week cycles of epirubicin (90 mg/m² per cycle).

Reporting group title	Pertuzumab+Trastuzumab+Epirubicin (Arm B)

Reporting group description:

For treatment part 1, arm B patients received 2 3-week cycles of pertuzumab (starting with 840 mg iv on cycle 1, followed by 420 mg iv for the subsequent cycle) and 2 3-week cycles of trastuzumab (starting with 600 mg sc or 8 mg/kg iv on cycle 1, followed by 600 mg sc or 6 mg/kg iv for the subsequent cycle).
For treatment part 2, arm B patients received 4 3-week cycles of atezolizumab (1200 mg iv per cycle), 4 3-week cycles pertuzumab (420 mg iv per cycle), 4 3-week cycles trastuzumab (600 mg sc or 6 mg/kg iv per cycle) as well as 4 3-week cycles of epirubicin (90 mg/m² per cycle).

Reporting group values	Atezolizumab+Pertuzumab+Trastuzumab+Epirubicin (Arm A)	Pertuzumab+Trastuzumab+Epirubicin (Arm B)	Total
Number of subjects	29	29	58
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	24	22	46
From 65-84 years	5	7	12
85 years and over	0	0	0
Age continuous			
Units: years			
median	57	58	
full range (min-max)	33 to 77	38 to 82	-
Gender categorical			
Units: Subjects			
Female	29	29	58
Male	0	0	0
Menopausal status			
Menopausal status at randomization			
Units: Subjects			
Premenopausal (incl. perimenopausal)	15	9	24
Postmenopausal	14	20	34

TILs			
Amount of Tumor Infiltrating Lymphocytes (TILs)			
Units: Subjects			
<5%	3	3	6
>=5%	26	26	52
Hormone receptor status			
Hormone receptor status at randomization			
Units: Subjects			
Negative	8	8	16
Positive	21	21	42
Clinical prognostic stage Units: Subjects			
<=IIA	23	22	45
>=IIB	6	7	13
cT-stage			
Clinical tumor stage			
Units: Subjects			
T1c	9	7	16
T2	16	19	35
T3	4	1	5
T4b	0	1	1
T4c	0	1	1
cN-stage			
Clinical nodal status			
Units: Subjects			
N0	17	18	35
N1	11	10	21
N2	0	1	1
N2a	1	0	1
Tumor grade Units: Subjects			
G2	12	16	28
G3	17	13	30
Histological tumor type Units: Subjects			
Invasive carcinoma of no special type (NST)	23	25	48
Invasive lobular carcinoma	2	0	2
Mixed invasive NST and lobular carcinoma	0	1	1
Other	4	3	7
cM-stage			
Clinical metastasis status			
Units: Subjects			
M0	29	29	58
HER2 status			
Status of human epidermal growth factor receptor 2			
Units: Subjects			
Positive	29	29	58

BMI			
Body Mass Index			
Units: kg/m²			
median	23.6	25.8	
full range (min-max)	19.5 to 37.8	19.1 to 39.4	-

Subject analysis sets

Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT population consists of all patients who were randomized. All cases with missing primary outcome of pathologic complete response (pCR yes/no) are considered as no pCR.

Reporting group values	ITT		
Number of subjects	58		
Age categorical			
Units: Subjects			
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)	46		
From 65-84 years	12		
85 years and over	0		
Age continuous			
Units: years			
median	57		
full range (min-max)	33 to 82		
Gender categorical			
Units: Subjects			
Female	58		
Male	0		
Menopausal status			
Menopausal status at randomization			
Units: Subjects			
Premenopausal (incl. perimenopausal)	24		
Postmenopausal	34		
TILs			
Amount of Tumor Infiltrating Lymphocytes (TILs)			
Units: Subjects			
<5%	6		
>=5%	52		
Hormone receptor status			
Hormone receptor status at randomization			
Units: Subjects			
Negative	16		

Positive	42		
Clinical prognostic stage Units: Subjects			
<=IIA	45		
>=IIB	13		
cT-stage			
Clinical tumor stage			
Units: Subjects			
T1c	16		
T2	35		
T3	5		
T4b	1		
T4c	1		
cN-stage			
Clinical nodal status			
Units: Subjects			
N0	35		
N1	21		
N2	1		
N2a	1		
Tumor grade Units: Subjects			
G2	28		
G3	30		
Histological tumor type Units: Subjects			
Invasive carcinoma of no special type (NST)	48		
Invasive lobular carcinoma	2		
Mixed invasive NST and lobular carcinoma	1		
Other	7		
cM-stage			
Clinical metastasis status			
Units: Subjects			
M0	58		
HER2 status			
Status of human epidermal growth factor receptor 2			
Units: Subjects			
Positive	58		
BMI			
Body Mass Index			
Units: kg/m²			
median	24.5		
full range (min-max)	19.1 to 39.4		

End points

End points reporting groups

Reporting group title	Atezolizumab+Pertuzumab+Trastuzumab+Epirubicin (Arm A)

Reporting group description:

For treatment part 1, arm A patients received 2 3-week cycles of pertuzumab (starting with 840 mg iv on cycle 1, followed by 420 mg iv for the subsequent cycle), 2 3-week cycles of trastuzumab (starting with 600 mg sc or 8 mg/kg iv on cycle 1, followed by 600 mg sc or 6 mg/kg iv for the subsequent cycle) and 2 3-week cycles of atezolizumab (1200 mg iv per cycle).
For treatment part 2, arm A patients received 4 3-week cycles of atezolizumab (1200 mg iv per cycle), 4 3-week cycles pertuzumab (420 mg iv per cycle), 4 3-week cycles trastuzumab (600 mg sc or 6 mg/kg iv per cycle) as well as 4 3-week cycles of epirubicin (90 mg/m² per cycle).

Reporting group title	Pertuzumab+Trastuzumab+Epirubicin (Arm B)

Reporting group description:

For treatment part 1, arm B patients received 2 3-week cycles of pertuzumab (starting with 840 mg iv on cycle 1, followed by 420 mg iv for the subsequent cycle) and 2 3-week cycles of trastuzumab (starting with 600 mg sc or 8 mg/kg iv on cycle 1, followed by 600 mg sc or 6 mg/kg iv for the subsequent cycle).
For treatment part 2, arm B patients received 4 3-week cycles of atezolizumab (1200 mg iv per cycle), 4 3-week cycles pertuzumab (420 mg iv per cycle), 4 3-week cycles trastuzumab (600 mg sc or 6 mg/kg iv per cycle) as well as 4 3-week cycles of epirubicin (90 mg/m² per cycle).

Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT population consists of all patients who were randomized. All cases with missing primary outcome of pathologic complete response (pCR yes/no) are considered as no pCR.

Primary: Pathologic complete response (pCR)

End point title	Pathologic complete response (pCR)[1]

End point description:

Proportion (%) of patients with a pathologic complete response (pCR) together with its 95 %Wilson confidence interval in both arms combined and assessed in the ITT study population at the time of surgery is compared to a proportion of 40%

End point type	Primary

End point timeframe:

At surgery

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: The treatment arms were not compared against each other but the proportion (%) of patients with a pathologic complete response (pCR) in both arms combined was compared to a pre-defined proportion of 40%. It was not possible to document this single-arm comparison with a fixed value in the analysis part of the system. The
estimated rate with the 95% confidence interval was therefore included in the description.

End point values	ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	58[2]			
Units: Subjects				
pCR	35			
No PCR	23			

Notes:

[2] - The estimated pCR rate is 60.3% with a two-sided 95% confidence interval (CI) of [47.5, 71.9].

Statistical analyses

No statistical analyses for this end point

Secondary: Residual Cancer Burden (RCB)

End point title	Residual Cancer Burden (RCB)

End point description:

Proportion of patients with Residual Cancer Burden RCB 0/I (RCB index ≤1.36) together with its 95 %Wilson confidence interval in both arms combined and assessed in the ITT study population at the time of surgery

End point type	Secondary

End point timeframe:

At surgery

End point values	ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	58			
Units: Subjects				
RCB 0/I	44			
RCB II/III	11			
Not evaluated	3			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate (ORR)

End point title	Overall Response Rate (ORR)

End point description:

Proportion of patients with overall response defined as radiographic complete or radiographic partial response (rCR or rPR) according to modified Response Evaluation Criteria in Solid Tumors (RECIST) together with its 95 %Wilson confidence interval in both arms combined and assessed in the ITT study population at the time of surgery

End point type	Secondary

End point timeframe:

At surgery

End point values	ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	58			
Units: Subjects				
rCR+rPR (complete or partial response)	50			
rSD (stable disease)	6			
Not evaluated	2			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

(S)AE reporting was mandatory from the date of informed consent form signature (i.e., screening phase) until 42 days after the last dose of neoadjuvant study treatment.

Adverse event reporting additional description:

Screening Phase: only AEs deemed to be serious (SAEs) and related to protocol mandated and not routinely performed procedures have to be reported.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Pertuzumab+Trastuzumab+Epirubicin (Arm B)
Reporting group description: -	
Reporting group title	Atezolizumab+Pertuzumab+Trastuzumab+Epirubicin (Arm A)
Reporting group description: -	

Serious adverse events	Pertuzumab+Trastuzumab+Epirubicin (Arm B)	Atezolizumab+Pertuzumab+Trastuzumab+Epirubicin (Arm A)	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 29 (20.69%)	5 / 29 (17.24%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Infusion related reaction	Additional description: Infusion related reaction		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 29 (10.34%)	3 / 29 (10.34%)	
occurrences causally related to treatment / all	3 / 3	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiomyopathy	Additional description: Cardiomyopathy		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 29 (3.45%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia	Additional description: Febrile neutropenia		

alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 29 (3.45%)	2 / 29 (6.90%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
General physical health deterioration	Additional description: General physical health deterioration		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 29 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Alveolar osteitis	Additional description: Alveolar osteitis		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 29 (3.45%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19	Additional description: COVID-19		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 29 (3.45%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile infection	Additional description: Febrile infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 29 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Pertuzumab+Trastuzumab+Epirubicin (Arm B)	Atezolizumab+Pertuzumab+Trastuzumab+Epirubicin (Arm A)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	29 / 29 (100.00%)	29 / 29 (100.00%)	

Vascular disorders			
Hot flush	Additional description: Hot flush		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 29 (6.90%)	3 / 29 (10.34%)	
occurrences (all)	2	3	
Hypertension	Additional description: Hypertension		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 29 (6.90%)	2 / 29 (6.90%)	
occurrences (all)	2	2	
Hypotension	Additional description: Hypotension		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 29 (3.45%)	2 / 29 (6.90%)	
occurrences (all)	1	2	
Thrombophlebitis	Additional description: Thrombophlebitis		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 29 (0.00%)	2 / 29 (6.90%)	
occurrences (all)	0	2	
General disorders and administration site conditions			
Influenza like illness	Additional description: Influenza like illness		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 29 (0.00%)	2 / 29 (6.90%)	
occurrences (all)	0	2	
Chills	Additional description: Chills		
alternative assessment type: Non-systematic			
subjects affected / exposed	7 / 29 (24.14%)	7 / 29 (24.14%)	
occurrences (all)	7	8	
Fatigue	Additional description: Fatigue		
alternative assessment type: Non-systematic			
subjects affected / exposed	17 / 29 (58.62%)	14 / 29 (48.28%)	
occurrences (all)	35	29	
Pyrexia	Additional description: Pyrexia		
alternative assessment type: Non-systematic			
subjects affected / exposed	7 / 29 (24.14%)	5 / 29 (17.24%)	
occurrences (all)	8	8	
Pain	Additional description: Pain		

alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 29 (3.45%)	2 / 29 (6.90%)	
occurrences (all)	1	2	
Mucosal inflammation	Additional description: Mucosal inflammation		
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 29 (17.24%)	5 / 29 (17.24%)	
occurrences (all)	6	8	
Reproductive system and breast disorders			
Breast pain	Additional description: Breast pain		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 29 (3.45%)	2 / 29 (6.90%)	
occurrences (all)	1	2	
Vulvovaginal dryness	Additional description: Vulvovaginal dryness		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 29 (0.00%)	2 / 29 (6.90%)	
occurrences (all)	0	2	
Respiratory, thoracic and mediastinal disorders			
Cough	Additional description: Cough		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 29 (3.45%)	2 / 29 (6.90%)	
occurrences (all)	1	4	
Dyspnoea exertional	Additional description: Dyspnoea exertional		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 29 (6.90%)	0 / 29 (0.00%)	
occurrences (all)	2	0	
Epistaxis	Additional description: Epistaxis		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 29 (6.90%)	2 / 29 (6.90%)	
occurrences (all)	2	2	
Nasal dryness	Additional description: Nasal dryness		
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 29 (13.79%)	1 / 29 (3.45%)	
occurrences (all)	4	1	
Rhinorrhoea	Additional description: Rhinorrhoea		

alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 29 (3.45%)	2 / 29 (6.90%)	
occurrences (all)	1	2	
Psychiatric disorders			
Sleep disorder	Additional description: Sleep disorder		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 29 (0.00%)	3 / 29 (10.34%)	
occurrences (all)	0	3	
Injury, poisoning and procedural complications			
Infusion related reaction	Additional description: Infusion related reaction		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 29 (10.34%)	2 / 29 (6.90%)	
occurrences (all)	3	2	
Nervous system disorders			
Polyneuropathy	Additional description: Polyneuropathy		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 29 (6.90%)	3 / 29 (10.34%)	
occurrences (all)	2	5	
Paraesthesia	Additional description: Paraesthesia		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 29 (6.90%)	3 / 29 (10.34%)	
occurrences (all)	2	4	
Headache	Additional description: Headache		
alternative assessment type: Non-systematic			
subjects affected / exposed	8 / 29 (27.59%)	7 / 29 (24.14%)	
occurrences (all)	16	7	
Dysgeusia	Additional description: Dysgeusia		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 29 (3.45%)	3 / 29 (10.34%)	
occurrences (all)	1	4	
Ageusia	Additional description: Ageusia		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 29 (6.90%)	0 / 29 (0.00%)	
occurrences (all)	2	0	
Taste disorder	Additional description: Taste disorder		

alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 29 (10.34%)	2 / 29 (6.90%)	
occurrences (all)	5	3	
Blood and lymphatic system disorders			
Neutropenia	Additional description: Neutropenia		
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 29 (13.79%)	6 / 29 (20.69%)	
occurrences (all)	7	9	
Leukopenia	Additional description: Leukopenia		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 29 (3.45%)	3 / 29 (10.34%)	
occurrences (all)	1	3	
Anaemia	Additional description: Anaemia		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 29 (10.34%)	3 / 29 (10.34%)	
occurrences (all)	4	6	
Ear and labyrinth disorders			
Vertigo	Additional description: Vertigo		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 29 (3.45%)	3 / 29 (10.34%)	
occurrences (all)	4	10	
Eye disorders			
Visual impairment	Additional description: Visual impairment		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 29 (6.90%)	2 / 29 (6.90%)	
occurrences (all)	2	2	
Dry eye	Additional description: Dry eye		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 29 (10.34%)	1 / 29 (3.45%)	
occurrences (all)	4	1	
Gastrointestinal disorders			
Dyspepsia	Additional description: Dyspepsia		
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 29 (17.24%)	2 / 29 (6.90%)	
occurrences (all)	8	2	
Constipation	Additional description: Constipation		

alternative assessment type: Non-systematic			
subjects affected / exposed	8 / 29 (27.59%)	5 / 29 (17.24%)	
occurrences (all)	15	9	
Abnormal faeces	Additional description: Abnormal faeces		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 29 (6.90%)	0 / 29 (0.00%)	
occurrences (all)	2	0	
Abdominal pain upper	Additional description: Abdominal pain upper		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 29 (0.00%)	2 / 29 (6.90%)	
occurrences (all)	0	2	
Nausea	Additional description: Nausea		
alternative assessment type: Non-systematic			
subjects affected / exposed	20 / 29 (68.97%)	20 / 29 (68.97%)	
occurrences (all)	45	38	
Stomatitis	Additional description: Stomatitis		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 29 (10.34%)	2 / 29 (6.90%)	
occurrences (all)	4	2	
Vomiting	Additional description: Vomiting		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 29 (6.90%)	3 / 29 (10.34%)	
occurrences (all)	6	4	
Diarrhoea	Additional description: Diarrhoea		
alternative assessment type: Non-systematic			
subjects affected / exposed	18 / 29 (62.07%)	17 / 29 (58.62%)	
occurrences (all)	43	42	
Hepatobiliary disorders			
Hypertransaminasaemia	Additional description: Hypertransaminasaemia		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 29 (10.34%)	1 / 29 (3.45%)	
occurrences (all)	3	2	
Skin and subcutaneous tissue disorders			

Dry skin	Additional description: Dry skin		
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 29 (17.24%)	4 / 29 (13.79%)	
occurrences (all)	5	4	
Eczema	Additional description: Eczema		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 29 (10.34%)	0 / 29 (0.00%)	
occurrences (all)	5	0	
Intertrigo	Additional description: Intertrigo		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 29 (0.00%)	2 / 29 (6.90%)	
occurrences (all)	0	3	
Alopecia	Additional description: Alopecia		
alternative assessment type: Non-systematic			
subjects affected / exposed	8 / 29 (27.59%)	12 / 29 (41.38%)	
occurrences (all)	10	14	
Rash	Additional description: Rash		
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 29 (13.79%)	3 / 29 (10.34%)	
occurrences (all)	5	3	
Pruritus	Additional description: Pruritus		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 29 (3.45%)	3 / 29 (10.34%)	
occurrences (all)	2	3	
Nail disorder	Additional description: Nail disorder		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 29 (0.00%)	2 / 29 (6.90%)	
occurrences (all)	0	2	
Renal and urinary disorders			
Dysuria	Additional description: Dysuria		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 29 (0.00%)	2 / 29 (6.90%)	
occurrences (all)	0	2	
Endocrine disorders			

Immune-mediated hyperthyroidism	Additional description: Immune-mediated hyperthyroidism		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 29 (6.90%)	2 / 29 (6.90%)	
occurrences (all)	2	2	
Musculoskeletal and connective tissue disorders			
Arthralgia	Additional description: Arthralgia		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 29 (6.90%)	5 / 29 (17.24%)	
occurrences (all)	3	5	
Pain in extremity	Additional description: Pain in extremity		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 29 (6.90%)	1 / 29 (3.45%)	
occurrences (all)	3	1	
Myalgia	Additional description: Myalgia		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 29 (6.90%)	3 / 29 (10.34%)	
occurrences (all)	3	3	
Muscle spasms	Additional description: Muscle spasms		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 29 (6.90%)	1 / 29 (3.45%)	
occurrences (all)	2	1	
Back pain	Additional description: Back pain		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 29 (10.34%)	1 / 29 (3.45%)	
occurrences (all)	3	3	
Infections and infestations			
Urinary tract infection	Additional description: Urinary tract infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 29 (3.45%)	4 / 29 (13.79%)	
occurrences (all)	2	7	
Rhinitis	Additional description: Rhinitis		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 29 (6.90%)	2 / 29 (6.90%)	
occurrences (all)	2	2	
Respiratory tract infection	Additional description: Respiratory tract infection		

alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 29 (6.90%)	1 / 29 (3.45%)	
occurrences (all)	2	1	
Oral herpes	Additional description: Oral herpes		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 29 (0.00%)	2 / 29 (6.90%)	
occurrences (all)	0	3	
Nasopharyngitis	Additional description: Nasopharyngitis		
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 29 (17.24%)	1 / 29 (3.45%)	
occurrences (all)	5	1	
Candida infection	Additional description: Candida infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 29 (0.00%)	2 / 29 (6.90%)	
occurrences (all)	0	2	
Metabolism and nutrition disorders			
Decreased appetite	Additional description: Decreased appetite		
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 29 (13.79%)	6 / 29 (20.69%)	
occurrences (all)	6	7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported