



Clinical trial results:

DETECT V/CHEVENDO: A multicenter, randomized phase III study to compare chemo- versus endocrine therapy in combination with dual HER2-targeted therapy of Herceptin® (trastuzumab) and Perjeta® (pertuzumab) plus Kisqali® (ribociclib) in patients with HER2 positive and hormone-receptor positive metastatic breast cancer.

Summary

EudraCT number	2014-002249-22
Trial protocol	DE
Global end of trial date	29 November 2024

Results information

Result version number	v1 (current)
This version publication date	31 December 2025
First version publication date	31 December 2025

Trial information

Trial identification

Sponsor protocol code	DETECT-V/CHEVENDO
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02344472
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Universitätsklinikum Ulm
Sponsor organisation address	Albert-Einstein-Allee 29, Ulm, Germany, 89081
Public contact	Studienzentrale, Universitätsfrauenklinik Ulm, 0049 37150058520, studienzentrale.ufk@uniklinik-ulm.de
Scientific contact	Studienzentrale, Universitätsfrauenklinik Ulm, 0049 37150058520, studienzentrale.ufk@uniklinik-ulm.de

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 November 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 November 2024
Global end of trial reached?	Yes
Global end of trial date	29 November 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary objective (before amendment)

Assessment of safety of dual HER2-targeted ther. with Herceptin® (trastuzumab) and Perjeta® (pertuzumab) + endocrine ther. compared to dual HER2-targeted ther. with Herceptin® (trastuzumab) and Perjeta® (pertuzumab) + chemother. in patients with HER2-pos., hormone-receptor pos. metastatic breast cancer. Safety: Proportion of patients experiencing any AE (as defined by the modified AE score) during treatment period.

New primary objective

Assessment of tolerability of dual HER2-targeted ther. with Herceptin® and Perjeta® + Kisquali® and standard endocrine ther. compared to dual HER2-targeted ther. with Herceptin® and Perjeta® + chemother. (followed by endocrine therapy + ribociclib in combination with trastuzumab and pertuzumab as maintenance ther.) in patients with HER2-pos., hormone-receptor pos. metastatic breast cancer. Tolerability: Proportion of patients experiencing any AE as defined by the modified AE score during treatment period.

Protection of trial subjects:

Adequate drug supply of all IMPs for self-administration at home. IMP prescribed according to approved label with known side effect profil.

All therapies given in the study treatment period could be extended if medically indicated.

Adequate safety follow up for toxicity and efficacy. Safety and tolerability were assessed by evaluation of adverse events and serious adverse events (CTCAE) during course of trial and follow up.

Trial-related additional expenses (e.g. visits, blood samples) reduced to a minimum.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 September 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 262
Worldwide total number of subjects	262
EEA total number of subjects	262

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	161
From 65 to 84 years	98
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

FPI: 21.09.2015; LPO: 29.11.2024 in multiple centers in Germany

Pre-assignment

Screening details:

308 patients were screened in 61 study centers. 37 of the 308 patients did not meet all requirements for study inclusion and 271 patients from 58 study centers could be registered and randomized. The first patient was recruited on 21 September 2015, and the last patient was recruited on 30 November 2022.

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	Arm A: Chemotherapy

Arm description:

Study Design and Plan Protocol Version 1.1 03.06.2015:

Herceptin® + Perjeta® combined with mono-chemotherapy.

Patients enrolled after Amendment 1:

Herceptin® + Perjeta® combined with mono-chemotherapy, followed by maintenance therapy with Herceptin® and Perjeta® plus Kisqali® and endocrine therapy

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

Dosage and administration details:

Initial dosing: 840 mg Perjeta® as intravenous infusion over 60 minutes, d1; for subsequent infusions: 420 mg Perjeta® as intravenous infusion over 30-60 minutes, q3w.

Investigational medicinal product name	Herceptin®
Investigational medicinal product code	
Other name	Trastuzumab
Pharmaceutical forms	Powder and solvent for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Initial dosing: 8 mg/kg body weight Herceptin® as intravenous infusion over 60-90 minutes, d1; for subsequent infusions: 6 mg/kg body weight Herceptin® as intravenous infusion over 30 minutes, q3w.

Investigational medicinal product name	Kisqali®
Investigational medicinal product code	
Other name	Ribociclib
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Ribociclib capsules (3 x 200 mg) were taken orally per day (3-weeks-on/1-week-off schedule) in combination with standard endocrine therapy (as defined below).

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

Dosage and administration details:

75 mg/m² i.v. d1 q3w

Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Two chemotherapy regimens are available: 90 mg/m² i.v. d1, 8, 15 q4w or 80 mg/m² i.v. d1, 8, 15, 22 q4w; duration of the treatment with paclitaxel is at the discretion of the investigator, at least 4 months or until disease progression or unacceptable toxicity

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

Dosage and administration details:

2 x 1000 mg/m² p.o. d1-14 q3w; duration of the treatment with capecitabine is at the discretion of the investigator at least 4 months or until disease progression or unacceptable toxicity

Investigational medicinal product name	Vinorelbine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

30 mg/m² i.v. d1+d8 q3w; duration of the treatment with vinorelbine is at the discretion of the investigator (at least 4 months or until disease progression or unacceptable toxicity)

Investigational medicinal product name	Nab-Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

125 mg/m² d1, 8, 15 q4w; duration of the treatment with nab-paclitaxel is at the discretion of the investigator (at least 4 months or until disease progression or unacceptable toxicity)

Investigational medicinal product name	Eribulin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravascular use

Dosage and administration details:

1,23 mg/m² i.v. d1, 8 q3w; duration of the treatment with eribulin is at the discretion of the investigator (at least 4 months or until disease progression or unacceptable toxicity)

Arm title	Arm B: endocrine therapy
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Arm description:

Study Design and Plan Protocol Version 1.1 03.06.2015: Herceptin® + Perjeta® combined with endocrine therapy.

Patients enrolled after Amendment 1: Herceptin® + Perjeta® combined with endocrine therapy plus

Kisqali®	
Arm type	Experimental
Investigational medicinal product name	Perjeta®
Investigational medicinal product code	
Other name	Pertuzumab
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Initial dosing: 840 mg Perjeta® as intravenous infusion over 60 minutes, d1; for subsequent infusions: 420 mg Perjeta® as intravenous infusion over 30-60 minutes, q3w.	
Investigational medicinal product name	Herceptin®
Investigational medicinal product code	
Other name	Trastuzumab
Pharmaceutical forms	Powder and solvent for concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Initial dosing: 8 mg/kg body weight Herceptin® as intravenous infusion over 60-90 minutes, d1; for subsequent infusions: 6 mg/kg body weight Herceptin® as intravenous infusion over 30 minutes, q3w.	
Investigational medicinal product name	Kisqali®
Investigational medicinal product code	
Other name	Ribociclib
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use
Dosage and administration details:	
Ribociclib capsules (3 x 200 mg) were taken orally per day (3-weeks-on/1-week-off schedule) in combination with standard endocrine therapy (as defined below).	
Investigational medicinal product name	Exemestane
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
25 mg/d p.o.	
Investigational medicinal product name	Letrozole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
2,5 mg/d p.o.	
Investigational medicinal product name	Anastrozole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
1 mg/d p.o.	
Investigational medicinal product name	Fulvestrant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:	
500 mg i.m. d1+15+28, then 500 mg i.m. q28d	
Investigational medicinal product name	Leuprorelin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use
Dosage and administration details:	
3,75 mg 1 M Depot s.c. q4w, 11,25 mg 3 M Depot s.c.	
Investigational medicinal product name	Goserelin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use
Dosage and administration details:	
3,6 mg s.c. q4w	

Number of subjects in period 1	Arm A: Chemotherapy	Arm B: endocrine therapy
Started	130	132
Completed	130	132

Baseline characteristics

Reporting groups

Reporting group title	overall trial
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Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	262	262	
Age categorical			
Units: Subjects			
Adults (18-60 years)	134	134	
Adults (>60 years)	128	128	
Gender categorical			
Units: Subjects			
Female	262	262	
Male	0	0	

End points

End points reporting groups

Reporting group title	Arm A: Chemotherapy
Reporting group description:	
Study Design and Plan Protocol Version 1.1 03.06.2015: Herceptin® + Perjeta® combined with mono-chemotherapy.	
Patients enrolled after Amendment 1: Herceptin® + Perjeta® combined with mono-chemotherapy, followed by maintenance therapy with Herceptin® and Perjeta® plus Kisqali® and endocrine therapy	
Reporting group title	Arm B: endocrine therapy
Reporting group description:	
Study Design and Plan Protocol Version 1.1 03.06.2015: Herceptin® + Perjeta® combined with endocrine therapy.	
Patients enrolled after Amendment 1: Herceptin® + Perjeta® combined with endocrine therapy plus Kisqali®	

Primary: Tolerability and safety

End point title	Tolerability and safety
End point description:	
Tolerability is assessed by the proportion of patients experiencing any adverse event (as defined by the modified adverse event score) during the treatment period. The modified adverse event score includes all adverse events grade 3 or higher, except for neutropenia, which is only included if rated grade 4, and alopecia, rash, peripheral neuropathy and hand-foot syndrome, all of which are included if rated grade 2 or higher.	
End point type	Primary
End point timeframe:	
during treatment period	

End point values	Arm A: Chemotherapy	Arm B: endocrine therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	130	132		
Units: %				
number (not applicable)	52.3	76.9		

Statistical analyses

Statistical analysis title	Tolerability
Comparison groups	Arm A: Chemotherapy v Arm B: endocrine therapy

Number of subjects included in analysis	262
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Chi-squared

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Safety and tolerability were assessed by evaluation of adverse event (AE) and serious adverse event (SAE) reports using the international Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. The safety population comprised all randomized

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	7
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Reporting groups

Reporting group title	Chemotherapy-free
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Reporting group description: -	
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Reporting group title	Chemotherapy-containing
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Reporting group description: -	
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Serious adverse events	Chemotherapy-free	Chemotherapy-containing	
Total subjects affected by serious adverse events			
subjects affected / exposed	50 / 132 (37.88%)	48 / 130 (36.92%)	
number of deaths (all causes)	32	35	
number of deaths resulting from adverse events	10	9	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Brain neoplasm			
subjects affected / exposed	1 / 132 (0.76%)	0 / 130 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	3 / 132 (2.27%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Breast cancer metastatic			
subjects affected / exposed	1 / 132 (0.76%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Metastases to central nervous system			

subjects affected / exposed	1 / 132 (0.76%)	2 / 130 (1.54%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm progression			
subjects affected / exposed	1 / 132 (0.76%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Vascular disorders			
Embolism			
subjects affected / exposed	1 / 132 (0.76%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	2 / 132 (1.52%)	0 / 130 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Mastectomy			
subjects affected / exposed	0 / 132 (0.00%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chills			
subjects affected / exposed	1 / 132 (0.76%)	0 / 130 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	2 / 132 (1.52%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Fatigue			
subjects affected / exposed	1 / 132 (0.76%)	7 / 130 (5.38%)	
occurrences causally related to treatment / all	0 / 1	2 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	

General disorders and administration site conditions			
subjects affected / exposed	1 / 132 (0.76%)	4 / 130 (3.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Injection site reaction			
subjects affected / exposed	1 / 132 (0.76%)	0 / 130 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	2 / 132 (1.52%)	2 / 130 (1.54%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 132 (0.76%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	1 / 132 (0.76%)	0 / 130 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 132 (0.00%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	6 / 132 (4.55%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	2 / 10	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			

subjects affected / exposed	2 / 132 (1.52%)	0 / 130 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumomediastinum			
subjects affected / exposed	0 / 132 (0.00%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	2 / 132 (1.52%)	2 / 130 (1.54%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumothorax			
subjects affected / exposed	0 / 132 (0.00%)	2 / 130 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary fibrosis			
subjects affected / exposed	0 / 132 (0.00%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary hypertension			
subjects affected / exposed	1 / 132 (0.76%)	0 / 130 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Acute stress disorder			
subjects affected / exposed	0 / 132 (0.00%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			
subjects affected / exposed	1 / 132 (0.76%)	0 / 130 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			

Alanine aminotransferase increased subjects affected / exposed	1 / 132 (0.76%)	0 / 130 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram QT prolonged subjects affected / exposed	1 / 132 (0.76%)	0 / 130 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased subjects affected / exposed	1 / 132 (0.76%)	0 / 130 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fracture			
subjects affected / exposed	1 / 132 (0.76%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	1 / 132 (0.76%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	1 / 132 (0.76%)	0 / 130 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	0 / 132 (0.00%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 132 (0.00%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Atrial tachycardia			
subjects affected / exposed	1 / 132 (0.76%)	0 / 130 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular dysfunction			
subjects affected / exposed	1 / 132 (0.76%)	0 / 130 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	0 / 132 (0.00%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Ataxia			
subjects affected / exposed	0 / 132 (0.00%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischaemia			
subjects affected / exposed	1 / 132 (0.76%)	0 / 130 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 132 (0.76%)	0 / 130 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paresis			
subjects affected / exposed	0 / 132 (0.00%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 132 (0.76%)	0 / 130 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	3 / 132 (2.27%)	2 / 130 (1.54%)	
occurrences causally related to treatment / all	1 / 6	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	2 / 132 (1.52%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	2 / 132 (1.52%)	6 / 130 (4.62%)	
occurrences causally related to treatment / all	2 / 2	1 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 132 (0.76%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal pain			
subjects affected / exposed	1 / 132 (0.76%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 132 (0.00%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant gastrointestinal obstruction			
subjects affected / exposed	1 / 132 (0.76%)	0 / 130 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	2 / 132 (1.52%)	3 / 130 (2.31%)	
occurrences causally related to treatment / all	1 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Stomatitis			
subjects affected / exposed	0 / 132 (0.00%)	3 / 130 (2.31%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Vomiting			
subjects affected / exposed	1 / 132 (0.76%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 132 (0.00%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	1 / 132 (0.76%)	0 / 130 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatotoxicity			
subjects affected / exposed	1 / 132 (0.76%)	0 / 130 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Portal vein thrombosis			
subjects affected / exposed	1 / 132 (0.76%)	0 / 130 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 132 (0.76%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			

subjects affected / exposed	0 / 132 (0.00%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	1 / 132 (0.76%)	0 / 130 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Beta haemolytic streptococcal infection			
subjects affected / exposed	0 / 132 (0.00%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 132 (0.76%)	0 / 130 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis infective			
subjects affected / exposed	1 / 132 (0.76%)	0 / 130 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	1 / 132 (0.76%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 132 (0.76%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 132 (0.76%)	0 / 130 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			

subjects affected / exposed	2 / 132 (1.52%)	0 / 130 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis astroviral			
subjects affected / exposed	0 / 132 (0.00%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver abscess			
subjects affected / exposed	0 / 132 (0.00%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 132 (1.52%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Pseudomembranous colitis			
subjects affected / exposed	0 / 132 (0.00%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 132 (0.76%)	0 / 130 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Skin infection			
subjects affected / exposed	0 / 132 (0.00%)	2 / 130 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 132 (0.00%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	1 / 132 (0.76%)	0 / 130 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	1 / 132 (0.76%)	0 / 130 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	0 / 132 (0.00%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	3 / 132 (2.27%)	0 / 130 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatremia			
subjects affected / exposed	2 / 132 (1.52%)	0 / 130 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Chemotherapy-free	Chemotherapy-containing	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	129 / 132 (97.73%)	129 / 130 (99.23%)	
Investigations			
Neutrophil count decreased			
subjects affected / exposed	51 / 132 (38.64%)	29 / 130 (22.31%)	
occurrences (all)	70	53	
White blood cell decreased			
subjects affected / exposed	22 / 132 (16.67%)	24 / 130 (18.46%)	
occurrences (all)	38	50	
Alanine aminotransferase increased			

subjects affected / exposed occurrences (all)	19 / 132 (14.39%) 24	19 / 130 (14.62%) 35	
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	18 / 132 (13.64%) 22	16 / 130 (12.31%) 23	
GGT increased subjects affected / exposed occurrences (all)	11 / 132 (8.33%) 15	10 / 130 (7.69%) 13	
Vascular disorders			
Hypertension subjects affected / exposed occurrences (all)	16 / 132 (12.12%) 19	8 / 130 (6.15%) 18	
Hot flashes subjects affected / exposed occurrences (all)	16 / 132 (12.12%) 20	12 / 130 (9.23%) 12	
Nervous system disorders			
Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	15 / 132 (11.36%) 15	48 / 130 (36.92%) 51	
Headache subjects affected / exposed occurrences (all)	14 / 132 (10.61%) 21	12 / 130 (9.23%) 13	
General disorders and administration site conditions			
Fatigue subjects affected / exposed occurrences (all)	36 / 132 (27.27%) 43	54 / 130 (41.54%) 67	
General disorders and administration site conditions - Other, specify subjects affected / exposed occurrences (all)	9 / 132 (6.82%) 14	10 / 130 (7.69%) 11	
Blood and lymphatic system disorders			
Anemia subjects affected / exposed occurrences (all)	22 / 132 (16.67%) 35	23 / 130 (17.69%) 37	
Gastrointestinal disorders			

Diarrhea			
subjects affected / exposed	74 / 132 (56.06%)	85 / 130 (65.38%)	
occurrences (all)	101	145	
Nausea			
subjects affected / exposed	40 / 132 (30.30%)	49 / 130 (37.69%)	
occurrences (all)	51	60	
Mucositis oral			
subjects affected / exposed	14 / 132 (10.61%)	33 / 130 (25.38%)	
occurrences (all)	14	40	
Vomiting			
subjects affected / exposed	20 / 132 (15.15%)	16 / 130 (12.31%)	
occurrences (all)	23	19	
Respiratory, thoracic and mediastinal disorders			
Dyspnea			
subjects affected / exposed	15 / 132 (11.36%)	19 / 130 (14.62%)	
occurrences (all)	21	17	
Epistaxis			
subjects affected / exposed	17 / 132 (12.88%)	13 / 130 (10.00%)	
occurrences (all)	17	16	
Skin and subcutaneous tissue disorders			
Skin and subcutaneous tissue disorders			
subjects affected / exposed	23 / 132 (17.42%)	31 / 130 (23.85%)	
occurrences (all)	36	41	
Alopecia			
subjects affected / exposed	13 / 132 (9.85%)	38 / 130 (29.23%)	
occurrences (all)	15	38	
Dry skin			
subjects affected / exposed	13 / 132 (9.85%)	13 / 130 (10.00%)	
occurrences (all)	15	15	
Infections and infestations			
Infections and infestations - Other, specify			
subjects affected / exposed	15 / 132 (11.36%)	22 / 130 (16.92%)	
occurrences (all)	20	30	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 January 2019	<p>With amendment 1, patients enrolled after the amendment are in addition treated with the CDK4/6 inhibitor Kisqali® (ribociclib).</p> <p>With the addition of Kisqali, the project title was adapted, and the objectives were changed. The new objectives of the study are to assess safety and tolerability of a dual HER2-targeted therapy with Herceptin® and Perjeta® plus endocrine therapy and Kisqali® as compared to a dual HER2-targeted therapy with Herceptin® and Perjeta® plus chemotherapy followed by maintenance therapy with Herceptin® and Perjeta® plus endocrine therapy and Kisqali®.</p> <p>Moreover, tamoxifen was removed from the list of substances for endocrine therapy (due to a potential effect of ribociclib together with tamoxifen on QTcF prolongation), whereas the GnRH analogues leuporelin and goserelin were added for pre- and perimenopausal women. To the list of substances for chemotherapy, eribulin and nab®-paclitaxel were added.</p>
14 February 2020	<p>With Amendment no. 2, the study protocol was adapted with respect to the management of QTc prolongation under ribociclib treatment. Recommendations for dose reductions according to the current SmPC for ribociclib (Kisqali®) were added.</p>
16 August 2021	<p>With Amendment no. 3 (to protocol version 3.0 from 11 January 2021), recruitment was extended to November 2022 (LPI) and the limitation of 1st line patients to 60% was removed. Abraxane® (nab®-Paclitaxel) will be no longer provided as trial medication, thus Abraxane® chemotherapy option will be no longer available for participating patients. The synopsis was updated in Amendment 3 regarding the endocrine therapy of pre- and perimenopausal women since GnRH analogs leuporelin and goserelin were added as therapy option in combination with endocrine therapy. Tumor assessment according to RECIST during Follow Up is now recommended.</p> <p>The indications and safety aspects of the study medication Perjeta®, Kisqali®, Abraxane®, and Halaven® regarding the current IBs or SmPCs have been updated. Additionally, the study design regarding therapy options (switch between arms and discontinuation of ribociclib) and GnRH analogs were adjusted. A definition of interruption of therapy with Herceptin® and Perjeta® was applied to the protocol.</p>
28 March 2022	<p>With Amendment no. 4 (to protocol version 4.0 from 30 December 2021) the change of the Coordinating Investigator ('Leiter der klinischen Prüfung' according to §4 (25) German Drug Law) from Prof. Dr. Jens Huober to Dr. med. Fabienne Schochter, Department of Obstetrics and Gynecology University Hospital Ulm, Prittwitzstr.43, D-89075 Ulm, was issued.</p> <p>Furthermore, the protocol was adapted due to the stopped supply of eribulin (HALAVEN®) as study medication. Therefore, eribulin chemotherapy option was eliminated. Patients who were already under eribulin therapy received further therapy in accordance with the protocol. There was no change in safety-relevant risk for patients under eribulin therapy. The safety profile of study medication paclitaxel, anastrozole, capecitabine according to current reference safety information was updated. The reporting period of AEs/SAEs was defined. A note on the documentation of the proper intake of oral study medication and on weekly documentation of storage temperature of pertuzumab (Perjeta®) on temperature log was added.</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported