



Clinical trial results:

A multicenter phase II study in patients with HER2-negative metastatic breast cancer and persisting HER2-negative circulating tumor cells (CTCs).

Summary

EudraCT number	2013-001269-18
Trial protocol	DE
Global end of trial date	03 April 2024

Results information

Result version number	v1 (current)
This version publication date	24 December 2025
First version publication date	24 December 2025

Trial information

Trial identification

Sponsor protocol code	D-IVa/D-IVb
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02035813
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 73150058520, studienzentrale.ufk@uniklinik-ulm.de
Scientific contact	Studienzentrale, Universitätsfrauenklinik Ulm, 0049 73150058520, 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	10 January 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 January 2024
Global end of trial reached?	Yes
Global end of trial date	03 April 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Two independent cohorts:

Everolimus/Ribociclib cohort (DIVa)

The primary objective is to investigate the clinical efficacy of everolimus/ribociclib (as assessed by the CTC clearance rate) in combination with endocrine therapy in postmenopausal patients with hormone-receptor positive, HER2-negative metastatic breast cancer and persisting HER2-negative circulating tumor cells (CTCs).

Eribulin cohort (DIVb)

The primary objective is to investigate the clinical efficacy of eribulin (as assessed by progression-free survival, PFS) both in patients with HER2-negative, hormone-receptor positive metastatic breast cancer and indication to chemotherapy and triple-negative metastatic breast cancer both with persisting HER2-negative CTCs.

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. After treatment period the treatment with everolimus/ribociclib or eribulin can 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	12 February 2014
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	Germany: 225
Worldwide total number of subjects	225
EEA total number of subjects	225

Notes:

Subjects enrolled per age group

In utero	0
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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)	126
From 65 to 84 years	96
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

FPI (date of first enrolment): 12th Feb 2014; LPO: 10th January 2024 in multiple centers in Germany

Pre-assignment

Screening details:

Screening-Phase: N= 2000 metastatic breast cancer patients 1st-3rd line with HER2-negative primary tumor; CTC determination (Determination of HER2 status on CTCs); Inclusion criteria: indication for an endocrine therapy (ER+) and/or PgR+) and up to two lines of previous cytostatic treatment for mBC.

Period 1

Period 1 title	Intervention period (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	DETECT-IV a - Everolimus/Ribociclib cohort
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Everolimus
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Everolimus prescribed according to approved label. All patients receive everolimus + standard endocrine therapy and will take everolimus tablets orally per day and will also take standard endocrine therapy once daily

Investigational medicinal product name	Ribociclib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Ribociclib dosed for first 21 days out of 28 day cycle orally

Arm title	DETECT-IV b Eribulin
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Eribulin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Eribulin doses 1.23 mg/m² administered intravenously over 2-5 min on day 1, 8 of every 21 cycle.

Number of subjects in period 1	DETECT-IV a - Everolimus/Ribocicli b cohort	DETECT-IV b Eribulin
Started	116	109
Completed	116	109

Baseline characteristics

Reporting groups

Reporting group title	DETECT-IV a - Everolimus/Ribociclib cohort
Reporting group description: -	
Reporting group title	DETECT-IV b Eribulin
Reporting group description: -	

Reporting group values	DETECT-IV a - Everolimus/Ribociclib cohort	DETECT-IV b Eribulin	Total
Number of subjects	116	109	225
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)	58	68	126
From 65-84 years	55	41	96
85 years and over	3	0	3
Gender categorical Units: Subjects			
Female	116	109	225
Male	0	0	0

End points

End points reporting groups

Reporting group title	DETECT-IV a - Everolimus/Ribociclib cohort
Reporting group description: -	
Reporting group title	DETECT-IV b Eribulin
Reporting group description: -	

Primary: CTC-clearance rate

End point title	CTC-clearance rate ^{[1][2]}
End point description:	Proportion of patients with at least one CTC detected in 7.5 ml of peripheral blood drawn before treatment that show no evidence of CTCs in the blood after treatment.
End point type	Primary
End point timeframe:	siehe protocol definition - CTC clearance at end of intervention

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 study DETECT IV comprised two single (independent) cohorts (IVa and IVb), which are analysed separately and are not compared. The primary objective of the DETECT IV trial is to estimate treatment efficacy in patients. Treatment efficacy will be assessed by the CTC clearance rate for patients recruited in DETECT IVa and by PFS for patients recruited in DETECT IVb.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The study DETECT IV comprised two single (independent) cohorts (IVa and IVb), which are analysed separately and are not compared. The primary objective of the DETECT IV trial is to estimate treatment efficacy in patients. Treatment efficacy will be assessed by the CTC clearance rate for patients recruited in DETECT IVa and by PFS for patients recruited in DETECT IVb.

End point values	DETECT-IV a - Everolimus/Ribociclib cohort			
Subject group type	Reporting group			
Number of subjects analysed	46 ^[3]			
Units: Number of patients	21			

Notes:

[3] - Samples from 46 patients were available for this endpoint analysis.

Statistical analyses

No statistical analyses for this end point

Primary: Progression free survival

End point title	Progression free survival ^{[4][5]}
End point description:	PFS is defined as the time interval between the date of recruitment and the date of PD or death from any cause, whichever comes first.
End point type	Primary
End point timeframe:	defined in protocol

Notes:

[4] - 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 study DETECT IV comprised two single (independent) cohorts (IVa and IVb), which are analysed separately and are not compared. The primary objective of the DETECT IV trial is to estimate treatment efficacy in patients. Treatment efficacy will be assessed by the CTC clearance rate for patients recruited in DETECT IVa and by PFS for patients recruited in DETECT IVb.

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The study DETECT IV comprised two single (independent) cohorts (IVa and IVb), which are analysed separately and are not compared. The primary objective of the DETECT IV trial is to estimate treatment efficacy in patients. Treatment efficacy will be assessed by the CTC clearance rate for patients recruited in DETECT IVa and by PFS for patients recruited in DETECT IVb.

End point values	DETECT-IV b Eribulin			
Subject group type	Reporting group			
Number of subjects analysed	109			
Units: month				
median (confidence interval 95%)	4.6 (3.3 to 6.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival OS

End point title	Overall survival OS
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End point description:

End point type	Secondary
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End point timeframe:

according to protocol

End point values	DETECT-IV a - Everolimus/Rib ociclib cohort	DETECT-IV b Eribulin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	116	109		
Units: month				
median (confidence interval 95%)	24.1 (18.4 to 29.9)	13.4 (10.7 to 16.1)		

Statistical analyses

Statistical analysis title	Overall survival OS
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Statistical analysis description:

Overall survival (OS), defined as the time interval from start of treatment until death due to any cause. If a patient is not known to have died, survival is censored at the date of last contact

Comparison groups	DETECT-IV b Eribulin v DETECT-IV a - Everolimus/Ribociclib cohort
Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	other ^[6]
Parameter estimate	Median OS
Point estimate	13.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	10.7
upper limit	16.1

Notes:

[6] - Secondary objective, no comparison (single cohort), descriptive statistics only

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 randomize

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	7

Reporting groups

Reporting group title	D-IVa
Reporting group description: -	
Reporting group title	D-IV b
Reporting group description: -	

Serious adverse events	D-IVa	D-IV b	
Total subjects affected by serious adverse events			
subjects affected / exposed	66 / 108 (61.11%)	71 / 108 (65.74%)	
number of deaths (all causes)	74	89	
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to bone			
subjects affected / exposed	1 / 108 (0.93%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to central nervous system			
subjects affected / exposed	2 / 108 (1.85%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm progression			
subjects affected / exposed	1 / 108 (0.93%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Metastase to liver			

subjects affected / exposed	1 / 108 (0.93%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Malignant neoplasm progression			
subjects affected / exposed	1 / 108 (0.93%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metastases to meninges			
subjects affected / exposed	0 / 108 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vascular disorders			
Embolism			
subjects affected / exposed	0 / 108 (0.00%)	2 / 108 (1.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 108 (0.93%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	1 / 108 (0.93%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	1 / 108 (0.93%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	2 / 108 (1.85%)	2 / 108 (1.85%)	
occurrences causally related to treatment / all	1 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

General physical health deterioration			
subjects affected / exposed	3 / 108 (2.78%)	5 / 108 (4.63%)	
occurrences causally related to treatment / all	1 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 3	
Death			
subjects affected / exposed	0 / 108 (0.00%)	5 / 108 (4.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 5	
Pain			
subjects affected / exposed	0 / 108 (0.00%)	2 / 108 (1.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Immune system disorders			
Allergy to arthropod sting			
subjects affected / exposed	0 / 108 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Adnexa uteri cyst			
subjects affected / exposed	1 / 108 (0.93%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast inflammation			
subjects affected / exposed	0 / 108 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	5 / 108 (4.63%)	5 / 108 (4.63%)	
occurrences causally related to treatment / all	2 / 5	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haemoptysis			

subjects affected / exposed	1 / 108 (0.93%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pleural effusion			
subjects affected / exposed	2 / 108 (1.85%)	5 / 108 (4.63%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonitis			
subjects affected / exposed	1 / 108 (0.93%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 108 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 108 (0.93%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endoscopic retrograde cholangiopancreatography			
subjects affected / exposed	1 / 108 (0.93%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	1 / 108 (0.93%)	0 / 108 (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			
Lumbar vertebral fracture			

subjects affected / exposed	1 / 108 (0.93%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	0 / 108 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haemorrhage			
subjects affected / exposed	0 / 108 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 108 (0.93%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	0 / 108 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident	Additional description: Stroke		
subjects affected / exposed	1 / 108 (0.93%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorder			
subjects affected / exposed	1 / 108 (0.93%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Intracranial mass			
subjects affected / exposed	1 / 108 (0.93%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			

subjects affected / exposed	0 / 108 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	0 / 108 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Seizure			
subjects affected / exposed	0 / 108 (0.00%)	2 / 108 (1.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 108 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervus system disorder			
subjects affected / exposed	1 / 108 (0.93%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 108 (0.93%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	1 / 108 (0.93%)	4 / 108 (3.70%)	
occurrences causally related to treatment / all	1 / 1	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 108 (0.93%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			

Diplopia			
subjects affected / exposed	0 / 108 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	1 / 108 (0.93%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 108 (0.93%)	0 / 108 (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 / 108 (1.85%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	1 / 108 (0.93%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 108 (1.85%)	2 / 108 (1.85%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper*			
subjects affected / exposed	1 / 108 (0.93%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 108 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal pain			

subjects affected / exposed	0 / 108 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	0 / 108 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	0 / 108 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal obstruction			
subjects affected / exposed	0 / 108 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 108 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecalith			
subjects affected / exposed	0 / 108 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 108 (0.93%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	1 / 108 (0.93%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Renal and urinary disorders			

Akute kidney injury	subjects affected / exposed	3 / 108 (2.78%)	0 / 108 (0.00%)	
	occurrences causally related to treatment / all	0 / 4	0 / 0	
	deaths causally related to treatment / all	0 / 0	0 / 0	
Prerenal failure	subjects affected / exposed	1 / 108 (0.93%)	0 / 108 (0.00%)	
	occurrences causally related to treatment / all	0 / 1	0 / 0	
	deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction	subjects affected / exposed	0 / 108 (0.00%)	1 / 108 (0.93%)	
	occurrences causally related to treatment / all	0 / 0	0 / 1	
	deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders				
Bone pain	subjects affected / exposed	2 / 108 (1.85%)	2 / 108 (1.85%)	
	occurrences causally related to treatment / all	0 / 2	0 / 2	
	deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis	subjects affected / exposed	1 / 108 (0.93%)	0 / 108 (0.00%)	
	occurrences causally related to treatment / all	0 / 1	0 / 0	
	deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity	subjects affected / exposed	2 / 108 (1.85%)	0 / 108 (0.00%)	
	occurrences causally related to treatment / all	0 / 2	0 / 0	
	deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations				
Bronchitis	subjects affected / exposed	1 / 108 (0.93%)	0 / 108 (0.00%)	
	occurrences causally related to treatment / all	1 / 1	0 / 0	
	deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis	subjects affected / exposed	1 / 108 (0.93%)	1 / 108 (0.93%)	
	occurrences causally related to treatment / all	0 / 1	1 / 1	
	deaths causally related to treatment / all	0 / 0	0 / 0	

Infection			
subjects affected / exposed	1 / 108 (0.93%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 108 (0.93%)	2 / 108 (1.85%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	1 / 1	0 / 0	
Device related infection	Additional description: port infection		
subjects affected / exposed	1 / 108 (0.93%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 108 (0.93%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Helicobacter gastritis			
subjects affected / exposed	0 / 108 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	0 / 108 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningoencephalitis viral (Epstein-Barr virus associated)			
subjects affected / exposed	0 / 108 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	1 / 108 (0.93%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Electrolyte imbalance			
subjects affected / exposed	0 / 108 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 108 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	D-IVa	D-IV b	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	105 / 108 (97.22%)	106 / 108 (98.15%)	
Investigations			
Neutrophil count decreased			
subjects affected / exposed	18 / 108 (16.67%)	32 / 108 (29.63%)	
occurrences (all)	37	112	
White blood cell decreased			
subjects affected / exposed	26 / 108 (24.07%)	25 / 108 (23.15%)	
occurrences (all)	58	55	
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	28 / 108 (25.93%)	28 / 108 (25.93%)	
occurrences (all)	43	89	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	27 / 108 (25.00%)	59 / 108 (54.63%)	
occurrences (all)	35	82	
Gastrointestinal disorders			
Mucositis oral			
subjects affected / exposed	45 / 108 (41.67%)	18 / 108 (16.67%)	
occurrences (all)	77	23	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 February 2015	Version 2.0 vom 31.03.2014 Aufnahme von Eribulin
25 July 2016	Version 3.0 vom 15.02.2016 "Amendment 2: 1. Neuer primärer Endpunkt: CTC Clearance-Rate 2. Erhöhung der Vergütung (Everolimus Arm) 3. Mögliche Startdosis für Everolimus mit 5mg / Tag"
10 August 2018	Version 4.1 vom 18.12.2017 (nicht ausgehändigt, zusammen mit Amendment 4) "Amendment 3: 1. Aufnahme des CDK4/6 Inhibitors Ribociclib 2. Fulvestrant als mögliche endokrine Therapieoption"
10 August 2018	Version 5.0 vom 12.03.2018 "Amendment 4: Streichung von Tamoxifen in Kombination mit Ribociclib"

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported