# 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 |

### 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 additianl 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 |

| | |
|---|---|
| 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 reveive 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/Ribociclib 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<br>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<br>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 |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

according to protocol

| **End point values** | DETECT-IV a - Everolimus/Ribociclib 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 |
|---|---|

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 |

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

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported