



Clinical trial results:

Phase IB/II clinical trial of copanlisib in combination with trastuzumab in pretreated recurrent or metastatic HER2-positive breast cancer

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2015-003687-36 |
| Trial protocol | IE |
| Global end of trial date | 06 May 2022 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 25 April 2026 |
| First version publication date | 25 April 2026 |

Trial information

Trial identification

| | |
|-----------------------|----------------------|
| Sponsor protocol code | CTRIAL 15-02 (ICORG) |
|-----------------------|----------------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02705859 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Cancer Trials Ireland CLG |
| Sponsor organisation address | RCSI House, Dublin 01, Ireland, |
| Public contact | Ausra Teiserskiene, Cancer Trials Ireland CLG, +353 16677211, info@cancertrials.ie |
| Scientific contact | Prof Bryan Hennessy, Cancer Trials Ireland CLG, +353 16677211, info@cancertrials.ie |

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 | 09 April 2024 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 06 May 2022 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Phase Ib

1. To determine the Maximum Tolerated Dose (MTD), for copanlisib in combination with trastuzumab in patients with histologically confirmed HER2-positive breast cancer that are metastatic or incurable recurrent, following disease progression during, or after, treatment with at least one systemic treatment regimen in the metastatic or recurrent setting.

Phase II

1. To evaluate the anti-tumour efficacy of copanlisib in combination with trastuzumab in terms of Clinical Benefit Rate (CBR) in patients with PIK3CA wild type and mutated, histologically confirmed HER2-positive breast cancer that are metastatic or incurable recurrent, following disease progression during, or after, treatment with at least one systemic treatment regimen in the metastatic or recurrent setting (Phase II plus patients with PIK3CA wild type and mutated HER2-positive breast cancer treated at MTD in Phase Ib).

Protection of trial subjects:

Timely, accurate and complete reporting and analysis of safety information from clinical studies are crucial for the protection of patients and are mandated by regulatory agencies worldwide.

Background therapy: -

Evidence for comparator: -

| | |
|---|----------------|
| Actual start date of recruitment | 10 August 2016 |
| 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 | Ireland: 26 |
| Worldwide total number of subjects | 26 |
| EEA total number of subjects | 26 |

Notes:

Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 | 0 |

| | |
|---------------------------|----|
| months) | |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 24 |
| From 65 to 84 years | 2 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Participants will be patients of the study doctor and his/her medical team and approached about the study in clinic.

Pre-assignment

Screening details:

Potential patients will be screened and enrolled on the study on the basis of the Inclusion/Exclusion criteria specified in the protocol. Before registration, each potential patient must be given a patient information leaflet (PIL) and informed consent must be obtained from a patient according to the requirements of ICH GCP.

Period 1

| | |
|------------------------------|-----------------------------|
| Period 1 title | Phase Ib/II |
| Is this the baseline period? | Yes |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|-------|
| Are arms mutually exclusive? | Yes |
| Arm title | Arm 1 |

Arm description: -

| | |
|--|-----------------|
| Arm type | Experimental |
| Investigational medicinal product name | Copanlisib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

IV weekly for the first 3 weeks (on days 1, 8, 15) of a 28-day cycle 45 mg flat dosing

| | |
|--|-----------------|
| Investigational medicinal product name | Trastuzumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Trastuzumab IV weekly (4 mg/kg on Cycle 1 Day 1 followed by 2 mg/kg IV weekly from Day 8).

| | |
|------------------|-------|
| Arm title | Arm 2 |
|------------------|-------|

Arm description: -

| | |
|--|-----------------|
| Arm type | Experimental |
| Investigational medicinal product name | Copanlisib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

IV weekly for the first 3 weeks (on days 1, 8, 15) of a 28-day cycle 60 mg flat dosing

| | |
|--|-------------|
| Investigational medicinal product name | Trastuzumab |
| Investigational medicinal product code | |
| Other name | |

| | |
|--------------------------|-----------------|
| Pharmaceutical forms | Injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Trastuzumab IV weekly (4 mg/kg on Cycle 1 Day 1 followed by 2 mg/kg IV weekly from Day 8).

| Number of subjects in period 1 | Arm 1 | Arm 2 |
|--------------------------------|-------|-------|
| Started | 6 | 20 |
| Completed | 6 | 20 |

| Period 2 | |
|------------------------------|-------------------|
| Period 2 title | Full Analysis Set |
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|-----------|-------|
| Arm title | Arm 2 |
|-----------|-------|

Arm description:

The Full Analysis Set includes the 6 patients from Phase Ib treated at the MTD, and 13 of 14 enrolled patients from Phase II. The one Phase II patient excluded from the FAS had a toxicity reaction of hyperglycemia related to copanlisib treatment during Cycle 1. This patient was withdrawn from the study prior to post-baseline disease response assessment.

| | |
|--|-----------------|
| Arm type | Experimental |
| Investigational medicinal product name | Copanlisib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

IV weekly for the first 3 weeks (on days 1, 8, 15) of a 28-day cycle 60 mg flat dosing

| | |
|--|-----------------|
| Investigational medicinal product name | Trastuzumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Trastuzumab IV weekly (4 mg/kg on Cycle 1 Day 1 followed by 2 mg/kg IV weekly from Day 8).

| Number of subjects in period 2 ^[1] | Arm 2 |
|--|-------|
| | |
| Started | 19 |
| Completed | 19 |

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: The efficacy analyses were performed on the Full Analysis Set (FAS), which is defined as all patients who were given a starting copanlisib dose of 60 mg and either had at least one post-baseline response assessment or exhibited disease progression or died prior to their first scheduled post-baseline radiologic tumor response assessment.

The Full Analysis Set includes the 6 patients from Phase Ib treated at the MTD, and 13 of 14 enrolled patients from Phase II. The one Phase II patient excluded

Baseline characteristics

Reporting groups

| | |
|-----------------------|-------------|
| Reporting group title | Phase Ib/II |
|-----------------------|-------------|

Reporting group description: -

| Reporting group values | Phase Ib/II | Total | |
|---|---------------|-------|--|
| Number of subjects | 26 | 26 | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 24 | 24 | |
| From 65-84 years | 2 | 2 | |
| 85 years and over | 0 | 0 | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 52.23 | | |
| full range (min-max) | 40 to 79 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 26 | 26 | |
| Male | 0 | 0 | |
| Ethnic Group | | | |
| Units: Subjects | | | |
| Hispanic or Latino | | 0 | |
| Not Hispanic or Latino | 25 | 25 | |
| Not Reported | 1 | 1 | |
| Primary Tumor Location | | | |
| Units: Subjects | | | |
| Breast | 26 | 26 | |
| Primary Tumor Laterality | | | |
| Units: Subjects | | | |
| Left | 16 | 16 | |
| Right | 10 | 10 | |
| Height at Screening | | | |
| Units: centimetre | | | |
| arithmetic mean | 165.4 | | |
| full range (min-max) | 153.1 to 181 | - | |
| Weight at Screening | | | |
| Units: kilogram(s) | | | |
| arithmetic mean | 73.9 | | |
| full range (min-max) | 43.1 to 106.3 | - | |

| | | | |
|--|------------------------|---|--|
| Duration of Initial Diagnosis to Registration Units: day arithmetic mean full range (min-max) | 2225.04 315 to 5200 | - | |
| Duration from Most Recent Progression to Registration Units: day arithmetic mean full range (min-max) | 84.85 7 to 996 | - | |
| Duration from First Recurrence to Registration Units: day arithmetic mean full range (min-max) | 1314.5 312 to 4197 | - | |

Subject analysis sets

| | |
|----------------------------|-------------------|
| Subject analysis set title | Phase IB/II 60 mg |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

This subject analysis set includes all patients who received at least one dose of copanlisib 60 mg.

| | |
|----------------------------|-----------------|
| Subject analysis set title | Phase IB 45mg |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

This subject analysis set includes all patients who received at least one dose of copanlisib 45 mg.

| Reporting group values | Phase IB/II 60 mg | Phase IB 45mg | |
|---|-------------------|----------------|--|
| Number of subjects | 20 | 6 | |
| Age categorical Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 24 | 5 | |
| From 65-84 years | 2 | 1 | |
| 85 years and over | 0 | 0 | |
| Age continuous Units: years arithmetic mean full range (min-max) | 51.2 40 to 79 | 53 50 to 72 | |
| Gender categorical Units: Subjects | | | |
| Female | 20 | 6 | |
| Male | 0 | 0 | |
| Ethnic Group Units: Subjects | | | |
| Hispanic or Latino | 0 | | |

| | | | |
|---|----------------|---------------|--|
| Not Hispanic or Latino | 19 | 6 | |
| Not Reported | 1 | | |
| Primary Tumor Location | | | |
| Units: Subjects | | | |
| Breast | 20 | 6 | |
| Primary Tumor Laterality | | | |
| Units: Subjects | | | |
| Left | 12 | 4 | |
| Right | 8 | 2 | |
| Height at Screening | | | |
| Units: centimetre | | | |
| arithmetic mean | 165.55 | 164.92 | |
| full range (min-max) | 153.1 to 181.0 | 159 to 178 | |
| Weight at Screening | | | |
| Units: kilogram(s) | | | |
| arithmetic mean | 70.92 | 83.83 | |
| full range (min-max) | 43.1 to 101.1 | 57.1 to 106.3 | |
| Duration of Initial Diagnosis to Registration | | | |
| Units: day | | | |
| arithmetic mean | 2153.5 | 2463.5 | |
| full range (min-max) | 315 to 3571 | 593 to 5200 | |
| Duration from Most Recent Progression to Registration | | | |
| Units: day | | | |
| arithmetic mean | 93.9 | 54.7 | |
| full range (min-max) | 7 to 996 | 29 to 105 | |
| Duration from First Recurrence to Registration | | | |
| Units: day | | | |
| arithmetic mean | 1195.4 | 1711.5 | |
| full range (min-max) | 312 to 2757 | 574 to 4197 | |

End points

End points reporting groups

| | |
|---|-------------------|
| Reporting group title | Arm 1 |
| Reporting group description: - | |
| Reporting group title | Arm 2 |
| Reporting group description: - | |
| Reporting group title | Arm 2 |
| Reporting group description: | |
| The Full Analysis Set includes the 6 patients from Phase Ib treated at the MTD, and 13 of 14 enrolled patients from Phase II. The one Phase II patient excluded from the FAS had a toxicity reaction of hyperglycemia related to copanlisib treatment during Cycle 1. This patient was withdrawn from the study prior to post-baseline disease response assessment. | |
| Subject analysis set title | Phase IB/II 60 mg |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: | |
| This subject analysis set includes all patients who received at least one dose of copanlisib 60 mg. | |
| Subject analysis set title | Phase IB 45mg |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: | |
| This subject analysis set includes all patients who received at least one dose of copanlisib 45 mg. | |

Primary: Summary of Clinical Benefit

| | |
|--|--|
| End point title | Summary of Clinical Benefit ^[1] |
| End point description: | |
| The primary endpoint of Phase II was the anti-tumor efficacy analysis in terms of CBR. A target CBR of 65% was set based on the efficacy of existing treatments. Analysis of the CBR was performed on the FAS, which is defined as all patients who were given a starting copanlisib dose of 60 mg and either had at least one post-baseline response assessment or exhibited disease progression or died prior to their first scheduled post-baseline radiologic tumor response assessment. | |
| End point type | Primary |
| End point timeframe: | |
| CBR for this study was defined as CR or PR at any time during the study or SD lasting at least 24 weeks. In the analysis, SD lasting at least 24 weeks was defined as 168 or more between registration and the patient's first reported disease progression | |

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 CBR of 36.8% shown in this trial of copanlisib plus trastuzumab is marginally better than the 30% that was considered the lowest acceptable CBR for this trial due to a 34% CBR having been shown in Phase II-III trials for fellow PI3K inhibitor RAD001 plus trastuzumab in a similar population. The CBR of 36.8%, however, does not approach the conservative goal set for this trial of 65%. Since the two-sided 90% CI of (21.4%, 55.6%) around the CBR contains the null hypothesis of 30%, the statistic

| End point values | Arm 2 | | | |
|------------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 19 | | | |
| Units: Subject | | | | |
| Clinical Benefit Rate | 7 | | | |
| CR at any timepoint | 0 | | | |
| PR at any timepoint | 4 | | | |
| SD lasting at least 24 weeks | 5 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

| | |
|-----------------|------------------|
| End point title | Overall Survival |
|-----------------|------------------|

End point description:

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

End point timeframe:

overall survival time, which is defined as the time from registration to death from any cause.

| End point values | Arm 2 | | | |
|-------------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 19 | | | |
| Units: Subjects | | | | |
| Number of Patients with Event | 12 | | | |
| Number of Patients Censored | 7 | | | |
| Median Time to Event (days) | 450 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival Rate (95% CI)

| | |
|-----------------|--------------------------------|
| End point title | Overall Survival Rate (95% CI) |
|-----------------|--------------------------------|

End point description:

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

End point timeframe:

overall survival time, which is defined as the time from registration to death from any cause.

| End point values | Arm 2 | | | |
|-------------------------------|---------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 19 | | | |
| Units: days | | | | |
| median (full range (min-max)) | | | | |
| 1 Year (365 Days) | 56.1 (31.1 to 75.2) | | | |
| 2 Years (730 Days) | 37.4 (15.6 to 59.4) | | | |
| 3 Years (1095 Days) | 28.1 (8.5 to 52) | | | |
| 4 Years (1461 Days) | 28.1 (8.5 to 52) | | | |
| End of Study (1675 Days) | 28.1 (8.5 to 52) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival

| | |
|---|---------------------------|
| End point title | Progression Free Survival |
| End point description: | |
| To be consistent with the definition of stable disease lasting at least 24 weeks in the CBR analysis, termination of treatment or study follow-up reportedly due to progression is considered to be a progression event for the PFS analysis, even in the absence of a corresponding confirmatory radiologic assessment. In the absence of progression or death, patients were censored at the date of their last radiologic tumor assessment | |
| End point type | Secondary |
| End point timeframe: | |
| PFS is defined as the time from study registration to disease progression or death from any cause | |

| End point values | Arm 2 | | | |
|-------------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 19 | | | |
| Units: Subjects | | | | |
| Number of Patients with Event | 18 | | | |
| Number of Patients Censored | 1 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival Rate (95% CI)

| | |
|-----------------|---|
| End point title | Progression Free Survival Rate (95% CI) |
|-----------------|---|

End point description:

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

End point timeframe:

PFS is defined as the time from study registration to disease progression or death from any cause

| End point values | Arm 2 | | | |
|--------------------------------------|-----------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 19 | | | |
| Units: days | | | | |
| median (full range (min-max)) | | | | |
| Median Time to Event (days) (95% CI) | 113.0 (57.0 to 168.0) | | | |
| 6 Months (182 Days) | 22.6 (7.0 to 43.4) | | | |
| End of Study (295 Days) | 0 (0 to 0) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Treatment Failure

| | |
|-----------------|---------------------------|
| End point title | Time to Treatment Failure |
|-----------------|---------------------------|

End point description:

To be consistent with the PFS analysis, termination of treatment or study follow-up reportedly due to progression is considered to be a treatment failure event for the TTF analysis, even in the absence of a corresponding confirmatory radiologic assessment. In the absence of a treatment failure event, patients were censored at the date of their last radiologic tumor assessment.

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

End point timeframe:

Time from registration to the discontinuation of therapy for any reason (including death, progression, and toxicity) or add-on of any new anti-cancer therapy

| End point values | Arm 2 | | | |
|-------------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 19 | | | |
| Units: Subjects | | | | |
| Number of Patients with Event | 19 | | | |
| Number of Patients Censored | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Treatment Failure Rate (95% CI)

| | |
|-----------------|---|
| End point title | Time to Treatment Failure Rate (95% CI) |
|-----------------|---|

End point description:

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

End point timeframe:

Time from registration to the discontinuation of therapy for any reason (including death, progression, and toxicity), or add-on of any new anti cancer therapy

| End point values | Arm 2 | | | |
|--------------------------------------|-----------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 19 | | | |
| Units: days | | | | |
| median (full range (min-max)) | | | | |
| Median Time to Event (days) (95% CI) | 113.0 (51.0 to 168.0) | | | |
| 6 Months (182 Days) | 78.9 (59.0 to 93.4) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response

| | |
|-----------------|----------------------|
| End point title | Duration of Response |
|-----------------|----------------------|

End point description:

Of the 4 patients who achieved a partial response, the response duration ranged from 35 days to 115 days, with a median of 106 days.

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

End point timeframe:

Duration of response is calculated as the number of days from the first CR or PR to disease progression or death.

| End point values | Arm 2 | | | |
|-------------------------------|-------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 4 | | | |
| Units: days | | | | |
| median (full range (min-max)) | | | | |
| Median | 106.0 (35 to 115) | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment Emergent Adverse Events, those that occur same date or after administration of the first study dose.

Adverse event reporting additional description:

AE additional description

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 23.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--------------------------------|
| Reporting group title | Phase IB/II - 60 mg Copanlisib |
|-----------------------|--------------------------------|

Reporting group description: -

| | |
|-----------------------|-----------------------------|
| Reporting group title | Phase IB - 45 mg Copanlisib |
|-----------------------|-----------------------------|

Reporting group description: -

| Serious adverse events | Phase IB/II - 60 mg Copanlisib | Phase IB - 45 mg Copanlisib | |
|---|---|-----------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 8 / 20 (40.00%) | 5 / 6 (83.33%) | |
| number of deaths (all causes) | 12 | 5 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Lymphangiosis carcinomatosa | Additional description: Lymphangiosis carcinomatosa | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 6 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Infusion related reaction | Additional description: Infusion related reaction | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 6 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hip fracture | Additional description: Hip fracture | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 6 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |

| | | | |
|--|---|-----------------|----------------|
| Headache | Additional description: Headache | | |
| | subjects affected / exposed | 1 / 20 (5.00%) | 0 / 6 (0.00%) |
| | occurrences causally related to treatment / all | 1 / 1 | 0 / 0 |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Seizure | Additional description: Seizure | | |
| | subjects affected / exposed | 0 / 20 (0.00%) | 1 / 6 (16.67%) |
| | 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 | | | |
| | Additional description: Pain | | |
| | subjects affected / exposed | 1 / 20 (5.00%) | 0 / 6 (0.00%) |
| | occurrences causally related to treatment / all | 0 / 1 | 0 / 0 |
| Eye disorders | | | |
| | Additional description: Photophobia | | |
| | subjects affected / exposed | 1 / 20 (5.00%) | 0 / 6 (0.00%) |
| | occurrences causally related to treatment / all | 1 / 1 | 0 / 0 |
| Gastrointestinal disorders | | | |
| | Additional description: Abdominal pain | | |
| | subjects affected / exposed | 0 / 20 (0.00%) | 1 / 6 (16.67%) |
| | occurrences causally related to treatment / all | 0 / 0 | 1 / 1 |
| Nausea | | | |
| | Additional description: Nausea | | |
| | subjects affected / exposed | 1 / 20 (5.00%) | 0 / 6 (0.00%) |
| | occurrences causally related to treatment / all | 0 / 1 | 0 / 0 |
| Vomiting | | | |
| | Additional description: Vomiting | | |
| | subjects affected / exposed | 2 / 20 (10.00%) | 0 / 6 (0.00%) |
| | occurrences causally related to treatment / all | 1 / 2 | 0 / 0 |
| Hepatobiliary disorders | | | |
| | Additional description: Biliary obstruction | | |

| | | | |
|---|--|----------------|--|
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 6 (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 | | | |
| Dyspnoea | Additional description: Dyspnoea | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 6 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 1 / 6 (16.67%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Infection | Additional description: Infection | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 1 / 6 (16.67%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 6 (16.67%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 2 / 6 (33.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Hyperglycaemia | Additional description: Hyperglycaemia | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 6 (0.00%) | |
| occurrences causally related to treatment / all | 4 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 0 %

| Non-serious adverse events | Phase IB/II - 60 mg Copanlisib | Phase IB - 45 mg Copanlisib | |
|---|---|-----------------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 20 / 20 (100.00%) | 6 / 6 (100.00%) | |
| Vascular disorders | | | |
| Hot flush | Additional description: Hot flush | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 6 (16.67%) | |
| occurrences (all) | 0 | 1 | |
| Hypertension | Additional description: Hypertension | | |
| subjects affected / exposed | 5 / 20 (25.00%) | 5 / 6 (83.33%) | |
| occurrences (all) | 22 | 35 | |
| White coat hypertension | Additional description: White coat hypertension | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 6 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Surgical and medical procedures | | | |
| Nail operation | Additional description: Nail operation | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 6 (16.67%) | |
| occurrences (all) | 0 | 1 | |
| General disorders and administration site conditions | | | |
| Axillary pain | Additional description: Axillary pain | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 6 (16.67%) | |
| occurrences (all) | 0 | 1 | |
| Chest pain | Additional description: Chest pain | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 1 / 6 (16.67%) | |
| occurrences (all) | 1 | 1 | |
| Fatigue | Additional description: Fatigue | | |
| subjects affected / exposed | 8 / 20 (40.00%) | 4 / 6 (66.67%) | |
| occurrences (all) | 15 | 9 | |
| Generalised oedema | Additional description: Generalised oedema | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 6 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Infusion site extravasation | Additional description: Infusion site extravasation | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 6 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Infusion site pain | Additional description: Infusion site pain | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 6 (0.00%) | |
| occurrences (all) | 1 | 0 | |

| | | |
|--|--|---------------------|
| Medical device site pain subjects affected / exposed occurrences (all) | Additional description: Medical device site pain | |
| | 1 / 20 (5.00%) 1 | 0 / 6 (0.00%) 0 |
| Mucosal inflammation subjects affected / exposed occurrences (all) | Additional description: Mucosal inflammation | |
| | 4 / 20 (20.00%) 7 | 1 / 6 (16.67%) 4 |
| Oedema peripheral subjects affected / exposed occurrences (all) | Additional description: Oedema peripheral | |
| | 1 / 20 (5.00%) 3 | 1 / 6 (16.67%) 1 |
| Pain subjects affected / exposed occurrences (all) | Additional description: Pain | |
| | 1 / 20 (5.00%) 2 | 0 / 6 (0.00%) 0 |
| Peripheral swelling subjects affected / exposed occurrences (all) | Additional description: Peripheral swelling | |
| | 2 / 20 (10.00%) 5 | 0 / 6 (0.00%) 0 |
| Pyrexia subjects affected / exposed occurrences (all) | Additional description: Pyrexia | |
| | 3 / 20 (15.00%) 4 | 3 / 6 (50.00%) 6 |
| Reproductive system and breast disorders Breast pain subjects affected / exposed occurrences (all) | Additional description: Breast pain | |
| | 3 / 20 (15.00%) 3 | 3 / 6 (50.00%) 3 |
| Respiratory, thoracic and mediastinal disorders Dysphonia subjects affected / exposed occurrences (all) | Additional description: Dysphonia | |
| | 0 / 20 (0.00%) 0 | 1 / 6 (16.67%) 2 |
| Dyspnoea subjects affected / exposed occurrences (all) | Additional description: Dyspnoea | |
| | 3 / 20 (15.00%) 6 | 1 / 6 (16.67%) 2 |
| Cough subjects affected / exposed occurrences (all) | Additional description: Cough | |
| | 3 / 20 (15.00%) 5 | 3 / 6 (50.00%) 3 |
| Laryngeal inflammation subjects affected / exposed occurrences (all) | Additional description: Laryngeal inflammation | |
| | 1 / 20 (5.00%) 1 | 0 / 6 (0.00%) 0 |
| Nasal congestion | Additional description: Nasal congestion | |

| | | | |
|-----------------------------|---|----------------|--|
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 6 (16.67%) | |
| occurrences (all) | 0 | 1 | |
| Nasal discomfort | Additional description: Nasal discomfort | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 6 (16.67%) | |
| occurrences (all) | 0 | 1 | |
| Productive cough | Additional description: Productive cough | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 6 (16.67%) | |
| occurrences (all) | 0 | 1 | |
| Pleural effusion | Additional description: Pleural effusion | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 1 / 6 (16.67%) | |
| occurrences (all) | 1 | 2 | |
| Pulmonary embolism | Additional description: Pulmonary embolism | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 6 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Respiratory symptom | Additional description: Respiratory symptom | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 6 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Rhinorrhoea | Additional description: Rhinorrhoea | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 6 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Wheezing | Additional description: Wheezing | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 6 (16.67%) | |
| occurrences (all) | 0 | 1 | |
| Psychiatric disorders | | | |
| Anxiety | Additional description: Anxiety | | |
| subjects affected / exposed | 3 / 20 (15.00%) | 0 / 6 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Agitation | Additional description: Agitation | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 6 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Confusional state | Additional description: Confusional state | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 6 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Insomnia | Additional description: Insomnia | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 1 / 6 (16.67%) | |
| occurrences (all) | 1 | 1 | |

| | | | |
|--------------------------------------|--|----------------|--|
| Investigations | | | |
| Aspartate aminotransferase increased | Additional description: Aspartate aminotransferase increased | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 6 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Alanine aminotransferase increased | Additional description: Alanine aminotransferase increased | | |
| subjects affected / exposed | 2 / 20 (10.00%) | 0 / 6 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Blood creatinine increased | Additional description: Blood creatinine increased | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 6 (16.67%) | |
| occurrences (all) | 0 | 2 | |
| Blood bilirubin increased | Additional description: Blood bilirubin increased | | |
| subjects affected / exposed | 2 / 20 (10.00%) | 0 / 6 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Blood alkaline phosphatase increased | Additional description: Blood alkaline phosphatase increased | | |
| subjects affected / exposed | 2 / 20 (10.00%) | 0 / 6 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Blood pressure increased | Additional description: Blood pressure increased | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 6 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Blood glucose increased | Additional description: Blood glucose increased | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 6 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Gamma-glutamyltransferase increased | Additional description: Gamma-glutamyltransferase increased | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 6 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Haemoglobin decreased | Additional description: Haemoglobin decreased | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 6 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Neutrophil count decreased | Additional description: Neutrophil count decreased | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 6 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Platelet count decreased | Additional description: Platelet count decreased | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 6 (16.67%) | |
| occurrences (all) | 0 | 1 | |
| Weight decreased | Additional description: Weight decreased | | |

| | | | |
|--|---|----------------|--|
| subjects affected / exposed | 2 / 20 (10.00%) | 3 / 6 (50.00%) | |
| occurrences (all) | 2 | 4 | |
| Troponin increased | Additional description: Troponin increased | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 6 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Injury, poisoning and procedural complications | | | |
| Fall | Additional description: Fall | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 6 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Tooth fracture | Additional description: Tooth fracture | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 6 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Cardiac disorders | | | |
| Tachycardia | Additional description: Tachycardia | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 6 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Nervous system disorders | | | |
| Headache | Additional description: Headache | | |
| subjects affected / exposed | 4 / 20 (20.00%) | 1 / 6 (16.67%) | |
| occurrences (all) | 7 | 6 | |
| Migraine | Additional description: Migraine | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 6 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Paraesthesia | Additional description: Paraesthesia | | |
| subjects affected / exposed | 2 / 20 (10.00%) | 1 / 6 (16.67%) | |
| occurrences (all) | 12 | 2 | |
| Paralysis recurrent laryngeal nerve | Additional description: Paralysis recurrent laryngeal nerve | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 6 (16.67%) | |
| occurrences (all) | 0 | 1 | |
| Peripheral sensory neuropathy | Additional description: Peripheral sensory neuropathy | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 6 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Peripheral motor neuropathy | Additional description: Peripheral motor neuropathy | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 6 (16.67%) | |
| occurrences (all) | 0 | 1 | |
| Spinal cord compression | Additional description: Spinal cord compression | | |

| | | | |
|--|--|---------------------|--|
| subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 0 / 6 (0.00%) 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | Additional description: Anaemia | | |
| subjects affected / exposed occurrences (all) | 4 / 20 (20.00%) 8 | 1 / 6 (16.67%) 1 | |
| Neutropenia | Additional description: Neutropenia | | |
| subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 1 / 6 (16.67%) 1 | |
| Thrombocytopenia | Additional description: Thrombocytopenia | | |
| subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 1 / 6 (16.67%) 1 | |
| Eye disorders | | | |
| Dry eye | Additional description: Dry eye | | |
| subjects affected / exposed occurrences (all) | 2 / 20 (10.00%) 3 | 1 / 6 (16.67%) 1 | |
| Gastrointestinal disorders | | | |
| Abdominal discomfort | Additional description: Abdominal discomfort | | |
| subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 1 / 6 (16.67%) 1 | |
| Abdominal pain | Additional description: Abdominal pain | | |
| subjects affected / exposed occurrences (all) | 2 / 20 (10.00%) 3 | 1 / 6 (16.67%) 1 | |
| Diarrhoea | Additional description: Diarrhoea | | |
| subjects affected / exposed occurrences (all) | 8 / 20 (40.00%) 35 | 3 / 6 (50.00%) 8 | |
| Dry mouth | Additional description: Dry mouth | | |
| subjects affected / exposed occurrences (all) | 3 / 20 (15.00%) 4 | 0 / 6 (0.00%) 0 | |
| Dyspepsia | Additional description: Dyspepsia | | |
| subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 0 / 6 (0.00%) 0 | |
| Constipation | Additional description: Constipation | | |
| subjects affected / exposed occurrences (all) | 6 / 20 (30.00%) 15 | 3 / 6 (50.00%) 5 | |
| Colitis | Additional description: Colitis | | |

| | | | |
|--|--|----------------|--|
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 6 (16.67%) | |
| occurrences (all) | 0 | 1 | |
| Chapped lips | Additional description: Chapped lips | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 6 (16.67%) | |
| occurrences (all) | 0 | 1 | |
| Gastrooesophageal reflux disease | Additional description: Gastrooesophageal reflux disease | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 6 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Haemorrhoids | Additional description: Haemorrhoids | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 6 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Lip pain | Additional description: Lip pain | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 6 (16.67%) | |
| occurrences (all) | 0 | 1 | |
| Nausea | Additional description: Nausea | | |
| subjects affected / exposed | 11 / 20 (55.00%) | 3 / 6 (50.00%) | |
| occurrences (all) | 23 | 21 | |
| Oral mucosal blistering | Additional description: Oral mucosal blistering | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 6 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Oral disorder | Additional description: Oral disorder | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 1 / 6 (16.67%) | |
| occurrences (all) | 1 | 1 | |
| Paraesthesia oral | Additional description: Paraesthesia oral | | |
| subjects affected / exposed | 2 / 20 (10.00%) | 0 / 6 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Vomiting | Additional description: Vomiting | | |
| subjects affected / exposed | 8 / 20 (40.00%) | 4 / 6 (66.67%) | |
| occurrences (all) | 13 | 7 | |
| Stomatitis | Additional description: Stomatitis | | |
| subjects affected / exposed | 5 / 20 (25.00%) | 3 / 6 (50.00%) | |
| occurrences (all) | 14 | 8 | |
| Skin and subcutaneous tissue disorders | | | |
| Blood blister | Additional description: Blood blister | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 6 (16.67%) | |
| occurrences (all) | 0 | 1 | |

| | | |
|--|--|---------------------|
| Dry skin subjects affected / exposed occurrences (all) | Additional description: Dry skin | |
| | 3 / 20 (15.00%) 4 | 3 / 6 (50.00%) 5 |
| Dermatitis acneiform subjects affected / exposed occurrences (all) | Additional description: Dermatitis acneiform | |
| | 2 / 20 (10.00%) 4 | 2 / 6 (33.33%) 3 |
| Nail disorder subjects affected / exposed occurrences (all) | Additional description: Nail disorder | |
| | 1 / 20 (5.00%) 1 | 0 / 6 (0.00%) 0 |
| Pruritus subjects affected / exposed occurrences (all) | Additional description: Pruritus | |
| | 3 / 20 (15.00%) 3 | 0 / 6 (0.00%) 0 |
| Rash subjects affected / exposed occurrences (all) | Additional description: Rash | |
| | 7 / 20 (35.00%) 9 | 2 / 6 (33.33%) 3 |
| Rash erythematous subjects affected / exposed occurrences (all) | Additional description: Rash erythematous | |
| | 0 / 20 (0.00%) 0 | 1 / 6 (16.67%) 1 |
| Rash pruritic subjects affected / exposed occurrences (all) | Additional description: Rash pruritic | |
| | 1 / 20 (5.00%) 2 | 0 / 6 (0.00%) 0 |
| Scar pain subjects affected / exposed occurrences (all) | Additional description: Scar pain | |
| | 1 / 20 (5.00%) 1 | 0 / 6 (0.00%) 0 |
| Skin lesion subjects affected / exposed occurrences (all) | Additional description: Skin lesion | |
| | 0 / 20 (0.00%) 0 | 1 / 6 (16.67%) 1 |
| Rash maculo-papular subjects affected / exposed occurrences (all) | Additional description: Rash maculo-papular | |
| | 1 / 20 (5.00%) 3 | 2 / 6 (33.33%) 5 |
| Renal and urinary disorders Dysuria subjects affected / exposed occurrences (all) | Additional description: Dysuria | |
| | 1 / 20 (5.00%) 1 | 0 / 6 (0.00%) 0 |
| Haematuria | Additional description: Haematuria | |
| | | |

| | | | |
|---|--|----------------|--|
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 6 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Nocturia | Additional description: Nocturia | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 6 (16.67%) | |
| occurrences (all) | 0 | 1 | |
| Pollakiuria | Additional description: Pollakiuria | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 6 (16.67%) | |
| occurrences (all) | 0 | 1 | |
| Proteinuria | Additional description: Proteinuria | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 6 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | Additional description: Arthralgia | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 2 / 6 (33.33%) | |
| occurrences (all) | 0 | 2 | |
| Back pain | Additional description: Back pain | | |
| subjects affected / exposed | 2 / 20 (10.00%) | 2 / 6 (33.33%) | |
| occurrences (all) | 3 | 3 | |
| Flank pain | Additional description: Flank pain | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 6 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Muscle spasms | Additional description: Muscle spasms | | |
| subjects affected / exposed | 2 / 20 (10.00%) | 0 / 6 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Musculoskeletal chest pain | Additional description: Musculoskeletal chest pain | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 2 / 6 (33.33%) | |
| occurrences (all) | 1 | 2 | |
| Myalgia | Additional description: Myalgia | | |
| subjects affected / exposed | 3 / 20 (15.00%) | 0 / 6 (0.00%) | |
| occurrences (all) | 8 | 0 | |
| Neck pain | Additional description: Neck pain | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 1 / 6 (16.67%) | |
| occurrences (all) | 1 | 1 | |
| Pain in extremity | Additional description: Pain in extremity | | |

| | | | |
|--|---|---------------------|--|
| subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 1 / 6 (16.67%) 1 | |
| Infections and infestations | | | |
| Bronchitis | Additional description: Bronchitis | | |
| subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 0 / 6 (0.00%) 0 | |
| Cellulitis | Additional description: Cellulitis | | |
| subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 1 / 6 (16.67%) 1 | |
| Herpes simplex | Additional description: Herpes simplex | | |
| subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 0 / 6 (0.00%) 0 | |
| Infection | Additional description: Infection | | |
| subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 0 / 6 (0.00%) 0 | |
| Localised infection | Additional description: Localised infection | | |
| subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 1 / 6 (16.67%) 3 | |
| Lower respiratory tract infection | Additional description: Lower respiratory tract infection | | |
| subjects affected / exposed occurrences (all) | 2 / 20 (10.00%) 2 | 0 / 6 (0.00%) 0 | |
| Mastitis | Additional description: Mastitis | | |
| subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 2 / 6 (33.33%) 4 | |
| Mucosal infection | Additional description: Mucosal infection | | |
| subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 2 / 6 (33.33%) 2 | |
| Nail infection | Additional description: Nail infection | | |
| subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 1 / 6 (16.67%) 1 | |
| Nasopharyngitis | Additional description: Nasopharyngitis | | |
| subjects affected / exposed occurrences (all) | 2 / 20 (10.00%) 2 | 1 / 6 (16.67%) 1 | |
| Oral herpes | Additional description: Oral herpes | | |
| subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 0 / 6 (0.00%) 0 | |

| | | |
|------------------------------------|---|----------------|
| Paronychia | Additional description: Paronychia | |
| | 1 / 20 (5.00%) | 0 / 6 (0.00%) |
| subjects affected / exposed | 3 | 0 |
| occurrences (all) | | |
| Pneumonia | Additional description: Pneumonia | |
| | 0 / 20 (0.00%) | 3 / 6 (50.00%) |
| subjects affected / exposed | 0 | 5 |
| occurrences (all) | | |
| Skin infection | Additional description: Skin infection | |
| | 0 / 20 (0.00%) | 1 / 6 (16.67%) |
| subjects affected / exposed | 0 | 1 |
| occurrences (all) | | |
| Urinary tract infection | Additional description: Urinary tract infection | |
| | 2 / 20 (10.00%) | 2 / 6 (33.33%) |
| subjects affected / exposed | 2 | 4 |
| occurrences (all) | | |
| Vulvovaginal candidiasis | Additional description: Vulvovaginal candidiasis | |
| | 1 / 20 (5.00%) | 0 / 6 (0.00%) |
| subjects affected / exposed | 1 | 0 |
| occurrences (all) | | |
| Upper respiratory tract infection | Additional description: Upper respiratory tract infection | |
| | 0 / 20 (0.00%) | 1 / 6 (16.67%) |
| subjects affected / exposed | 0 | 1 |
| occurrences (all) | | |
| Metabolism and nutrition disorders | | |
| | | |
| Dehydration | Additional description: Dehydration | |
| | 1 / 20 (5.00%) | 2 / 6 (33.33%) |
| subjects affected / exposed | 2 | 2 |
| occurrences (all) | | |
| Decreased appetite | Additional description: Decreased appetite | |
| | 4 / 20 (20.00%) | 3 / 6 (50.00%) |
| subjects affected / exposed | 5 | 3 |
| occurrences (all) | | |
| Hypercalcaemia | Additional description: Hypercalcaemia | |
| | 0 / 20 (0.00%) | 1 / 6 (16.67%) |
| subjects affected / exposed | 0 | 1 |
| occurrences (all) | | |
| Hyperglycaemia | Additional description: Hyperglycaemia | |
| | 4 / 20 (20.00%) | 4 / 6 (66.67%) |
| subjects affected / exposed | 7 | 24 |
| occurrences (all) | | |
| Hypertriglyceridaemia | Additional description: Hypertriglyceridaemia | |
| | 1 / 20 (5.00%) | 0 / 6 (0.00%) |
| subjects affected / exposed | 1 | 0 |
| occurrences (all) | | |
| Hypoalbuminaemia | Additional description: Hypoalbuminaemia | |
| | | |

| | | | |
|-----------------------------|---|----------------|--|
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 6 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hypocalcaemia | Additional description: Hypocalcaemia | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 1 / 6 (16.67%) | |
| occurrences (all) | 2 | 2 | |
| Hypokalaemia | Additional description: Hypokalaemia | | |
| subjects affected / exposed | 2 / 20 (10.00%) | 2 / 6 (33.33%) | |
| occurrences (all) | 2 | 3 | |
| Hypophosphataemia | Additional description: Hypophosphataemia | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 6 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Iron deficiency | Additional description: Iron deficiency | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 6 (16.67%) | |
| occurrences (all) | 0 | 1 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 09 February 2016 | ICORG 15-02 Panther study Protocol Version 4 01February 2016 BAY 80-6946 (Copanlisib) Investigator's Brochure Amendment, Version 7.0 dated 23APR2015 CORRECTED Global Amendment 2.0 22DEC2015 Updated reconstruction instructions for the vials with the new fill volume as outlined in the corrected IB addendum |
| 27 June 2016 | ICORG 15-02 PanTHER Study Protocol Version 5 05 May 2016 ICORG Phase I Committee Charter Version 1/05-May-2016 |
| 13 February 2017 | Updates to several sections of the protocol to Protocol v6.0 (13Jan2017). The Investigator's Brochure (IB) was amended in response to questions received from the United Kingdom and Belgian Health Authorities. |
| 21 March 2018 | The protocol was amended to Protocol v7 (24Jan2018) in line with the recent completion of study Phase Ib and planned commencement of study Phase II. Updates have occurred to several sections of the protocol. The Investigator's Brochure (IB) v10.0 10 AUG 2017 Amendment Number: 1.0 04 JAN 2018 was amended in response to a request from a Health Authority regarding the expectedness table in Reference Safety Information (RSI) and following the recently published European Union (EU) Clinical Trial Facilitation Group (CTFG) guidance on RSI (published in NOV 2017). The expectedness Table 8-1 in the RSI section has been revised based on Serious Adverse Reactions (SARs) considered expected for safety reporting purposes. No new SARs have been added as compared to the RSI in IB v10.0. Additionally, the previous Table 8-1 reflecting the overall safety profile of copanlisib has been moved to Section 9.6 Undesirable Effects in the Core Safety Information (CSI). No changes to the protocol or Patient Information Leaflet are required. The benefit/risk profile of the study remains unchanged. |
| 31 October 2019 | This substantial amendment to Protocol v 8 (21Jun2019) included an amendment to inclusion criteria: PKI3CA mutation have been removed from the inclusion criteria and patients will be enrolled regardless of their PIK3CA mutation status. The rationale is based on the results of the Phase Ib part of PanTHER suggesting that PIK3CA mutation status did not impact on the likelihood of clinical benefit from Copanlisib/Trastuzumab and additional studies that have already been published. |

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| 09 September 2020 | <p>This substantial amendment to Protocol v9 (27Aug2020) concerns the following key change:</p> <ul style="list-style-type: none"> - At the time of the PanHER study protocol submission for Clinical Trial Application, Herceptin® (Roche Registration GmbH) was the only brand of trastuzumab approved by the European Medicines Agency. After the patent on Herceptin® expired in Europe in July 2014 this has led to biosimilars of trastuzumab being developed. Currently there are five trastuzumab biosimilars approved in Ireland. Due to the high cost of Herceptin® during the last year, Irish hospitals have been switching to trastuzumab biosimilars to reduce the cost of the cancer patient treatment. Limiting PanHER study patient treatment only to Herceptin® has a significant impact to study accrual and the cost for sites who are treating study patients. As such, the PanHER study protocol has been updated to allow other trastuzumab biosimilars to be used for study patients and give sites more flexibility for patient treatment. |
| 31 January 2022 | <p>All patients have finished protocol treatment and continue on the trial in the follow-up phase. The trial protocol has been amended to reduce the long-term follow-up for these patients. According to the amended protocol v10 (21Oct2021), it is planned that survival follow-up will be continued until death or until a maximum of one year after last patient last treatment visit, whichever occurs first. The last patient last treatment visit occurred in February 2021 and long-term follow-up will be completed by February 2022.</p> <p>Due to the small patient sample size, any estimates for overall survival are exploratory. Currently from 26 patients registered on study, 19 patients are now off study. Following up for more than one year is unlikely to provide much more definitive information for the trial.</p> |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported