



## Clinical trial results:

### Phase 2 Study of the Safety, Efficacy, and Pharmacokinetics of G1T28 in Patients with Metastatic Triple Negative Breast Cancer Receiving Gemcitabine and Carboplatin Chemotherapy

#### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2016-004466-26   |
| Trial protocol           | BE SI HR BG      |
| Global end of trial date | 28 February 2020 |

#### Results information

|                                   |   |
|-----------------------------------|---|
| Result version number             | v1 (current)  |
| This version publication date     | 01 April 2021   |
| First version publication date    | 01 April 2021   |
| Summary attachment (see zip file) | G1T28-04 Clinical Study Report Addendum_Final_15 Dec 2020 (G1T28-04 Clinical Study Report Addendum_Final_15 Dec 2020_published.pdf) |

#### Trial information

##### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | G1T28-04 |
|-----------------------|----------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02978716 |
| WHO universal trial number (UTN)   | -           |

Notes:

##### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | G1 Therapeutics, Inc  |
| Sponsor organisation address | 700 Park Offices Drive, Suite 200, Research Triangle Park, NC, United States, 27709       |
| Public contact               | Clinical Trial Info, G1 Therapeutics, Inc, +1 9192139835, clinicalinfo@g1therapeutics.com |
| Scientific contact           | Clinical Trial Info, G1 Therapeutics, Inc, +1 9192139835, clinicalinfo@g1therapeutics.com |

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 December 2020 |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 28 June 2019     |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 28 February 2020 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

Assess the safety and tolerability of trilaciclib administered with GC (gemcitabine and carboplatin) therapy

Protection of trial subjects:

This study was conducted in full conformance with the ethical principles of the Declaration of Helsinki (as amended in Tokyo, Venice, Hong Kong, and South Africa) or with the laws and regulations of the country in which the research was conducted, whichever afforded the greater protection to the individual. A Data Safety Monitoring Committee (DMC) reviewed safety of trilaciclib for all participants enrolled. DMC monitored accumulating safety and disposition data approximately every 4 months. The committee consisted of individuals with extensive multicenter clinical study experience drawn from the fields of clinical oncology (specifically, TNBC) and biostatistics. These individuals were entirely independent of the conduct of the study.

Background therapy:

Gemcitabine and Carboplatin (GC) were administered IV in accordance with their respective prescribing information.

Subjects received Gemcitabine 1000 mg/m<sup>2</sup> and Carboplatin area under the curve (AUC) = 2 administered IV on Days 1 and 8 (Groups 1 and 2) or on Days 2 and 9 (Group 3) of each 21-day cycle.

On chemotherapy dosing days, trilaciclib was always administered first, followed by GC.

GC could be administered immediately following trilaciclib but not until the completion of the trilaciclib infusion. Trilaciclib was only administered with GC therapy. If administration of GC therapy was discontinued, administration of trilaciclib was also discontinued

Evidence for comparator: -

|   |                             |
|---|-----------------------------|
| Actual start date of recruitment                          | 02 February 2017            |
| Long term follow-up planned                               | Yes                         |
| Long term follow-up rationale                             | Safety, Scientific research |
| Long term follow-up duration                              | 2 Months                    |
| Independent data monitoring committee (IDMC) involvement? | Yes                         |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Belgium: 1         |
| Country: Number of subjects enrolled | Croatia: 5         |
| Country: Number of subjects enrolled | Bulgaria: 1        |
| Country: Number of subjects enrolled | United States: 113 |
| Country: Number of subjects enrolled | Serbia: 14         |
| Country: Number of subjects enrolled | North Macedonia: 8 |

|                                    |     |
|------------------------------------|-----|
| Worldwide total number of subjects | 142 |
| EEA total number of subjects       | 7   |

Notes:

| <b>Subjects enrolled per age group</b>    |     |
|---|-----|
| 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)                      | 105 |
| From 65 to 84 years                       | 36  |
| 85 years and over                         | 1   |

## Subject disposition

### Recruitment

Recruitment details:

Subjects were enrolled at 27 sites in the US, and 7 sites in Europe (out of total 35 sites in the US and 15 sites in Europe that participated in the trial). The first subject enrolled on 02 February 2017, and the last participant completed on 28 February 2020. Subjects were enrolled from 02 February 2017 to 10 May 2018.

### Pre-assignment

Screening details:

Subjects were screened within 28 days before the first dose of the treatment. Informed consent was obtained up to 28 days prior to first study drug administration. For tumor assessment, all sites of disease were assessed radiologically at screening.

40 enrolled subjects failed to meet randomization criteria, hence 102 subjects were randomized

### Period 1

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

Blinding implementation details:

Open label study.

### Arms

|                              |                           |
|------------------------------|---------------------------|
| Are arms mutually exclusive? | Yes                       |
| <b>Arm title</b>             | Group 1 (G/C Day 1 and 8) |

Arm description:

Subjects receiving standard Gemcitabine and Carboplatin therapy (Days 1 and 8 of 21-day cycles) only. Gemcitabine 1000 mg/m<sup>2</sup> and carboplatin AUC 2 administered IV.

Study drug administration was continued until disease progression, unacceptable toxicity, withdrawal of consent, or discontinuation by the investigator, whichever occurred first.

|  |                                  |
|--|----------------------------------|
| Arm type                               | Active comparator                |
| Investigational medicinal product name | Gemcitabine                      |
| Investigational medicinal product code |                                  |
| Other name                             |                                  |
| Pharmaceutical forms                   | Powder for solution for infusion |
| Routes of administration               | Intravenous use                  |

Dosage and administration details:

The dose used for gemcitabine was 1000 mg/m<sup>2</sup>. This dose represents the standard-of-care dose used to treat patients with triple negative breast cancer. This drug was commercially available and administered according to the products respective prescribing information.

|  |                       |
|--|-----------------------|
| Investigational medicinal product name | Carboplatin           |
| Investigational medicinal product code |                       |
| Other name                             |                       |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

Dosage and administration details:

The carboplatin dose was to be calculated using the Calvert formula, with a target AUC 2 (maximum of 300 mg). These doses represent the standard-of-care doses used to treat participants with TNBC. This product was commercially available and administered according to respective prescribing information.

The Calvert formula was calculated as follows:

• Total carboplatin dose (mg) = (target AUC) × (glomerular filtration rate [GFR] + 25)

Because each patient's estimated GFR was based on serum creatinine measurements, the dose of

carboplatin was capped at 300 mg to avoid potential toxicity due to overdosing. The cap dose of 300 mg for carboplatin was based on a GFR estimate that was capped at 125 mL/min for patients with normal renal function (ie, maximum carboplatin dose = target AUC of 2 mg•min/mL × 150 mL/min = 300 mg).

|                  |   |
|------------------|---|
| <b>Arm title</b> | Group 2 (Trilaciclib Day 1 and 8 and G/C Day 1 and 8) |
|------------------|---|

**Arm description:**

Subjects receiving Trilaciclib administered IV on Days 1 and 8 of 21-day cycles , plus Gemcitabine and Carboplatin therapy (Days 1 and 8 of 21-day cycles).

Gemcitabine 1000 mg/m<sup>2</sup> and carboplatin AUC 2 (maximum 300 mg) administered IV.

In Group 2, trilaciclib (240 mg/m<sup>2</sup>) was administered as an IV infusion over 30 (±5) minutes prior to each GC treatment (on Days 1 and 8).

There were no inpatient dose modifications of trilaciclib during the study.

Trilaciclib was administered only with GC therapy. If administration of all chemotherapy was held or discontinued, administration of trilaciclib was also to be held or discontinued.

Chemotherapy could not be administered until after completion of the trilaciclib infusion.

Study drug administration was continued until disease progression, unacceptable toxicity, withdrawal of consent, or discontinuation by the investigator, whichever occurred first.

|  |  |
|--|--|
| Arm type                               | Experimental                                     |
| Investigational medicinal product name | Trilaciclib                                      |
| Investigational medicinal product code | G1T28  |
| Other name                             |  |
| Pharmaceutical forms                   | Powder for concentrate for solution for infusion |
| Routes of administration               | Intravenous use                                  |

**Dosage and administration details:**

Trilaciclib (G1T28) Sterile Powder for Infusion was supplied as a sterile powder with 300-mg G1T28 (as the dihydrochloride salt) in a single-use, 30-mL, clear glass vial. D-mannitol (US Pharmacopeia) was added as a cake-forming agent, and citrate buffer was added to maintain the reconstituted pH at 4.0 to 5.0. Sodium hydroxide and/or hydrochloric acid may have been added for pH adjustment during manufacturing. Each vial should have been reconstituted with 30 mL of either dextrose 5% in water or sodium chloride solution 0.9%. The reconstituted solution containing 240 mg/m<sup>2</sup> (10 mg/mL) was subsequently diluted prior to administration by IV infusion. Reconstituted and diluted trilaciclib was administered within 12 hours after preparation at room temperature, by IV infusion over approximately 30 (±5) min. If there was any drug remaining in the infusion bag at the end of the 30 (±5) min, the infusion was continued at the same rate until the entire contents of the bag had been administered.

|  |                                  |
|--|----------------------------------|
| Investigational medicinal product name | Gemcitabine                      |
| Investigational medicinal product code |                                  |
| Other name                             |                                  |
| Pharmaceutical forms                   | Powder for solution for infusion |
| Routes of administration               | Intravenous use                  |

**Dosage and administration details:**

Dosage and administration details the same as reported for Group 1.

|  |                       |
|--|-----------------------|
| Investigational medicinal product name | Carboplatin           |
| Investigational medicinal product code |                       |
| Other name                             |                       |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

**Dosage and administration details:**

Dosage and administration details the same as reported for Group 1.

|                  |   |
|------------------|---|
| <b>Arm title</b> | Group 3 (Trilaciclib Day 1, 2, 8 and 9 and G/C Day 2 and 9) |
|------------------|---|

**Arm description:**

Subjects receiving Trilaciclib administered IV on Days 1, 2, 8, and 9 of 21-day cycles, plus Gemcitabine and Carboplatin therapy (Days 2 and 9 of 21-day cycles).

Gemcitabine 1000 mg/m<sup>2</sup> and carboplatin AUC 2 (maximum 300 mg) administered IV.

In Group 3, trilaciclib (240 mg/m<sup>2</sup>) was administered as an IV infusion over 30 (±5) minutes on Days 1, 2, 8, and 9 plus Gemcitabine and Carboplatin therapy which was administered on Days 2 and 9.

There were no inpatient dose modifications of trilaciclib during the study.

If administration of all chemotherapy was held or discontinued, administration of trilaciclib was also to be held or discontinued. Chemotherapy could not be administered until after completion of the trilaciclib infusion.

Study drug administration was continued until disease progression, unacceptable toxicity, withdrawal of consent, or discontinuation by the investigator, whichever occurred first.

|  |  |
|--|--|
| Arm type                               | Experimental                                     |
| Investigational medicinal product name | Trilaciclib                                      |
| Investigational medicinal product code | G1T28  |
| Other name                             |  |
| Pharmaceutical forms                   | Powder for concentrate for solution for infusion |
| Routes of administration               | Intravenous use                                  |

Dosage and administration details:

Dosage and administration details the same as reported for Group 2.

|  |                       |
|--|-----------------------|
| Investigational medicinal product name | Carboplatin           |
| Investigational medicinal product code |                       |
| Other name                             |                       |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

Dosage and administration details:

Dosage and administration details the same as reported for Group 1.

|  |                                  |
|--|----------------------------------|
| Investigational medicinal product name | Gemcitabine                      |
| Investigational medicinal product code |                                  |
| Other name                             |                                  |
| Pharmaceutical forms                   | Powder for solution for infusion |
| Routes of administration               | Intravenous use                  |

Dosage and administration details:

Dosage and administration details the same as reported for Group 1.

| Number of subjects in period 1 <sup>[1]</sup> | Group 1 (G/C Day 1 and 8) | Group 2 (Trilaciclib Day 1 and 8 and G/C Day 1 and 8) | Group 3 (Trilaciclib Day 1, 2, 8 and 9 and G/C Day 2 and 9) |
|---|---------------------------|---|---|
|   |                           |   |   |
| Started                                       | 34                        | 33  | 35  |
| Treated                                       | 30                        | 33  | 35  |
| Completed                                     | 0                         | 0   | 0   |
| Not completed                                 | 34                        | 33  | 35  |
| Consent withdrawn by subject                  | 6                         | 4   | 5   |
| Other   | 1                         | 3   | -   |
| Death   | 25                        | 13  | 20  |
| Lost to follow-up                             | -                         | -   | 1   |
| Sponsor terminated study                      | 2                         | 13  | 9   |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 142 subjects were enrolled, however there were 40 screen failures prior to randomization. Therefore 102 subjects were randomized 1:1:1, leading to the disposition as captured in baseline period: 34 subjects in Group 1, 33 subjects in Group 2 and 35

subjects in Group 3.

## Baseline characteristics

### Reporting groups

|                       |                           |
|-----------------------|---------------------------|
| Reporting group title | Group 1 (G/C Day 1 and 8) |
|-----------------------|---------------------------|

Reporting group description:

Subjects receiving standard Gemcitabine and Carboplatin therapy (Days 1 and 8 of 21-day cycles) only. Gemcitabine 1000 mg/m<sup>2</sup> and carboplatin AUC 2 administered IV.

Study drug administration was continued until disease progression, unacceptable toxicity, withdrawal of consent, or discontinuation by the investigator, whichever occurred first.

|                       |   |
|-----------------------|---|
| Reporting group title | Group 2 (Trilaciclib Day 1 and 8 and G/C Day 1 and 8) |
|-----------------------|---|

Reporting group description:

Subjects receiving Trilaciclib administered IV on Days 1 and 8 of 21-day cycles , plus Gemcitabine and Carboplatin therapy (Days 1 and 8 of 21-day cycles).

Gemcitabine 1000 mg/m<sup>2</sup> and carboplatin AUC 2 (maximum 300 mg) administered IV.

In Group 2, trilaciclib (240 mg/m<sup>2</sup>) was administered as an IV infusion over 30 (±5) minutes prior to each GC treatment (on Days 1 and 8).

There were no inpatient dose modifications of trilaciclib during the study.

Trilaciclib was administered only with GC therapy. If administration of all chemotherapy was held or discontinued, administration of trilaciclib was also to be held or discontinued.

Chemotherapy could not be administered until after completion of the trilaciclib infusion.

Study drug administration was continued until disease progression, unacceptable toxicity, withdrawal of consent, or discontinuation by the investigator, whichever occurred first.

|                       |   |
|-----------------------|---|
| Reporting group title | Group 3 (Trilaciclib Day 1, 2, 8 and 9 and G/C Day 2 and 9) |
|-----------------------|---|

Reporting group description:

Subjects receiving Trilaciclib administered IV on Days 1, 2, 8, and 9 of 21-day cycles, plus Gemcitabine and Carboplatin therapy (Days 2 and 9 of 21-day cycles).

Gemcitabine 1000 mg/m<sup>2</sup> and carboplatin AUC 2 (maximum 300 mg) administered IV.

In Group 3, trilaciclib (240 mg/m<sup>2</sup>) was administered as an IV infusion over 30 (±5) minutes on Days 1, 2, 8, and 9 plus Gemcitabine and Carboplatin therapy which was administered on Days 2 and 9.

There were no inpatient dose modifications of trilaciclib during the study.

If administration of all chemotherapy was held or discontinued, administration of trilaciclib was also to be held or discontinued. Chemotherapy could not be administered until after completion of the trilaciclib infusion.

Study drug administration was continued until disease progression, unacceptable toxicity, withdrawal of consent, or discontinuation by the investigator, whichever occurred first.

| Reporting group values                | Group 1 (G/C Day 1 and 8) | Group 2 (Trilaciclib Day 1 and 8 and G/C Day 1 and 8) | Group 3 (Trilaciclib Day 1, 2, 8 and 9 and G/C Day 2 and 9) |
|---------------------------------------|---------------------------|---|---|
| Number of subjects                    | 34                        | 33  | 35  |
| Age categorical<br>Units: Subjects    |                           |   |   |
| 75 years and over                     | 2                         | 2   | 0   |
| From 65 -75 years                     | 6                         | 7   | 9   |
| From 18-65 years                      | 26                        | 24  | 26  |
| Age continuous<br>Units: years        |                           |   |   |
| arithmetic mean                       | 55                        | 56  | 58  |
| standard deviation                    | ± 13.6                    | ± 12.1  | ± 9.5   |
| Gender categorical<br>Units: Subjects |                           |   |   |
| Female                                | 34                        | 32  | 35  |



|      |   |   |   |
|------|---|---|---|
| Male | 0 | 1 | 0 |
|------|---|---|---|

|   |         |         |         |
|---|---------|---------|---------|
| Race  |         |         |         |
| Units: Subjects   |         |         |         |
| White   | 28      | 22      | 28      |
| Black or African American   | 5       | 7       | 2       |
| Asian   | 0       | 2       | 4       |
| Other   | 1       | 2       | 1       |
| Ethnicity   |         |         |         |
| Units: Subjects   |         |         |         |
| Hispanic or Latino  | 2       | 5       | 2       |
| Not Hispanic or Latino  | 32      | 28      | 33      |
| Country   |         |         |         |
| Units: Subjects   |         |         |         |
| USA   | 28      | 28      | 27      |
| Non-USA   | 6       | 5       | 8       |
| ECOG stratification (derived)   |         |         |         |
| ECOG = eastern cooperative oncology group; Where not collected on the randomization page, values were derived from other eCRF pages |         |         |         |
| Units: Subjects   |         |         |         |
| Grade 0   | 15      | 17      | 21      |
| Grade 1   | 19      | 16      | 14      |
| Number of prior lines of therapy (derived)  |         |         |         |
| where not collected on the randomisation page, values were derived from other eCRF pages  |         |         |         |
| Units: Subjects   |         |         |         |
| None  | 21      | 22      | 21      |
| 1 or 2  | 13      | 11      | 14      |
| Number of prior lines of therapy (eCRF)   |         |         |         |
| Units: Subjects   |         |         |         |
| None  | 18      | 19      | 17      |
| One   | 11      | 11      | 14      |
| Two   | 5       | 3       | 4       |
| Liver involvement   |         |         |         |
| Units: Subjects   |         |         |         |
| Yes   | 8       | 8       | 10      |
| No  | 26      | 25      | 25      |
| Smoking history   |         |         |         |
| Units: Subjects   |         |         |         |
| Never Smoked  | 24      | 24      | 25      |
| Former Smokers  | 9       | 9       | 8       |
| Current Smokers   | 1       | 0       | 2       |
| Body Weight   |         |         |         |
| Units: kg   |         |         |         |
| arithmetic mean   | 76.8    | 72.1    | 72.9    |
| standard deviation  | ± 17.48 | ± 15.60 | ± 15.48 |
| Height  |         |         |         |
| Units: cm   |         |         |         |
| arithmetic mean   | 162.6   | 163.2   | 162.6   |
| standard deviation  | ± 7.19  | ± 8.09  | ± 8.03  |
| BMI   |         |         |         |

|   |             |             |             |
|---|-------------|-------------|-------------|
| Body Mass Index is calculated as $[\text{weight (kg)}] / [\text{height (m)}]^2$ .   |             |             |             |
| Units: $\text{kg/m}^2$  |             |             |             |
| arithmetic mean   | 28.97       | 27.07       | 27.47       |
| standard deviation  | $\pm 5.962$ | $\pm 5.708$ | $\pm 5.028$ |
| Body Surface Area   |             |             |             |
| BSA is computed using DuBois-DuBois formula as $0.20247 \times [\text{height (m)}]^{0.725} \times [\text{weight (kg)}]^{0.425}$ |             |             |             |
| Units: $\text{m}^2$   |             |             |             |
| arithmetic mean   | 1.81        | 1.77        | 1.77        |
| standard deviation  | $\pm 0.199$ | $\pm 0.194$ | $\pm 0.202$ |

|   |       |  |  |
|---|-------|--|--|
| <b>Reporting group values</b>   | Total |  |  |
| Number of subjects  | 102   |  |  |
| Age categorical   |       |  |  |
| Units: Subjects   |       |  |  |
| 75 years and over   | 4     |  |  |
| From 65 -75 years   | 22    |  |  |
| From 18-65 years  | 76    |  |  |
| Age continuous  |       |  |  |
| Units: years  |       |  |  |
| arithmetic mean   | -     |  |  |
| standard deviation  |       |  |  |
| Gender categorical  |       |  |  |
| Units: Subjects   |       |  |  |
| Female  | 101   |  |  |
| Male  | 1     |  |  |
| Race  |       |  |  |
| Units: Subjects   |       |  |  |
| White   | 78    |  |  |
| Black or African American   | 14    |  |  |
| Asian   | 6     |  |  |
| Other   | 4     |  |  |
| Ethnicity   |       |  |  |
| Units: Subjects   |       |  |  |
| Hispanic or Latino  | 9     |  |  |
| Not Hispanic or Latino  | 93    |  |  |
| Country   |       |  |  |
| Units: Subjects   |       |  |  |
| USA   | 83    |  |  |
| Non-USA   | 19    |  |  |
| ECOG stratification (derived)   |       |  |  |
| ECOG = eastern cooperative oncology group; Where not collected on the randomization page, values were derived from other eCRF pages |       |  |  |
| Units: Subjects   |       |  |  |
| Grade 0   | 53    |  |  |
| Grade 1   | 49    |  |  |
| Number of prior lines of therapy (derived)  |       |  |  |
| where not collected on the randomisation page, values were derived from other eCRF pages  |       |  |  |
| Units: Subjects   |       |  |  |
| None  | 64    |  |  |
| 1 or 2  | 38    |  |  |
| Number of prior lines of therapy (eCRF)   |       |  |  |

|   |    |  |  |
|---|----|--|--|
| Units: Subjects   |    |  |  |
| None  | 54 |  |  |
| One   | 36 |  |  |
| Two   | 12 |  |  |
| Liver involvement   |    |  |  |
| Units: Subjects   |    |  |  |
| Yes   | 26 |  |  |
| No  | 76 |  |  |
| Smoking history   |    |  |  |
| Units: Subjects   |    |  |  |
| Never Smoked  | 73 |  |  |
| Former Smokers  | 26 |  |  |
| Current Smokers   | 3  |  |  |
| Body Weight   |    |  |  |
| Units: kg   |    |  |  |
| arithmetic mean   |    |  |  |
| standard deviation  | -  |  |  |
| Height  |    |  |  |
| Units: cm   |    |  |  |
| arithmetic mean   |    |  |  |
| standard deviation  | -  |  |  |
| BMI   |    |  |  |
| Body Mass Index is calculated as $[\text{weight (kg)}] / [\text{height (m)}]^2$ .   |    |  |  |
| Units: $\text{kg/m}^2$  |    |  |  |
| arithmetic mean   |    |  |  |
| standard deviation  | -  |  |  |
| Body Surface Area   |    |  |  |
| BSA is computed using DuBois-DuBois formula as $0.20247 \times [\text{height (m)}]^{0.725} \times [\text{weight (kg)}]^{0.425}$ |    |  |  |
| Units: $\text{m}^2$   |    |  |  |
| arithmetic mean   |    |  |  |
| standard deviation  | -  |  |  |

## End points

### End points reporting groups

|   |   |
|---|---|
| Reporting group title   | Group 1 (G/C Day 1 and 8)                                   |
| Reporting group description:  |   |
| Subjects receiving standard Gemcitabine and Carboplatin therapy (Days 1 and 8 of 21-day cycles) only. Gemcitabine 1000 mg/m <sup>2</sup> and carboplatin AUC 2 administered IV.   |   |
| Study drug administration was continued until disease progression, unacceptable toxicity, withdrawal of consent, or discontinuation by the investigator, whichever occurred first.  |   |
| Reporting group title   | Group 2 (Trilaciclib Day 1 and 8 and G/C Day 1 and 8)       |
| Reporting group description:  |   |
| Subjects receiving Trilaciclib administered IV on Days 1 and 8 of 21-day cycles , plus Gemcitabine and Carboplatin therapy (Days 1 and 8 of 21-day cycles).   |   |
| Gemcitabine 1000 mg/m <sup>2</sup> and carboplatin AUC 2 (maximum 300 mg) administered IV.  |   |
| In Group 2, trilaciclib (240 mg/m <sup>2</sup> ) was administered as an IV infusion over 30 (±5) minutes prior to each GC treatment (on Days 1 and 8).  |   |
| There were no inpatient dose modifications of trilaciclib during the study.   |   |
| Trilaciclib was administered only with GC therapy. If administration of all chemotherapy was held or discontinued, administration of trilaciclib was also to be held or discontinued.   |   |
| Chemotherapy could not be administered until after completion of the trilaciclib infusion.  |   |
| Study drug administration was continued until disease progression, unacceptable toxicity, withdrawal of consent, or discontinuation by the investigator, whichever occurred first.  |   |
| Reporting group title   | Group 3 (Trilaciclib Day 1, 2, 8 and 9 and G/C Day 2 and 9) |
| Reporting group description:  |   |
| Subjects receiving Trilaciclib administered IV on Days 1, 2, 8, and 9 of 21-day cycles, plus Gemcitabine and Carboplatin therapy (Days 2 and 9 of 21-day cycles).   |   |
| Gemcitabine 1000 mg/m <sup>2</sup> and carboplatin AUC 2 (maximum 300 mg) administered IV.  |   |
| In Group 3, trilaciclib (240 mg/m <sup>2</sup> ) was administered as an IV infusion over 30 (±5) minutes on Days 1, 2, 8, and 9 plus Gemcitabine and Carboplatin therapy which was administered on Days 2 and 9.              |   |
| There were no inpatient dose modifications of trilaciclib during the study.   |   |
| If administration of all chemotherapy was held or discontinued, administration of trilaciclib was also to be held or discontinued. Chemotherapy could not be administered until after completion of the trilaciclib infusion. |   |
| Study drug administration was continued until disease progression, unacceptable toxicity, withdrawal of consent, or discontinuation by the investigator, whichever occurred first.  |   |

### Primary: Duration of severe (Grade 4) neutropenia in Cycle 1

|  |   |
|--|---|
| End point title  | Duration of severe (Grade 4) neutropenia in Cycle 1 |
| End point description:   |   |
| Duration of severe neutropenia (DSN) was defined as the number of days from the date of the first absolute neutrophil count (ANC) value of $<0.5 \times 10^9$ cells/L observed between Day 1 Cycle X and the end of Cycle X to the date of the first ANC value $\geq 0.5 \times 10^9$ /L that met the following: (1) occurred after the ANC value of $<0.5 \times 10^9$ cells/L and (2) no other ANC values $<0.5 \times 10^9$ cells/L occurred between this day and the end of Cycle X. DSN is set to 0 for patients who did not experience SN in Cycle X, including those who were randomized but never treated. |   |
| A 2-sided p-value was calculated for the nonparametric ANCOVA. The nonparametric ANCOVA included the study baseline ANC value as a covariate, with the stratification factors of lines of systemic therapy (0 vs 1 or 2) and liver involvement (Yes vs No) and treatment as fixed effects.   |   |
| End point type   | Primary   |
| End point timeframe:   |   |
| From patient randomization to the end of the Cycle 1   |   |

| <b>End point values</b>                          | Group 1 (G/C Day 1 and 8) | Group 2 (Trilaciclib Day 1 and 8 and G/C Day 1 and 8) | Group 3 (Trilaciclib Day 1, 2, 8 and 9 and G/C Day 2 and 9) |  |
|--|---------------------------|---|---|--|
| Subject group type                               | Reporting group           | Reporting group                                       | Reporting group   |  |
| Number of subjects analysed                      | 34                        | 33  | 35  |  |
| Units: days                                      |                           |   |   |  |
| arithmetic mean (standard deviation)             |                           |   |   |  |
| Duration of severe neutropenia in Cycle 1 (days) | 1 (± 2.2)                 | 2 (± 3.5)   | 1 (± 2.6)   |  |

## Statistical analyses

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Duration of SN in Cycle 1 in Group 3 vs Group 1   |
| Statistical analysis description:  |   |
| Model-based point estimates for treatment effect, together with their 95% CIs, were presented along with the 2-sided p-values for the tests except for the analyses where the multiplicity adjustment was applied, in which 1-sided p-values were reported for the primary comparison conducted between Group 3 and Group 1. |   |
| Comparison groups  | Group 3 (Trilaciclib Day 1, 2, 8 and 9 and G/C Day 2 and 9) v Group 1 (G/C Day 1 and 8) |
| Number of subjects included in analysis  | 69  |
| Analysis specification   | Pre-specified   |
| Analysis type  | superiority   |
| P-value  | = 0.7048 <sup>[1]</sup>   |
| Method   | ANCOVA  |
| Parameter estimate   | Mean difference (Group 3 – Group 1)   |
| Point estimate   | 0.3   |
| Confidence interval  |   |
| level  | 95 %  |
| sides  | 2-sided   |
| lower limit  | -0.8  |
| upper limit  | 1.5   |
| Variability estimate   | Standard error of the mean  |
| Dispersion value   | 0.58  |

Notes:

[1] - The 1-sided p-value was calculated using a nonparametric ANCOVA.

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Duration of SN in Cycle 1 in Group 2 vs Group 1                                   |
| Comparison groups                 | Group 2 (Trilaciclib Day 1 and 8 and G/C Day 1 and 8) v Group 1 (G/C Day 1 and 8) |

|   |                                     |
|---|-------------------------------------|
| Number of subjects included in analysis | 67                                  |
| Analysis specification                  | Pre-specified                       |
| Analysis type                           | superiority                         |
| P-value                                 | = 0.3364                            |
| Method                                  | ANCOVA                              |
| Parameter estimate                      | Mean difference (Group 2 – Group 1) |
| Point estimate                          | 0.8                                 |
| Confidence interval                     |                                     |
| level                                   | 95 %                                |
| sides                                   | 2-sided                             |
| lower limit                             | -0.6                                |
| upper limit                             | 2.3                                 |
| Variability estimate                    | Standard error of the mean          |
| Dispersion value                        | 0.71                                |

### Primary: Occurrence of severe (Grade 4) neutropenia

|  |  |
|--|--|
| End point title  | Occurrence of severe (Grade 4) neutropenia |
| End point description:   |  |
| <p>The occurrence of SN, is a binary response variable (Yes, No). It was summarized using descriptive statistics by treatment group and was analyzed to compare a trilaciclib group and GC only using modified Poisson regression to account for the variable duration of the treatment period for each patient. The model included baseline ANC as a covariate, with the stratification factors of prior lines of systemic therapy (0 versus 1 or 2) and liver involvement (Yes versus No) and treatment as fixed effects. The logarithm transformation of the number of cycles was included as an offset variable in the modeling. The 2-sided p-value is calculated using stratified exact CMH method to account for the number of prior lines of therapy (0 versus 1 - 2) and liver involvement as the stratification factors.</p> |  |
| End point type   | Primary                                    |
| End point timeframe:   |  |
| From randomization to the Database Lock 1 (data cutoff date 30 July 2018 - Final myelopreservation efficacy results)   |  |

| End point values            | Group 1 (G/C Day 1 and 8) | Group 2 (Trilaciclib Day 1 and 8 and G/C Day 1 and 8) | Group 3 (Trilaciclib Day 1, 2, 8 and 9 and G/C Day 2 and 9) |  |
|-----------------------------|---------------------------|---|---|--|
| Subject group type          | Reporting group           | Reporting group                                       | Reporting group   |  |
| Number of subjects analysed | 34                        | 33  | 35  |  |
| Units: Number of patients   | 9                         | 12  | 8   |  |

### Statistical analyses

|   |  |
|---|--|
| Statistical analysis title  | Occurrence of SN in Group 3 vs Group 1 |
| Statistical analysis description:   |  |
| <p>Model-based point estimates for treatment effect, together with their 95% CIs, were presented along with the 2-sided p-values for the tests except for the analyses where the multiplicity adjustment was applied, in which 1-sided p-values were reported for the primary comparison conducted between Group 3 and Group 1.</p> |  |

|   |   |
|---|---|
| Comparison groups                       | Group 3 (Trilaciclib Day 1, 2, 8 and 9 and G/C Day 2 and 9) v Group 1 (G/C Day 1 and 8) |
| Number of subjects included in analysis | 69  |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority   |
| P-value                                 | = 0.2382 <sup>[2]</sup>   |
| Method                                  | modified Poisson regression   |
| Parameter estimate                      | Adjusted rate ratio   |
| Point estimate                          | 0.776   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 0.386   |
| upper limit                             | 1.559   |
| Variability estimate                    | Standard error of the mean  |
| Dispersion value                        | 0.2762  |

Notes:

[2] - The 1-sided p-value was calculated using a modified Poisson regression.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Occurrence of SN in Group 2 vs Group 1 |
|-----------------------------------|--|

Statistical analysis description:

Model-based point estimates for treatment effect, together with their 95% CIs, were presented along with the 2-sided p-values for the tests except for the analyses where the multiplicity adjustment was applied, in which 1-sided p-values were reported for the primary comparison conducted between Group 3 and Group 1.

|   |   |
|---|---|
| Comparison groups                       | Group 2 (Trilaciclib Day 1 and 8 and G/C Day 1 and 8) v Group 1 (G/C Day 1 and 8) |
| Number of subjects included in analysis | 67  |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority   |
| P-value                                 | = 0.3133  |
| Method                                  | modified Poisson regression   |
| Parameter estimate                      | Adjusted rate ratio   |
| Point estimate                          | 0.961   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 0.457   |
| upper limit                             | 2.019   |
| Variability estimate                    | Standard error of the mean  |
| Dispersion value                        | 0.364   |

## Secondary: Occurrence of best overall response

|                 |                                     |
|-----------------|-------------------------------------|
| End point title | Occurrence of best overall response |
|-----------------|-------------------------------------|

End point description:

For all patients, the RECIST v1.1 tumor response data were used to determine each patient's visit response (time point response [TPR]) according to RECIST v1.1 and the BOR. The TPR at each visit was determined in 2 ways: (1) derived programmatically at the time of analysis using the information from target lesions, non-target lesions, and new lesions based on data collected through eCRF; and (2) judged by the investigator as collected in the eCRF.

Objective response rate (ORR:CR + PR) was calculated using a strict interpretation of RECIST v1.1.

The analyses are based on the response evaluable analysis set.

|  |           |
|--|-----------|
| End point type   | Secondary |
| End point timeframe:   |           |
| From randomization until the Database Lock 2 (data cutoff date 28 June 2019 includes relevant results for safety and anti-tumor efficacy analysis) |           |

| End point values                      | Group 1 (G/C Day 1 and 8) | Group 2 (Trilaciclib Day 1 and 8 and G/C Day 1 and 8) | Group 3 (Trilaciclib Day 1, 2, 8 and 9 and G/C Day 2 and 9) |  |
|---------------------------------------|---------------------------|---|---|--|
| Subject group type                    | Reporting group           | Reporting group                                       | Reporting group   |  |
| Number of subjects analysed           | 24                        | 30  | 31  |  |
| Units: Number of patients             |                           |   |   |  |
| Complete response (CR)                | 0                         | 0   | 0   |  |
| Partial response (PR)                 | 7                         | 15  | 11  |  |
| Stable disease (SD)                   | 11                        | 9   | 15  |  |
| Progressive disease (PD)              | 6                         | 5   | 3   |  |
| Not evaluable (NE)                    | 0                         | 0   | 1   |  |
| Unconfirmed CR                        | 0                         | 0   | 0   |  |
| Unconfirmed PR                        | 1                         | 1   | 7   |  |
| Objective response rate (ORR:CR + PR) | 7                         | 15  | 11  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Duration of objective response (CR or PR per RECIST v1.1 as assessed by investigator)

|                 |   |
|-----------------|---|
| End point title | Duration of objective response (CR or PR per RECIST v1.1 as assessed by investigator) |
|-----------------|---|

End point description:

Duration of Response (DOR) is the time between first response by RECIST Version 1.1 of CR or PR and the first date that progressive disease is documented by RECIST Version 1.1, or death. Patients who do not experience PD or death will be censored at the last tumor assessment date. Only those patients with confirmed responses will be included in this analysis

Confidence Interval Calculated using the Kaplan-Meier method  
Not evaluable: 999999

The analyses are based on the response evaluable analysis set.

|  |           |
|--|-----------|
| End point type   | Secondary |
| End point timeframe:   |           |
| From randomization until the Database Lock 2 (data cutoff date 28 June 2019 includes relevant results for safety and anti-tumor efficacy analysis) |           |



| End point values                          | Group 1 (G/C Day 1 and 8) | Group 2 (Trilaciclib Day 1 and 8 and G/C Day 1 and 8) | Group 3 (Trilaciclib Day 1, 2, 8 and 9 and G/C Day 2 and 9) |  |
|---|---------------------------|---|---|--|
| Subject group type                        | Reporting group           | Reporting group                                       | Reporting group   |  |
| Number of subjects analysed               | 24                        | 30  | 31  |  |
| Units: months                             |                           |   |   |  |
| arithmetic mean (confidence interval 95%) |                           |   |   |  |
| Duration of response (months) - 25%       | 7.5 (5.1 to 7.8)          | 6.3 (3.2 to 12.5)                                     | 9.6 (4.2 to 9.6)  |  |
| Duration of response (months) - Median    | 7.8 (5.1 to 999999)       | 12.5 (4.8 to 17.8)                                    | 9.6 (4.2 to 12.6)   |  |
| Duration of response (months) - 75%       | 999999 (5.1 to 999999)    | 17.8 (7.6 to 17.8)                                    | 12.0 (9.6 to 12.6)  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Overall survival

|                 |                  |
|-----------------|------------------|
| End point title | Overall survival |
|-----------------|------------------|

End point description:

Overall survival is calculated as the time (months) from date of randomization to the date of death due to any cause. Patients who do not die during the study will be censored at the date last known to be alive. Patients lacking data beyond the date of randomization will have their survival time censored at date of randomization. OS will not be censored if a patient receives other anti-tumor treatments after the study drugs.

OS was analyzed with Kaplan-Meier method and summarized with median, 25 and 75 percentiles, survival rates at 3, 6, 9, and 12 months along with 95% confidence intervals (CI).

The HR and its 95% CI were calculated using the Cox regression model with treatment and stratification factors (SF) of number of prior lines of therapy (0 vs 1 or 2) and liver involvement. p-value was calculated using the stratified log-rank test to account for the no. of prior lines of therapy (0 vs 1 or 2) and liver involvement as SF.

Values which are not evaluable represented as 99999.

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

End point timeframe:

From randomization until the Final Database Lock (data cutoff date 17 Jul 2020)

| End point values                                | Group 1 (G/C Day 1 and 8) | Group 2 (Trilaciclib Day 1 and 8 and G/C Day 1 and 8) | Group 3 (Trilaciclib Day 1, 2, 8 and 9 and G/C Day 2 and 9) |  |
|---|---------------------------|---|---|--|
| Subject group type                              | Reporting group           | Reporting group                                       | Reporting group   |  |
| Number of subjects analysed                     | 34                        | 33  | 35  |  |
| Units: months                                   |                           |   |   |  |
| arithmetic mean (confidence interval 95%)       |                           |   |   |  |
| Probability of being alive (95% CI) at 3 months | 0.90 (0.73 to 0.97)       | 0.97 (0.80 to 1.00)                                   | 1.00 (1.00 to 1.00)   |  |
| Probability of being alive (95% CI) at 6 months | 0.73 (0.53 to 0.85)       | 0.81 (0.62 to 0.91)                                   | 0.91 (0.75 to 0.97)   |  |

|  |                     |                        |                      |  |
|--|---------------------|------------------------|----------------------|--|
| Probability of being alive (95% CI) at 9 months  | 0.62 (0.42 to 0.77) | 0.77 (0.58 to 0.88)    | 0.72 (0.53 to 0.84)  |  |
| Probability of being alive (95% CI) at 12 months | 0.50 (0.31 to 0.67) | 0.69 (0.49 to 0.83)    | 0.72 (0.53 to 0.84)  |  |
| Overall survival (months) - 25%                  | 5.8 (2.8 to 9.7)    | 9.4 (3.4 to 19.6)      | 8.8 (6.0 to 15.3)    |  |
| Overall survival (months) - Median               | 12.6 (6.3 to 15.6)  | 99999 (10.2 to 99999)  | 17.8 (12.9 to 32.7)  |  |
| Overall survival (months) - 75%                  | 17.8 (12.8 to 25.0) | 99999 (99999 to 99999) | 32.7 (19.8 to 99999) |  |

## Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Overall Survival in Group 3 vs Group 1  |
| Comparison groups                       | Group 3 (Trilaciclib Day 1, 2, 8 and 9 and G/C Day 2 and 9) v Group 1 (G/C Day 1 and 8) |
| Number of subjects included in analysis | 69  |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority   |
| P-value                                 | = 0.0004  |
| Method                                  | Regression, Cox   |
| Parameter estimate                      | Hazard ratio (HR)   |
| Point estimate                          | 0.4   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 0.22  |
| upper limit                             | 0.74  |
| Variability estimate                    | Standard error of the mean  |
| Dispersion value                        | 0.125   |

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Overall Survival in Group 2 vs Group 1  |
| Comparison groups                       | Group 2 (Trilaciclib Day 1 and 8 and G/C Day 1 and 8) v Group 1 (G/C Day 1 and 8) |
| Number of subjects included in analysis | 67  |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority   |
| P-value                                 | = 0.0016  |
| Method                                  | Regression, Cox   |
| Parameter estimate                      | Hazard ratio (HR)   |
| Point estimate                          | 0.31  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 0.15  |
| upper limit                             | 0.63  |
| Variability estimate                    | Standard error of the mean  |
| Dispersion value                        | 0.111   |

---

**Secondary: Progression-free survival (per RECIST v1.1 as assessed by investigator)**

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|                 |   |
|-----------------|---|
| End point title | Progression-free survival (per RECIST v1.1 as assessed by investigator) |
|-----------------|---|

End point description:

Progression-free survival (PFS) was defined as the time (number of months) from date of randomization until date of documented radiologic disease progression per RECIST v1.1 or death due to any cause, whichever came first.

OPFS was analyzed with Kaplan-Meier method and summarized with median, 25% and 75% percentiles, survival rates at 3, 6, 9, and 12 months along with 95% confidence intervals (CI).

Values which are not evaluable are represented as 99999.

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

End point timeframe:

From randomization until the Database Lock 2 (data cutoff date 28 June 2019 includes relevant results for safety and anti-tumor efficacy analysis)

---

| End point values                                   | Group 1 (G/C Day 1 and 8) | Group 2 (Trilaciclib Day 1 and 8 and G/C Day 1 and 8) | Group 3 (Trilaciclib Day 1, 2, 8 and 9 and G/C Day 2 and 9) |  |
|--|---------------------------|---|---|--|
| Subject group type                                 | Reporting group           | Reporting group                                       | Reporting group   |  |
| Number of subjects analysed                        | 34                        | 33  | 35  |  |
| Units: months                                      |                           |   |   |  |
| arithmetic mean (confidence interval 95%)          |                           |   |   |  |
| Probability of being progression free at 3 months  | 0.72 (0.52 to 0.85)       | 0.81 (0.62 to 0.91)                                   | 0.88 (0.70 to 0.95)   |  |
| Probability of being progression free at 6 months  | 0.49 (0.28 to 0.67)       | 0.72 (0.51 to 0.85)                                   | 0.75 (0.55 to 0.88)   |  |
| Probability of being progression free at 9 months  | 0.42 (0.21 to 0.62)       | 0.53 (0.31 to 0.70)                                   | 0.44 (0.23 to 0.64)   |  |
| Probability of being progression free at 12 months | 0.17 (0.03 to 0.40)       | 0.26 (0.10 to 0.46)                                   | 0.38 (0.17 to 0.58)   |  |
| Progression Free Survival (months) - 25%           | 2.2 (1.2 to 5.4)          | 5.3 (1.2 to 7.9)                                      | 6.2 (1.2 to 7.1)  |  |
| Progression Free Survival (months) - Median        | 5.7 (3.3 to 9.2)          | 9.4 (6.1 to 11.9)                                     | 7.3 (6.2 to 13.9)   |  |
| Progression Free Survival (months) - 75%           | 9.9 (8.3 to 99999)        | 13.0 (9.7 to 20.1)                                    | 13.9 (9.0 to 99999)   |  |

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**Statistical analyses**

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No statistical analyses for this end point

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**Secondary: Relative dose intensity of gemcitabine and carboplatin**

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|                 |  |
|-----------------|--|
| End point title | Relative dose intensity of gemcitabine and carboplatin |
|-----------------|--|

End point description:

Relative dose intensity was defined as 100% times the actual dose intensity divided by the planned dose

intensity. The planned dose intensity was defined as the cumulative planned dose through the study divided by (number of cycles×3 weeks).

|  |           |
|--|-----------|
| End point type   | Secondary |
| End point timeframe:   |           |
| From randomization until the Database Lock 2 (data cutoff date 28 June 2019 includes relevant results for safety and anti-tumor efficacy analysis) |           |

| End point values                     | Group 1 (G/C Day 1 and 8) | Group 2 (Trilaciclib Day 1 and 8 and G/C Day 1 and 8) | Group 3 (Trilaciclib Day 1, 2, 8 and 9 and G/C Day 2 and 9) |  |
|--------------------------------------|---------------------------|---|---|--|
| Subject group type                   | Reporting group           | Reporting group                                       | Reporting group   |  |
| Number of subjects analysed          | 30                        | 33  | 35  |  |
| Units: Relative dose intensity (%)   |                           |   |   |  |
| arithmetic mean (standard deviation) |                           |   |   |  |
| Carboplatin                          | 77.5 (± 19.2)             | 79.1 (± 15.88)  | 81.7 (± 16.09)  |  |
| Gemcitabine                          | 79.1 (± 18.29)            | 80.8 (± 12.51)  | 81.0 (± 14.49)  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Duration of exposure

|  |                      |
|--|----------------------|
| End point title  | Duration of exposure |
| End point description:   |                      |
| Duration of exposure (days) = First dose date of study drug from the last cycle – first dose date of study drug + 21.                              |                      |
| End point type   | Secondary            |
| End point timeframe:   |                      |
| From randomization until the Database Lock 2 (data cutoff date 28 June 2019 includes relevant results for safety and anti-tumor efficacy analysis) |                      |

| End point values                     | Group 1 (G/C Day 1 and 8) | Group 2 (Trilaciclib Day 1 and 8 and G/C Day 1 and 8) | Group 3 (Trilaciclib Day 1, 2, 8 and 9 and G/C Day 2 and 9) |  |
|--------------------------------------|---------------------------|---|---|--|
| Subject group type                   | Reporting group           | Reporting group                                       | Reporting group   |  |
| Number of subjects analysed          | 30                        | 33  | 35  |  |
| Units: day                           |                           |   |   |  |
| arithmetic mean (standard deviation) | 139 (± 109.1)             | 193 (± 149.0)   | 173 (± 107.3)   |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of cycles received

|                 |                           |
|-----------------|---------------------------|
| End point title | Number of cycles received |
|-----------------|---------------------------|

End point description:

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

End point timeframe:

From randomization until the Database Lock 2 (data cutoff date 28 June 2019 includes relevant results for safety and anti-tumor efficacy analysis)

| End point values                     | Group 1 (G/C Day 1 and 8) | Group 2 (Trilaciclib Day 1 and 8 and G/C Day 1 and 8) | Group 3 (Trilaciclib Day 1, 2, 8 and 9 and G/C Day 2 and 9) |  |
|--------------------------------------|---------------------------|---|---|--|
| Subject group type                   | Reporting group           | Reporting group                                       | Reporting group   |  |
| Number of subjects analysed          | 30                        | 33  | 35  |  |
| Units: number of cycle               |                           |   |   |  |
| arithmetic mean (standard deviation) | 6 (± 5.0)                 | 9 (± 6.6)   | 8 (± 4.8)   |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Cumulative dose of gemcitabine

|                 |                                |
|-----------------|--------------------------------|
| End point title | Cumulative dose of gemcitabine |
|-----------------|--------------------------------|

End point description:

Chemotherapy Exposure Endpoint

Sum of the total doses by cycle (mg/m<sup>2</sup>) administered to a patient in the duration of exposure, i.e. total number of cycles received [(mg/m<sup>2</sup>)]

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

End point timeframe:

From randomization until the Database Lock 2 (data cutoff date 28 June 2019 includes relevant results for safety and anti-tumor efficacy analysis)

| End point values                     | Group 1 (G/C Day 1 and 8) | Group 2 (Trilaciclib Day 1 and 8 and G/C Day 1 and 8) | Group 3 (Trilaciclib Day 1, 2, 8 and 9 and G/C Day 2 and 9) |  |
|--------------------------------------|---------------------------|---|---|--|
| Subject group type                   | Reporting group           | Reporting group                                       | Reporting group   |  |
| Number of subjects analysed          | 30                        | 33  | 35  |  |
| Units: mg/m <sup>2</sup>             |                           |   |   |  |
| arithmetic mean (standard deviation) |                           |   |   |  |
| Gemcitabine                          | 10694.3 (± 9029.11)       | 14680.9 (± 11557.90)                                  | 13277.2 (± 8722.51)   |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Cumulative dose of carboplatin

|                 |                                |
|-----------------|--------------------------------|
| End point title | Cumulative dose of carboplatin |
|-----------------|--------------------------------|

End point description:

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

End point timeframe:

From randomization until the Database Lock 2 (data cutoff date 28 June 2019 includes relevant results for safety and anti-tumor efficacy analysis)

| End point values                     | Group 1 (G/C Day 1 and 8) | Group 2 (Trilaciclib Day 1 and 8 and G/C Day 1 and 8) | Group 3 (Trilaciclib Day 1, 2, 8 and 9 and G/C Day 2 and 9) |  |
|--------------------------------------|---------------------------|---|---|--|
| Subject group type                   | Reporting group           | Reporting group                                       | Reporting group   |  |
| Number of subjects analysed          | 30                        | 33  | 35  |  |
| Units: AUC                           |                           |   |   |  |
| arithmetic mean (standard deviation) | 20.3 (± 16.47)            | 27.8 (± 21.21)  | 26.0 (± 16.33)  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Occurrence of Grade 3 and 4 hematologic laboratory values

|                 |   |
|-----------------|---|
| End point title | Occurrence of Grade 3 and 4 hematologic laboratory values |
|-----------------|---|

End point description:

The occurrence of Grade 3 and 4 hematologic toxicities was a binary endpoint. If a patient had at least 1 cycle with at least one Grade 3 or 4 hematologic toxicities during the treatment period, the patient was assigned as Yes to the occurrence of Grade 3 and 4 hematologic toxicities; otherwise, it was No. If a patient did not have an event, the value of 0 was assigned to that patient.

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

End point timeframe:

From randomization to the Database Lock 1 (data cutoff date 30 July 2018 - Final myelopreservation efficacy results)

| End point values            | Group 1 (G/C Day 1 and 8) | Group 2 (Trilaciclib Day 1 and 8 and G/C Day 1 and 8) | Group 3 (Trilaciclib Day 1, 2, 8 and 9 and G/C Day 2 and 9) |  |
|-----------------------------|---------------------------|---|---|--|
| Subject group type          | Reporting group           | Reporting group                                       | Reporting group   |  |
| Number of subjects analysed | 34                        | 33  | 35  |  |
| Units: Number of patients   | 25                        | 30  | 27  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Occurrence of Grade 3 or 4 thrombocytopenia, i.e. decreased platelet count

|                 |  |
|-----------------|--|
| End point title | Occurrence of Grade 3 or 4 thrombocytopenia, i.e. decreased platelet count |
|-----------------|--|

End point description:

Occurrence of Grade 3 or 4 thrombocytopenia, i.e. decreased platelet count is a subset of Occurrence of Grade 3 and 4 hematologic laboratory values.

Thus refer to the endpoint Occurrence of Grade 3 and 4 hematologic laboratory values.

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

End point timeframe:

From randomization to the Database Lock 1 (data cutoff date 30 July 2018 - Final myelopreservation efficacy results)

| End point values            | Group 1 (G/C Day 1 and 8) | Group 2 (Trilaciclib Day 1 and 8 and G/C Day 1 and 8) | Group 3 (Trilaciclib Day 1, 2, 8 and 9 and G/C Day 2 and 9) |  |
|-----------------------------|---------------------------|---|---|--|
| Subject group type          | Reporting group           | Reporting group                                       | Reporting group   |  |
| Number of subjects analysed | 34                        | 33  | 35  |  |
| Units: Number of patients   | 21                        | 12  | 19  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: A composite (MAHE) endpoint defined to include the following: all-cause hospitalizations, all-cause dose reductions, febrile neutropenia, RBC transfusions on/after Week 5, prolonged severe neutropenia (duration >5 days), platelet transfusions

|                 |  |
|-----------------|--|
| End point title | A composite (MAHE) endpoint defined to include the following: all-cause hospitalizations, all-cause dose reductions, febrile neutropenia, RBC transfusions on/after Week 5, prolonged severe neutropenia (duration >5 days), platelet transfusions |
|-----------------|--|

End point description:

A composite endpoint referred to as MAHE incorporates the measurement of several clinically

meaningful aspects of myelosuppression into a single endpoint by summing of the total number of events across a set of pre-specified components. The event level data for each individual component was also summarized. The components were as follows: All-cause hospitalizations; All-cause dose reductions: Dose (mg/m<sup>2</sup>) reductions were not permitted for trilaciclib. Dose reductions for gemcitabine or carboplatin were collected on the dosing page; Febrile Neutropenia; Prolonged Severe Neutropenia: Each cycle with a duration of SN > 5 days was counted as an event; RBC transfusion on/after Week 5; Platelet transfusion.

The adjusted rate ratio (trilaciclib - GC only), its 95% CI, and p-value are calculated using negative binomial method adjusting for duration of treatment in the window in weeks, accounting for the number of prior lines of therapy (0vs1-2) and liver involvement as stratification factor

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

End point timeframe:

From randomization to the Database Lock 1 (data cutoff date 30 July 2018 - Final myelopreservation efficacy results)

| End point values                                  | Group 1 (G/C Day 1 and 8) | Group 2 (Trilaciclib Day 1 and 8 and G/C Day 1 and 8) | Group 3 (Trilaciclib Day 1, 2, 8 and 9 and G/C Day 2 and 9) |  |
|---|---------------------------|---|---|--|
| Subject group type                                | Reporting group           | Reporting group                                       | Reporting group   |  |
| Number of subjects analysed                       | 34                        | 33  | 35  |  |
| Units: event rate                                 |                           |   |   |  |
| number (not applicable)                           |                           |   |   |  |
| All-cause hospitalizations, event rate (per week) | 0.023                     | 0.014   | 0.005   |  |
| All-cause dose reductions, event rate (per cycle) | 0.141                     | 0.118   | 0.133   |  |
| Febrile neutropenia TEAEs, event rate (per week)  | 0.002                     | 0.001   | 0.000   |  |
| RBC transfusions on/after Week 5, e.r. (per week) | 0.046                     | 0.019   | 0.016   |  |
| Platelet transfusions, event rate (per week)      | 0.019                     | 0.004   | 0.012   |  |
| Prolonged SN (>5 days), event rate (per cycle)    | 0.071                     | 0.105   | 0.022   |  |
| MAHE composite, event rate (per week)             | 0.153                     | 0.108   | 0.080   |  |

## Statistical analyses

|   |   |
|---|---|
| Statistical analysis title              | MAHE composite endpoint in Group 3 vs Group 1   |
| Comparison groups                       | Group 3 (Trilaciclib Day 1, 2, 8 and 9 and G/C Day 2 and 9) v Group 1 (G/C Day 1 and 8) |
| Number of subjects included in analysis | 69  |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority   |
| P-value                                 | = 0.0091 <sup>[3]</sup>   |
| Method                                  | Negative binomial regression  |
| Parameter estimate                      | Adjusted rate ratio   |
| Point estimate                          | 0.49  |



|                      |                            |
|----------------------|----------------------------|
| Confidence interval  |                            |
| level                | 95 %                       |
| sides                | 2-sided                    |
| lower limit          | 0.271                      |
| upper limit          | 0.885                      |
| Variability estimate | Standard error of the mean |
| Dispersion value     | 0.148                      |

Notes:

[3] - One-sided p-value is calculated using a negative binomial regression.

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | MAHE composite endpoint in Group 2 vs Group 1                                     |
| Comparison groups                       | Group 2 (Trilaciclib Day 1 and 8 and G/C Day 1 and 8) v Group 1 (G/C Day 1 and 8) |
| Number of subjects included in analysis | 67  |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority   |
| P-value                                 | = 0.2056  |
| Method                                  | Negative binomial regression  |
| Parameter estimate                      | Adjusted rate ratio   |
| Point estimate                          | 0.686   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 0.383   |
| upper limit                             | 1.23  |
| Variability estimate                    | Standard error of the mean  |
| Dispersion value                        | 0.2043  |

## Secondary: Occurrence of infection SAEs

|  |                              |
|--|------------------------------|
| End point title  | Occurrence of infection SAEs |
| End point description:   |                              |
| The occurrence during the treatment period was defined as a binary variable (Yes or No); Yes if total number of events $\geq 1$ was observed, No for other scenarios. If a patient did not have an event, the value of 0 was assigned to that patient. |                              |
| The criterion for identifying the proper infection SAE records was as follows: If the system organ class (SOC) from Medical Dictionary for Regulatory Activities (MedDRA) takes value "INFECTIONS AND INFESTATIONS," and the AE was a serious event.   |                              |
| Any occurrence of infection SAE during the treatment period. Treatment period was defined as the duration from the date of first dose of study drug up to 30 days after the start of study drug in the last cycle.                                     |                              |
| End point type   | Secondary                    |
| End point timeframe:   |                              |
| From randomization to the Database Lock 1 (data cutoff date 30 July 2018 - Final myelopreservation efficacy results)   |                              |

| End point values            | Group 1 (G/C Day 1 and 8) | Group 2 (Trilaciclib Day 1 and 8 and G/C Day 1 and 8) | Group 3 (Trilaciclib Day 1, 2, 8 and 9 and G/C Day 2 and 9) |  |
|-----------------------------|---------------------------|---|---|--|
| Subject group type          | Reporting group           | Reporting group                                       | Reporting group   |  |
| Number of subjects analysed | 34                        | 33  | 35  |  |
| Units: Number of patients   | 2                         | 0   | 0   |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Occurrence of platelet transfusions

|                 |                                     |
|-----------------|-------------------------------------|
| End point title | Occurrence of platelet transfusions |
|-----------------|-------------------------------------|

End point description:

The occurrence during the treatment period was defined as a binary variable (Yes or No); Yes if the total number of events  $\geq 1$  was observed and No for other scenarios. If a patient did not have an event, the value of 0 will be assigned to that patient.

Each platelet transfusion with a unique start date during the treatment period was defined as a separate event

The adjusted rate ratio (Treatment Group versus Group 1) and its 95% CI are calculated using modified Poisson method adjusting for duration of treatment in days, accounting for the number of prior lines of therapy (0 versus 1 - 2) and liver involvement as the stratification factors and baseline platelet count as a covariate.

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

End point timeframe:

From randomization to the Database Lock 1 (data cutoff date 30 July 2018 - Final myelopreservation efficacy results)

| End point values            | Group 1 (G/C Day 1 and 8) | Group 2 (Trilaciclib Day 1 and 8 and G/C Day 1 and 8) | Group 3 (Trilaciclib Day 1, 2, 8 and 9 and G/C Day 2 and 9) |  |
|-----------------------------|---------------------------|---|---|--|
| Subject group type          | Reporting group           | Reporting group                                       | Reporting group   |  |
| Number of subjects analysed | 34                        | 33  | 35  |  |
| Units: Number of patients   | 4                         | 3   | 6   |  |

## Statistical analyses

|                            |   |
|----------------------------|---|
| Statistical analysis title | Occurrence of platelet trans in Group 3 vs Group 1                                      |
| Comparison groups          | Group 3 (Trilaciclib Day 1, 2, 8 and 9 and G/C Day 2 and 9) v Group 1 (G/C Day 1 and 8) |

|   |                             |
|---|-----------------------------|
| Number of subjects included in analysis | 69                          |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority                 |
| P-value                                 | = 0.4924 <sup>[4]</sup>     |
| Method                                  | modified Poisson regression |
| Parameter estimate                      | Adjusted rate ratio         |
| Point estimate                          | 0.988                       |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | 0.294                       |
| upper limit                             | 3.317                       |
| Variability estimate                    | Standard error of the mean  |
| Dispersion value                        | 0.6105                      |

Notes:

[4] - The 1-sided p-value was calculated using a modified Poisson regression.

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Occurrence of platelet trans in Group 2 vs Group 1                                |
| Comparison groups                       | Group 2 (Trilaciclib Day 1 and 8 and G/C Day 1 and 8) v Group 1 (G/C Day 1 and 8) |
| Number of subjects included in analysis | 67  |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority   |
| P-value                                 | = 0.8518 <sup>[5]</sup>   |
| Method                                  | modified Poisson regression   |
| Parameter estimate                      | Adjusted rate ratio   |
| Point estimate                          | 0.527   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 0.116   |
| upper limit                             | 2.399   |
| Variability estimate                    | Standard error of the mean  |
| Dispersion value                        | 0.4077  |

Notes:

[5] - The 2-sided p-value is calculated using stratified exact CMH method to account for the number of prior lines of therapy (0 versus 1 or 2) and liver involvement as the stratification factors

## Secondary: Occurrence of granulocyte colony-stimulating factor administration

|                 |  |
|-----------------|--|
| End point title | Occurrence of granulocyte colony-stimulating factor administration |
|-----------------|--|

End point description:

The occurrence during the treatment period was defined as a binary variable (Yes or No); Yes if the total number of events  $\geq 1$  was observed and No for other scenarios. If a patient did not have an event, the value of 0 will be assigned to that patient.

The criterion for selecting proper records is as follows: If the chemical subgroup from the World Health Organization-Drug Dictionary (WHO-DD) Version Sep2017 (ie, TEXT4 for CODE4) takes value "COLONY STIMULATING FACTOR," the medication was classified as G-CSF.

The adjusted rate ratio (Treatment Group versus Group 1) and its 95% CI are calculated using modified Poisson method adjusting for number of cycles, accounting for the number of prior lines of therapy (0 versus 1 - 2) and liver involvement as the stratification factors and baseline ANC as a covariate.

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

End point timeframe:

From randomization to the Database Lock 1 (data cutoff date 30 July 2018 - Final myelopreservation efficacy results)

| End point values            | Group 1 (G/C Day 1 and 8) | Group 2 (Trilaciclib Day 1 and 8 and G/C Day 1 and 8) | Group 3 (Trilaciclib Day 1, 2, 8 and 9 and G/C Day 2 and 9) |  |
|-----------------------------|---------------------------|---|---|--|
| Subject group type          | Reporting group           | Reporting group                                       | Reporting group   |  |
| Number of subjects analysed | 34                        | 33  | 35  |  |
| Units: Number of patients   | 16                        | 21  | 14  |  |

### Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | G-SCF administration in Group 3 vs Group 1  |
| Comparison groups                       | Group 3 (Trilaciclib Day 1, 2, 8 and 9 and G/C Day 2 and 9) v Group 1 (G/C Day 1 and 8) |
| Number of subjects included in analysis | 69  |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority   |
| P-value                                 | = 0.0685 <sup>[6]</sup>   |
| Method                                  | modified Poisson regression   |
| Parameter estimate                      | Adjusted rate ratio   |
| Point estimate                          | 0.645   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 0.362   |
| upper limit                             | 1.15  |
| Variability estimate                    | Standard error of the mean  |
| Dispersion value                        | 0.1902  |

Notes:

[6] - The 1-sided p-value was calculated using a modified Poisson regression.

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | G-SCF administration in Group 2 vs Group 1  |
| Comparison groups                       | Group 2 (Trilaciclib Day 1 and 8 and G/C Day 1 and 8) v Group 1 (G/C Day 1 and 8) |
| Number of subjects included in analysis | 67  |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority   |
| P-value                                 | = 0.148 <sup>[7]</sup>  |
| Method                                  | modified Poisson regression   |
| Parameter estimate                      | Adjusted rate ratio   |
| Point estimate                          | 0.936   |

|                      |                            |
|----------------------|----------------------------|
| Confidence interval  |                            |
| level                | 95 %                       |
| sides                | 2-sided                    |
| lower limit          | 0.583                      |
| upper limit          | 1.502                      |
| Variability estimate | Standard error of the mean |
| Dispersion value     | 0.226                      |

Notes:

[7] - The 2-sided p-value is calculated using stratified exact CMH method to account for the number of prior lines of therapy (0 versus 1 or 2) and liver involvement as the stratification factors

## Secondary: Occurrence of erythropoiesis stimulating agent administration

|                 |   |
|-----------------|---|
| End point title | Occurrence of erythropoiesis stimulating agent administration |
|-----------------|---|

End point description:

The occurrence during the treatment period was defined as a binary variable (Yes or No); Yes if total number of events  $\geq 1$  was observed, No for other scenarios. If a patient did not have an event, the value of 0 was assigned to that patient.

The criterion to select proper records was as follows: If the chemical subgroup from WHO-DD Version September 2017 (ie, TEXT4 for CODE4) takes value "OTHER ANTIANEMIC PREPARATIONS", the medication was classified as ESAs.

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

End point timeframe:

From randomization to the Database Lock 1 (data cutoff date 30 July 2018 - Final myelopreservation efficacy results)

| End point values            | Group 1 (G/C Day 1 and 8) | Group 2 (Trilaciclib Day 1 and 8 and G/C Day 1 and 8) | Group 3 (Trilaciclib Day 1, 2, 8 and 9 and G/C Day 2 and 9) |  |
|-----------------------------|---------------------------|---|---|--|
| Subject group type          | Reporting group           | Reporting group                                       | Reporting group   |  |
| Number of subjects analysed | 34                        | 33  | 35  |  |
| Units: Number of patients   | 4                         | 2   | 3   |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Occurrence of intravenous antibiotics use

|                 |   |
|-----------------|---|
| End point title | Occurrence of intravenous antibiotics use |
|-----------------|---|

End point description:

The occurrence during the treatment period was defined as a binary variable (Yes or No); Yes if total number of events  $\geq 1$  was observed, No for other scenarios. If a patient did not have an event, the value of 0 was assigned to that patient.

The criteria for identifying an IV antibiotic administration event was (1) if the Therapeutic subgroup from WHO-DD Version September 2017 (ie, TEXT2 for CODE2) takes value "ANTIBACTERIALS FOR SYSTEMIC USE", and (2) the route of medication was "intravenous" or the route was "other" with the detailed specification as "IVPB".

Any occurrence of IV antibiotic administration during the treatment period. Treatment period was

defined as the duration from the date of first dose of study drug up to 30 days after the start of study drug in the last cycle.

|  |           |
|--|-----------|
| End point type   | Secondary |
| End point timeframe:   |           |
| From randomization to the Database Lock 1 (data cutoff date 30 July 2018 - Final myelopreservation efficacy results) |           |

| End point values            | Group 1 (G/C Day 1 and 8) | Group 2 (Trilaciclib Day 1 and 8 and G/C Day 1 and 8) | Group 3 (Trilaciclib Day 1, 2, 8 and 9 and G/C Day 2 and 9) |  |
|-----------------------------|---------------------------|---|---|--|
| Subject group type          | Reporting group           | Reporting group                                       | Reporting group   |  |
| Number of subjects analysed | 34                        | 33  | 35  |  |
| Units: Number of patients   | 6                         | 5   | 0   |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: All-cause dose reductions, event rate (per cycle)

|   |   |
|---|---|
| End point title   | All-cause dose reductions, event rate (per cycle) |
| End point description:  |   |
| Dose reductions were not permitted for trilaciclib. Dose reductions for gemcitabine or carboplatin were collected on the dosing page. No more than 3 dose modifications for toxicity in total were allowed for any patient. All dose reductions were counted as a separate event. Discontinuations of an individual component of the chemotherapy regimen were counted as a dose reduction IF the patient continued the other chemotherapy drug as a monotherapy. |   |
| Event rate was calculated as the total number of cycles with an event divided by the total number of cycles. The adjusted rate ratio (Treatment Group versus Group 1), its 95% CI, and p-value were calculated using negative binomial method adjusting for number of cycles, accounting for the number of prior lines of therapy (0 versus 1 - 2) and liver involvement as the stratification factors.   |   |
| End point type  | Secondary   |
| End point timeframe:  |   |
| From randomization to the Database Lock 1 (data cutoff date 30 July 2018 - Final myelopreservation efficacy results)  |   |

| End point values            | Group 1 (G/C Day 1 and 8) | Group 2 (Trilaciclib Day 1 and 8 and G/C Day 1 and 8) | Group 3 (Trilaciclib Day 1, 2, 8 and 9 and G/C Day 2 and 9) |  |
|-----------------------------|---------------------------|---|---|--|
| Subject group type          | Reporting group           | Reporting group                                       | Reporting group   |  |
| Number of subjects analysed | 34                        | 33  | 35  |  |
| Units: Event rate per cycle |                           |   |   |  |
| number (not applicable)     | 0.141                     | 0.118   | 0.133   |  |

## Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Dose reductions in Group 3 vs Group 1   |
| Comparison groups                       | Group 3 (Trilaciclib Day 1, 2, 8 and 9 and G/C Day 2 and 9) v Group 1 (G/C Day 1 and 8) |
| Number of subjects included in analysis | 69  |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority   |
| P-value                                 | = 0.49 <sup>[8]</sup>   |
| Method                                  | Negative binomial method  |
| Parameter estimate                      | Adjusted rate ratio   |
| Point estimate                          | 0.991   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 0.475   |
| upper limit                             | 2.067   |
| Variability estimate                    | Standard error of the mean  |
| Dispersion value                        | 0.3718  |

Notes:

[8] - The 1-sided p-value was calculated using a negative binomial regression.

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Dose reductions in Group 2 vs Group 1   |
| Comparison groups                       | Group 2 (Trilaciclib Day 1 and 8 and G/C Day 1 and 8) v Group 1 (G/C Day 1 and 8) |
| Number of subjects included in analysis | 67  |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority   |
| P-value                                 | = 0.5541  |
| Method                                  | Negative binomial method  |
| Parameter estimate                      | Adjusted rate ratio   |
| Point estimate                          | 0.82  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 0.426   |
| upper limit                             | 1.58  |
| Variability estimate                    | Standard error of the mean  |
| Dispersion value                        | 0.2744  |

## Secondary: Occurrence of Febrile Neutropenia

|                 |                                   |
|-----------------|-----------------------------------|
| End point title | Occurrence of Febrile Neutropenia |
|-----------------|-----------------------------------|

**End point description:**

Each FN event was captured in AE data of electronic database, and "FEBRILE NEUTROPENIA" was a PT that could be used to identify the proper AE records; each FN event with a unique start date during the treatment period was defined as a separate event.

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

**End point timeframe:**

From randomization to the Database Lock 1 (data cutoff date 30 July 2018 - Final myelopreservation efficacy results)

| <b>End point values</b>     | Group 1 (G/C Day 1 and 8) | Group 2 (Trilaciclib Day 1 and 8 and G/C Day 1 and 8) | Group 3 (Trilaciclib Day 1, 2, 8 and 9 and G/C Day 2 and 9) |  |
|-----------------------------|---------------------------|---|---|--|
| Subject group type          | Reporting group           | Reporting group                                       | Reporting group   |  |
| Number of subjects analysed | 34                        | 33  | 35  |  |
| Units: Number of patients   | 1                         | 1   | 0   |  |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Occurrence of RBC Transfusions on/After Week 5 on Study**

|                 |   |
|-----------------|---|
| End point title | Occurrence of RBC Transfusions on/After Week 5 on Study |
|-----------------|---|

**End point description:**

Each RBC transfusion with a unique start date on/after 5 weeks on study during the treatment period was defined as a separate event.

The adjusted rate ratio (Treatment Group versus Group 1) and its 95% CI were calculated using modified Poisson method adjusting for duration of treatment in days, accounting for the number of prior lines of therapy (0 versus 1 - 2) and liver involvement as the stratification factors and baseline hemoglobin as a covariate.

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

**End point timeframe:**

From week 5 until Database Lock 1 (data cutoff date 30 July 2018 - Final myelopreservation efficacy results)

| <b>End point values</b>     | Group 1 (G/C Day 1 and 8) | Group 2 (Trilaciclib Day 1 and 8 and G/C Day 1 and 8) | Group 3 (Trilaciclib Day 1, 2, 8 and 9 and G/C Day 2 and 9) |  |
|-----------------------------|---------------------------|---|---|--|
| Subject group type          | Reporting group           | Reporting group                                       | Reporting group   |  |
| Number of subjects analysed | 34                        | 33  | 35  |  |
| Units: Number of patients   | 12                        | 11  | 8   |  |



## Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | RBC transfusions on/after W5 in Group3 vs Group1  |
| Comparison groups                       | Group 3 (Trilaciclib Day 1, 2, 8 and 9 and G/C Day 2 and 9) v Group 1 (G/C Day 1 and 8) |
| Number of subjects included in analysis | 69  |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority   |
| P-value                                 | = 0.0374 <sup>[9]</sup>   |
| Method                                  | modified Poisson regression   |
| Parameter estimate                      | Adjusted rate ratio   |
| Point estimate                          | 0.493   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 0.226   |
| upper limit                             | 1.073   |
| Variability estimate                    | Standard error of the mean  |
| Dispersion value                        | 0.1957  |

Notes:

[9] - The 1-sided p-value was calculated using a modified Poisson regression

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | RBC transfusions on/after W5 in Group2 vs Group1                                  |
| Comparison groups                       | Group 2 (Trilaciclib Day 1 and 8 and G/C Day 1 and 8) v Group 1 (G/C Day 1 and 8) |
| Number of subjects included in analysis | 67  |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority   |
| P-value                                 | = 0.7564 <sup>[10]</sup>  |
| Method                                  | modified Poisson regression   |
| Parameter estimate                      | Adjusted rate ratio   |
| Point estimate                          | 0.885   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 0.447   |
| upper limit                             | 1.754   |
| Variability estimate                    | Standard error of the mean  |
| Dispersion value                        | 0.3089  |

Notes:

[10] - The 2-sided p-value is calculated using stratified exact CMH method to account for the number of prior lines of therapy (0 versus 1 or 2) and liver involvement as the stratification factors.

## Secondary: Dose modifications - Cycle delays

|   |                                   |
|---|-----------------------------------|
| End point title   | Dose modifications - Cycle delays |
| End point description:  |                                   |
| After Cycle 1, patients need to meet pre-specified laboratory parameter criteria before initiating Cycle 2 and each subsequent cycle of chemotherapy. If the patient is unable to start a new cycle at that next visit, then the cycle is delayed, the reason entered, and the question is asked again at the next visit until the patient either starts a new cycle or discontinues treatment. |                                   |
| Other reasons for cycle delays primarily included investigator decision and administrative reasons (eg, holidays).  |                                   |
| End point type  | Secondary                         |

End point timeframe:

From randomization until the Database Lock 2 (data cutoff date 28 June 2019 includes relevant results for safety and anti-tumor efficacy analysis)

| End point values                              | Group 1 (G/C Day 1 and 8) | Group 2 (Trilaciclib Day 1 and 8 and G/C Day 1 and 8) | Group 3 (Trilaciclib Day 1, 2, 8 and 9 and G/C Day 2 and 9) |  |
|---|---------------------------|---|---|--|
| Subject group type                            | Reporting group           | Reporting group                                       | Reporting group   |  |
| Number of subjects analysed                   | 30                        | 33  | 35  |  |
| Units: Number of patients                     |                           |   |   |  |
| Number of patients with any cycle delays      | 17                        | 19  | 22  |  |
| 0 cycles delayed                              | 10                        | 14  | 11  |  |
| 1 cycle delayed                               | 11                        | 6   | 6   |  |
| 2 cycles delayed                              | 1                         | 7   | 6   |  |
| 3 or more cycles delayed                      | 5                         | 6   | 10  |  |
| Cycles delayed due to hematologic toxicity    | 13                        | 14  | 16  |  |
| Cycles delayed due to nonhematologic toxicity | 1                         | 5   | 7   |  |
| Cycles delayed due to other reasons           | 5                         | 11  | 7   |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Dose modifications - Skipped Doses

|  |                                    |
|--|------------------------------------|
| End point title  | Dose modifications - Skipped Doses |
| End point description:   |                                    |
| To receive Day 8/9 dose of each cycle, patients need to meet pre-specified laboratory parameter criteria. If the criteria is not met, the Day 8/9 doses are skipped. |                                    |
| Other reasons for skipped doses primarily included investigator decision and administrative reasons (eg, holidays).  |                                    |
| End point type   | Secondary                          |
| End point timeframe:   |                                    |
| From randomization until the Database Lock 2 (data cutoff date 28 June 2019 includes relevant results for safety and anti-tumor efficacy analysis)                   |                                    |

| End point values            | Group 1 (G/C Day 1 and 8) | Group 2 (Trilaciclib Day 1 and 8 and G/C Day 1 and 8) | Group 3 (Trilaciclib Day 1, 2, 8 and 9 and G/C Day 2 and 9) |  |
|-----------------------------|---------------------------|---|---|--|
| Subject group type          | Reporting group           | Reporting group                                       | Reporting group   |  |
| Number of subjects analysed | 30                        | 33  | 35  |  |
| Units: Number of patients   |                           |   |   |  |

|  |    |    |    |  |
|--|----|----|----|--|
| Number of patients with any skipped doses    | 15 | 20 | 13 |  |
| 0 doses skipped                              | 13 | 13 | 22 |  |
| 1 dose skipped                               | 8  | 9  | 5  |  |
| 2 doses skipped                              | 4  | 4  | 7  |  |
| 3 or more doses skipped                      | 3  | 7  | 1  |  |
| Doses skipped due to hematologic toxicity    | 13 | 19 | 11 |  |
| Doses skipped due to nonhematologic toxicity | 3  | 5  | 2  |  |
| Doses skipped due to other reasons           | 1  | 2  | 4  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Dose modifications - Dose interruptions

|                 |   |
|-----------------|---|
| End point title | Dose modifications - Dose interruptions |
|-----------------|---|

End point description:

Trilaciclib dose interruption for Group 1 is not applicable, represented as 0 in the table.

Dose interruptions for all drugs are captured on the dosing page and were summarized for each study drug.

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

End point timeframe:

From randomization until the Database Lock 2 (data cutoff date 28 June 2019 includes relevant results for safety and anti-tumor efficacy analysis)

| End point values            | Group 1 (G/C Day 1 and 8) | Group 2 (Trilaciclib Day 1 and 8 and G/C Day 1 and 8) | Group 3 (Trilaciclib Day 1, 2, 8 and 9 and G/C Day 2 and 9) |  |
|-----------------------------|---------------------------|---|---|--|
| Subject group type          | Reporting group           | Reporting group                                       | Reporting group   |  |
| Number of subjects analysed | 30                        | 33  | 35  |  |
| Units: Number of patients   |                           |   |   |  |
| Trilaciclib interruptions   | 0                         | 3   | 5   |  |
| Carboplatin interruptions   | 1                         | 1   | 0   |  |
| Gemcitabine interruptions   | 2                         | 4   | 0   |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Dose modifications - Dose Reductions

|                 |                                      |
|-----------------|--------------------------------------|
| End point title | Dose modifications - Dose Reductions |
|-----------------|--------------------------------------|

End point description:

Dose (mg/m<sup>2</sup>) reductions were not permitted for trilaciclib. Dose reductions for carboplatin and gemcitabine were determined by comparing the planned dose on the respective drug administration pages between the current cycle and the previous cycle.

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

End point timeframe:

From randomization until the Database Lock 2 (data cutoff date 28 June 2019 includes relevant results for safety and anti-tumor efficacy analysis)

| End point values                      | Group 1 (G/C Day 1 and 8) | Group 2 (Trilaciclib Day 1 and 8 and G/C Day 1 and 8) | Group 3 (Trilaciclib Day 1, 2, 8 and 9 and G/C Day 2 and 9) |  |
|---------------------------------------|---------------------------|---|---|--|
| Subject group type                    | Reporting group           | Reporting group                                       | Reporting group   |  |
| Number of subjects analysed           | 30                        | 33  | 35  |  |
| Units: Number of patients             |                           |   |   |  |
| Any carboplatin dose reductions       | 10                        | 13  | 15  |  |
| 0 carboplatin dose reductions         | 20                        | 20  | 20  |  |
| 1 carboplatin dose reductions         | 8                         | 5   | 11  |  |
| 2 carboplatin dose reductions         | 2                         | 8   | 4   |  |
| 3 or more carboplatin dose reductions | 0                         | 0   | 0   |  |
| Any gemcitabine dose reductions       | 13                        | 20  | 17  |  |
| 0 gemcitabine dose reductions         | 17                        | 13  | 18  |  |
| 1 gemcitabine dose reductions         | 11                        | 20  | 15  |  |
| 2 gemcitabine dose reductions         | 2                         | 0   | 2   |  |
| 3 or more gemcitabine dose reductions | 0                         | 0   | 0   |  |

## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Occurrence of Adverse Events

|                 |                              |
|-----------------|------------------------------|
| End point title | Occurrence of Adverse Events |
|-----------------|------------------------------|

End point description:

Treatment-Emergent Adverse Events (TEAE)

Serious Adverse Events (SAE)

An AE was any untoward medical occurrence in a patient administered a medicinal product that did not necessarily have a causal relationship with this treatment; therefore, an AE could be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the study (investigational) product.

The ICH topic E2A on Clinical Safety Data Management, Definitions, and Standards for Expedited Reporting defines an SAE as any untoward medical occurrence that at any dose:

- Resulted in death
- Was life threatening
- Required inpatient hospitalization or prolongation of existing hospitalization
- Resulted in persistent or significant disability/incapacity
- Was a congenital anomaly/birth defect

|   |                     |
|---|---------------------|
| End point type  | Other pre-specified |
| End point timeframe:  |                     |
| From randomization until the Final Database Lock (data cutoff date 17 Jul 2020) |                     |

| End point values  | Group 1 (G/C Day 1 and 8) | Group 2 (Trilaciclib Day 1 and 8 and G/C Day 1 and 8) | Group 3 (Trilaciclib Day 1, 2, 8 and 9 and G/C Day 2 and 9) |  |
|---|---------------------------|---|---|--|
| Subject group type                                      | Reporting group           | Reporting group                                       | Reporting group   |  |
| Number of subjects analysed                             | 30                        | 33  | 35  |  |
| Units: Number of patients with TEAE                     |                           |   |   |  |
| Number of patients with any TEAE                        | 30                        | 33  | 34  |  |
| Number related to any study drug                        | 26                        | 31  | 34  |  |
| Number leading to treatment discontinuation             | 10                        | 14  | 11  |  |
| Number of patients with any TEAE of Grade $\geq 3$      | 27                        | 29  | 29  |  |
| Number of patients with any TEAE of Grade $\geq 4$      | 13                        | 14  | 12  |  |
| Number of TEAE Grade $\geq 3$ related to any study drug | 24                        | 27  | 27  |  |
| Number of patients with any SAE                         | 10                        | 11  | 4   |  |
| Number of patients with SAE related to study drug       | 2                         | 3   | 0   |  |
| Number of patients with TEAE leading to death           | 1                         | 0   | 0   |  |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Safety evaluations were conducted at baseline and throughout the study.

Safety surveillance reporting of AEs and SAEs commenced at the time of informed consent and continued through 30 days after the last dose of study drug (safety follow-up phone call)

Adverse event reporting additional description:

A subject with multiple Treatment Emergent AE entries in the same SOC (PT) is only counted once within a particular SOC (PT). Included AEs that started on or after the first dose of study drug (gemcitabine, carboplatin, trilaciclib) as well as AEs with unknown/not reported onset date.

Includes information obtained in final DBL 17Jul2020

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 20.1 |
|--------------------|------|

### Reporting groups

|                       |                           |
|-----------------------|---------------------------|
| Reporting group title | Group 1 (G/C Day 1 and 8) |
|-----------------------|---------------------------|

Reporting group description:

Subjects receiving standard Gemcitabine and Carboplatin therapy (Days 1 and 8 of 21-day cycles) only. Gemcitabine 1000 mg/m<sup>2</sup> and carboplatin AUC 2 administered IV.

|                       |   |
|-----------------------|---|
| Reporting group title | Group 2 (Trilaciclib Day 1 and 8 and G/C Day 1 and 8) |
|-----------------------|---|

Reporting group description:

Subjects receiving Trilaciclib administered IV on Days 1 and 8 of 21-day cycles , plus Gemcitabine and Carboplatin therapy (Days 1 and 8 of 21-day cycles).

Gemcitabine 1000 mg/m<sup>2</sup> and carboplatin AUC 2 administered IV.

In Group 2, trilaciclib (240 mg/m<sup>2</sup>) was administered as an IV infusion over 30 (±5) minutes prior to each GC treatment (on Days 1 and 8).

There were no inpatient dose modifications of trilaciclib during the study.

Trilaciclib was administered only with GC therapy. If administration of all chemotherapy was held or discontinued, administration of trilaciclib was also to be held or discontinued.

Chemotherapy could not be administered until after completion of the trilaciclib infusion.

Study drug administration was continued until disease progression, unacceptable toxicity, withdrawal of consent, or discontinuation by the investigator, whichever occurred first.

|                       |   |
|-----------------------|---|
| Reporting group title | Group 3 (Trilaciclib Day 1, 2, 8 and 9 and G/C Day 2 and 9) |
|-----------------------|---|

Reporting group description:

Subjects receiving Trilaciclib administered IV on Days 1, 2, 8, and 9 of 21-day cycles, plus Gemcitabine and Carboplatin therapy (Days 2 and 9 of 21-day cycles).

Gemcitabine 1000 mg/m<sup>2</sup> and carboplatin AUC 2 (maximum 300 mg) administered IV.

In Group 3, trilaciclib (240 mg/m<sup>2</sup>) was administered as an IV infusion over 30 (±5) minutes on Days 1, 2, 8, and 9 plus Gemcitabine and Carboplatin therapy which was administered on Days 2 and 9.

There were no inpatient dose modifications of trilaciclib during the study. Trilaciclib was administered only with GC therapy. If administration of all chemotherapy was held or discontinued, administration of trilaciclib was also to be held or discontinued. Chemotherapy could not be administered until after completion of the trilaciclib infusion.

Study drug administration was continued until disease progression, unacceptable toxicity, withdrawal of consent, or discontinuation by the investigator, whichever occurred first.

| Serious adverse events                            | Group 1 (G/C Day 1 and 8) | Group 2 (Trilaciclib Day 1 and 8 and G/C Day 1 and 8) | Group 3 (Trilaciclib Day 1, 2, 8 and 9 and G/C Day 2 and 9) |
|---|---------------------------|---|---|
| Total subjects affected by serious adverse events |                           |   |   |
| subjects affected / exposed                       | 10 / 30 (33.33%)          | 11 / 33 (33.33%)                                      | 4 / 35 (11.43%)   |

|   |                |                |                |
|---|----------------|----------------|----------------|
| number of deaths (all causes)                               | 25             | 13             | 20             |
| number of deaths resulting from adverse events              | 1              | 0              | 0              |
| <b>Vascular disorders</b>                                   |                |                |                |
| <b>Embolism</b>   |                |                |                |
| subjects affected / exposed                                 | 0 / 30 (0.00%) | 1 / 33 (3.03%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all             | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all                  | 0 / 0          | 0 / 0          | 0 / 0          |
| <b>Hypertension</b>   |                |                |                |
| subjects affected / exposed                                 | 1 / 30 (3.33%) | 0 / 33 (0.00%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all             | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all                  | 0 / 0          | 0 / 0          | 0 / 0          |
| <b>Hypotension</b>  |                |                |                |
| subjects affected / exposed                                 | 1 / 30 (3.33%) | 0 / 33 (0.00%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all             | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all                  | 0 / 0          | 0 / 0          | 0 / 0          |
| <b>General disorders and administration site conditions</b> |                |                |                |
| <b>Non-cardiac chest pain</b>                               |                |                |                |
| subjects affected / exposed                                 | 0 / 30 (0.00%) | 0 / 33 (0.00%) | 1 / 35 (2.86%) |
| occurrences causally related to treatment / all             | 0 / 0          | 0 / 0          | 0 / 2          |
| deaths causally related to treatment / all                  | 0 / 0          | 0 / 0          | 0 / 0          |
| <b>Pain</b>   |                |                |                |
| subjects affected / exposed                                 | 1 / 30 (3.33%) | 0 / 33 (0.00%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all             | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all                  | 0 / 0          | 0 / 0          | 0 / 0          |
| <b>Respiratory, thoracic and mediastinal disorders</b>      |                |                |                |
| <b>Dyspnoea</b>   |                |                |                |
| subjects affected / exposed                                 | 1 / 30 (3.33%) | 1 / 33 (3.03%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all             | 0 / 2          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all                  | 0 / 0          | 0 / 0          | 0 / 0          |
| <b>Pleural effusion</b>                                     |                |                |                |
| subjects affected / exposed                                 | 0 / 30 (0.00%) | 2 / 33 (6.06%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all             | 0 / 0          | 1 / 2          | 0 / 0          |
| deaths causally related to treatment / all                  | 0 / 0          | 0 / 0          | 0 / 0          |
| <b>Pulmonary embolism</b>                                   |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 30 (0.00%) | 2 / 33 (6.06%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Acute respiratory failure                       |                |                |                |
| subjects affected / exposed                     | 0 / 30 (0.00%) | 1 / 33 (3.03%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Obstructive airways disorder                    |                |                |                |
| subjects affected / exposed                     | 0 / 30 (0.00%) | 1 / 33 (3.03%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pleuritic pain                                  |                |                |                |
| subjects affected / exposed                     | 0 / 30 (0.00%) | 0 / 33 (0.00%) | 1 / 35 (2.86%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Psychiatric disorders                           |                |                |                |
| Suicidal ideation                               |                |                |                |
| subjects affected / exposed                     | 0 / 30 (0.00%) | 0 / 33 (0.00%) | 1 / 35 (2.86%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Investigations                                  |                |                |                |
| Platelet count decreased                        |                |                |                |
| subjects affected / exposed                     | 0 / 30 (0.00%) | 2 / 33 (6.06%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Injury, poisoning and procedural complications  |                |                |                |
| Lumbar vertebral fracture                       |                |                |                |
| subjects affected / exposed                     | 0 / 30 (0.00%) | 1 / 33 (3.03%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Subdural haematoma                              |                |                |                |
| subjects affected / exposed                     | 0 / 30 (0.00%) | 0 / 33 (0.00%) | 1 / 35 (2.86%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |



|   |                |                |                |
|---|----------------|----------------|----------------|
| Cardiac disorders                               |                |                |                |
| Acute left ventricular failure                  |                |                |                |
| subjects affected / exposed                     | 0 / 30 (0.00%) | 0 / 33 (0.00%) | 1 / 35 (2.86%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Acute myocardial infarction                     |                |                |                |
| subjects affected / exposed                     | 1 / 30 (3.33%) | 0 / 33 (0.00%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Cardiac arrest                                  |                |                |                |
| subjects affected / exposed                     | 0 / 30 (0.00%) | 0 / 33 (0.00%) | 1 / 35 (2.86%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pericardial effusion                            |                |                |                |
| subjects affected / exposed                     | 0 / 30 (0.00%) | 1 / 33 (3.03%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Right ventricular failure                       |                |                |                |
| subjects affected / exposed                     | 1 / 30 (3.33%) | 0 / 33 (0.00%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 0          | 0 / 0          |
| Nervous system disorders                        |                |                |                |
| Syncope   |                |                |                |
| subjects affected / exposed                     | 0 / 30 (0.00%) | 1 / 33 (3.03%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Blood and lymphatic system disorders            |                |                |                |
| Febrile neutropenia                             |                |                |                |
| subjects affected / exposed                     | 1 / 30 (3.33%) | 1 / 33 (3.03%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Normochromic normocytic anaemia                 |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 30 (0.00%) | 1 / 33 (3.03%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Thrombocytopenia                                |                |                |                |
| subjects affected / exposed                     | 1 / 30 (3.33%) | 0 / 33 (0.00%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastrointestinal disorders                      |                |                |                |
| Abdominal pain                                  |                |                |                |
| subjects affected / exposed                     | 0 / 30 (0.00%) | 0 / 33 (0.00%) | 1 / 35 (2.86%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Ascites   |                |                |                |
| subjects affected / exposed                     | 1 / 30 (3.33%) | 0 / 33 (0.00%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Enteritis                                       |                |                |                |
| subjects affected / exposed                     | 1 / 30 (3.33%) | 0 / 33 (0.00%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Faecaloma                                       |                |                |                |
| subjects affected / exposed                     | 1 / 30 (3.33%) | 0 / 33 (0.00%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Oesophageal stenosis                            |                |                |                |
| subjects affected / exposed                     | 0 / 30 (0.00%) | 1 / 33 (3.03%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Varices oesophageal                             |                |                |                |
| subjects affected / exposed                     | 1 / 30 (3.33%) | 0 / 33 (0.00%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Renal and urinary disorders                     |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Haematuria                                      |                |                |                |
| subjects affected / exposed                     | 0 / 30 (0.00%) | 1 / 33 (3.03%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Urinary tract obstruction                       |                |                |                |
| subjects affected / exposed                     | 0 / 30 (0.00%) | 1 / 33 (3.03%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Musculoskeletal and connective tissue disorders |                |                |                |
| Myositis  |                |                |                |
| subjects affected / exposed                     | 0 / 30 (0.00%) | 1 / 33 (3.03%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Infections and infestations                     |                |                |                |
| Cellulitis                                      |                |                |                |
| subjects affected / exposed                     | 2 / 30 (6.67%) | 0 / 33 (0.00%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Bacteraemia                                     |                |                |                |
| subjects affected / exposed                     | 0 / 30 (0.00%) | 1 / 33 (3.03%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Lung infection                                  |                |                |                |
| subjects affected / exposed                     | 0 / 30 (0.00%) | 1 / 33 (3.03%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Septic shock                                    |                |                |                |
| subjects affected / exposed                     | 1 / 30 (3.33%) | 0 / 33 (0.00%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Metabolism and nutrition disorders              |                |                |                |
| Diabetic ketoacidosis                           |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 1 / 30 (3.33%) | 0 / 33 (0.00%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| <b>Hypercalcaemia</b>                           |                |                |                |
| subjects affected / exposed                     | 0 / 30 (0.00%) | 0 / 33 (0.00%) | 1 / 35 (2.86%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

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

| <b>Non-serious adverse events</b>                           | Group 1 (G/C Day 1 and 8) | Group 2 (Trilaciclib Day 1 and 8 and G/C Day 1 and 8) | Group 3 (Trilaciclib Day 1, 2, 8 and 9 and G/C Day 2 and 9) |
|---|---------------------------|---|---|
| Total subjects affected by non-serious adverse events       |                           |   |   |
| subjects affected / exposed                                 | 30 / 30 (100.00%)         | 33 / 33 (100.00%)                                     | 34 / 35 (97.14%)  |
| <b>Vascular disorders</b>                                   |                           |   |   |
| <b>Hypertension</b>   |                           |   |   |
| subjects affected / exposed                                 | 2 / 30 (6.67%)            | 2 / 33 (6.06%)  | 1 / 35 (2.86%)  |
| occurrences (all)   | 2                         | 2   | 7   |
| <b>Hot flush</b>  |                           |   |   |
| subjects affected / exposed                                 | 2 / 30 (6.67%)            | 2 / 33 (6.06%)  | 0 / 35 (0.00%)  |
| occurrences (all)   | 2                         | 2   | 0   |
| <b>Thrombophlebitis superficial</b>                         |                           |   |   |
| subjects affected / exposed                                 | 0 / 30 (0.00%)            | 1 / 33 (3.03%)  | 3 / 35 (8.57%)  |
| occurrences (all)   | 0                         | 1   | 7   |
| <b>Hypotension</b>  |                           |   |   |
| subjects affected / exposed                                 | 0 / 30 (0.00%)            | 0 / 33 (0.00%)  | 2 / 35 (5.71%)  |
| occurrences (all)   | 0                         | 0   | 2   |
| <b>Haematoma</b>  |                           |   |   |
| subjects affected / exposed                                 | 0 / 30 (0.00%)            | 0 / 33 (0.00%)  | 1 / 35 (2.86%)  |
| occurrences (all)   | 0                         | 0   | 1   |
| <b>General disorders and administration site conditions</b> |                           |   |   |
| <b>Fatigue</b>  |                           |   |   |
| subjects affected / exposed                                 | 11 / 30 (36.67%)          | 14 / 33 (42.42%)                                      | 16 / 35 (45.71%)  |
| occurrences (all)   | 17                        | 22  | 35  |
| <b>Oedema peripheral</b>                                    |                           |   |   |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 4 / 30 (13.33%) | 4 / 33 (12.12%) | 4 / 35 (11.43%) |
| occurrences (all)                               | 5               | 7               | 8               |
| Pyrexia   |                 |                 |                 |
| subjects affected / exposed                     | 3 / 30 (10.00%) | 6 / 33 (18.18%) | 2 / 35 (5.71%)  |
| occurrences (all)                               | 3               | 8               | 2               |
| Pain  |                 |                 |                 |
| subjects affected / exposed                     | 4 / 30 (13.33%) | 2 / 33 (6.06%)  | 3 / 35 (8.57%)  |
| occurrences (all)                               | 6               | 2               | 3               |
| Chills  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 30 (0.00%)  | 6 / 33 (18.18%) | 1 / 35 (2.86%)  |
| occurrences (all)                               | 0               | 7               | 1               |
| Influenza like illness                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 30 (0.00%)  | 0 / 33 (0.00%)  | 4 / 35 (11.43%) |
| occurrences (all)                               | 0               | 0               | 5               |
| Catheter site pain                              |                 |                 |                 |
| subjects affected / exposed                     | 1 / 30 (3.33%)  | 0 / 33 (0.00%)  | 2 / 35 (5.71%)  |
| occurrences (all)                               | 1               | 0               | 2               |
| Chest pain                                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 30 (3.33%)  | 0 / 33 (0.00%)  | 2 / 35 (5.71%)  |
| occurrences (all)                               | 1               | 0               | 2               |
| Chest discomfort                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 30 (0.00%)  | 0 / 33 (0.00%)  | 2 / 35 (5.71%)  |
| occurrences (all)                               | 0               | 0               | 4               |
| Infusion site pain                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 30 (0.00%)  | 0 / 33 (0.00%)  | 2 / 35 (5.71%)  |
| occurrences (all)                               | 0               | 0               | 2               |
| Mucosal inflammation                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 30 (0.00%)  | 2 / 33 (6.06%)  | 0 / 35 (0.00%)  |
| occurrences (all)                               | 0               | 2               | 0               |
| Reproductive system and breast disorders        |                 |                 |                 |
| Breast pain                                     |                 |                 |                 |
| subjects affected / exposed                     | 3 / 30 (10.00%) | 1 / 33 (3.03%)  | 3 / 35 (8.57%)  |
| occurrences (all)                               | 3               | 4               | 3               |
| Respiratory, thoracic and mediastinal disorders |                 |                 |                 |

|   |                       |                        |                        |
|---|-----------------------|------------------------|------------------------|
| Dyspnoea<br>subjects affected / exposed<br>occurrences (all)                    | 3 / 30 (10.00%)<br>3  | 9 / 33 (27.27%)<br>10  | 6 / 35 (17.14%)<br>7   |
| Cough<br>subjects affected / exposed<br>occurrences (all)                       | 2 / 30 (6.67%)<br>2   | 8 / 33 (24.24%)<br>8   | 7 / 35 (20.00%)<br>9   |
| Nasal congestion<br>subjects affected / exposed<br>occurrences (all)            | 1 / 30 (3.33%)<br>1   | 2 / 33 (6.06%)<br>4    | 4 / 35 (11.43%)<br>4   |
| Oropharyngeal pain<br>subjects affected / exposed<br>occurrences (all)          | 1 / 30 (3.33%)<br>1   | 1 / 33 (3.03%)<br>1    | 2 / 35 (5.71%)<br>2    |
| Pleural effusion<br>subjects affected / exposed<br>occurrences (all)            | 0 / 30 (0.00%)<br>0   | 3 / 33 (9.09%)<br>4    | 0 / 35 (0.00%)<br>0    |
| Upper-airway cough syndrome<br>subjects affected / exposed<br>occurrences (all) | 1 / 30 (3.33%)<br>1   | 2 / 33 (6.06%)<br>2    | 1 / 35 (2.86%)<br>1    |
| Psychiatric disorders   |                       |                        |                        |
| Anxiety<br>subjects affected / exposed<br>occurrences (all)                     | 3 / 30 (10.00%)<br>3  | 2 / 33 (6.06%)<br>2    | 4 / 35 (11.43%)<br>4   |
| Depression<br>subjects affected / exposed<br>occurrences (all)                  | 3 / 30 (10.00%)<br>3  | 5 / 33 (15.15%)<br>5   | 1 / 35 (2.86%)<br>1    |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)                    | 4 / 30 (13.33%)<br>4  | 1 / 33 (3.03%)<br>1    | 4 / 35 (11.43%)<br>4   |
| Investigations  |                       |                        |                        |
| Neutrophil count decreased<br>subjects affected / exposed<br>occurrences (all)  | 8 / 30 (26.67%)<br>20 | 12 / 33 (36.36%)<br>50 | 11 / 35 (31.43%)<br>30 |
| Platelet count decreased<br>subjects affected / exposed<br>occurrences (all)    | 8 / 30 (26.67%)<br>38 | 8 / 33 (24.24%)<br>13  | 12 / 35 (34.29%)<br>44 |
| Alanine aminotransferase increased  |                       |                        |                        |

|  |                 |                 |                  |
|--|-----------------|-----------------|------------------|
| subjects affected / exposed                    | 3 / 30 (10.00%) | 4 / 33 (12.12%) | 4 / 35 (11.43%)  |
| occurrences (all)                              | 5               | 6               | 4                |
| Aspartate aminotransferase increased           |                 |                 |                  |
| subjects affected / exposed                    | 3 / 30 (10.00%) | 4 / 33 (12.12%) | 4 / 35 (11.43%)  |
| occurrences (all)                              | 6               | 5               | 7                |
| White blood cell count decreased               |                 |                 |                  |
| subjects affected / exposed                    | 2 / 30 (6.67%)  | 4 / 33 (12.12%) | 2 / 35 (5.71%)   |
| occurrences (all)                              | 7               | 7               | 5                |
| Blood alkaline phosphatase increased           |                 |                 |                  |
| subjects affected / exposed                    | 2 / 30 (6.67%)  | 2 / 33 (6.06%)  | 0 / 35 (0.00%)   |
| occurrences (all)                              | 2               | 2               | 0                |
| Weight decreased                               |                 |                 |                  |
| subjects affected / exposed                    | 0 / 30 (0.00%)  | 2 / 33 (6.06%)  | 1 / 35 (2.86%)   |
| occurrences (all)                              | 0               | 3               | 1                |
| Haemoglobin decreased                          |                 |                 |                  |
| subjects affected / exposed                    | 0 / 30 (0.00%)  | 2 / 33 (6.06%)  | 0 / 35 (0.00%)   |
| occurrences (all)                              | 0               | 2               | 0                |
| Weight increased                               |                 |                 |                  |
| subjects affected / exposed                    | 0 / 30 (0.00%)  | 0 / 33 (0.00%)  | 2 / 35 (5.71%)   |
| occurrences (all)                              | 0               | 0               | 2                |
| Injury, poisoning and procedural complications |                 |                 |                  |
| Infusion related reaction                      |                 |                 |                  |
| subjects affected / exposed                    | 1 / 30 (3.33%)  | 7 / 33 (21.21%) | 4 / 35 (11.43%)  |
| occurrences (all)                              | 1               | 35              | 6                |
| Nervous system disorders                       |                 |                 |                  |
| Headache                                       |                 |                 |                  |
| subjects affected / exposed                    | 6 / 30 (20.00%) | 9 / 33 (27.27%) | 14 / 35 (40.00%) |
| occurrences (all)                              | 9               | 11              | 22               |
| Dizziness                                      |                 |                 |                  |
| subjects affected / exposed                    | 6 / 30 (20.00%) | 4 / 33 (12.12%) | 6 / 35 (17.14%)  |
| occurrences (all)                              | 8               | 7               | 11               |
| Dysgeusia                                      |                 |                 |                  |
| subjects affected / exposed                    | 0 / 30 (0.00%)  | 5 / 33 (15.15%) | 1 / 35 (2.86%)   |
| occurrences (all)                              | 0               | 5               | 1                |
| Cognitive disorders                            |                 |                 |                  |

|  |                        |                        |                        |
|--|------------------------|------------------------|------------------------|
| subjects affected / exposed<br>occurrences (all)                           | 1 / 30 (3.33%)<br>1    | 2 / 33 (6.06%)<br>2    | 1 / 35 (2.86%)<br>1    |
| Restless legs syndrome<br>subjects affected / exposed<br>occurrences (all) | 0 / 30 (0.00%)<br>0    | 2 / 33 (6.06%)<br>2    | 1 / 35 (2.86%)<br>1    |
| Burning sensation<br>subjects affected / exposed<br>occurrences (all)      | 0 / 30 (0.00%)<br>0    | 0 / 33 (0.00%)<br>0    | 2 / 35 (5.71%)<br>2    |
| Blood and lymphatic system disorders                                       |                        |                        |                        |
| Anaemia<br>subjects affected / exposed<br>occurrences (all)                | 22 / 30 (73.33%)<br>61 | 16 / 33 (48.48%)<br>46 | 15 / 35 (42.86%)<br>35 |
| Neutropenia<br>subjects affected / exposed<br>occurrences (all)            | 13 / 30 (43.33%)<br>49 | 15 / 33 (45.45%)<br>79 | 12 / 35 (34.29%)<br>31 |
| Thrombocytopenia<br>subjects affected / exposed<br>occurrences (all)       | 13 / 30 (43.33%)<br>68 | 13 / 33 (39.39%)<br>55 | 11 / 35 (31.43%)<br>55 |
| Leukopenia<br>subjects affected / exposed<br>occurrences (all)             | 5 / 30 (16.67%)<br>9   | 3 / 33 (9.09%)<br>12   | 1 / 35 (2.86%)<br>3    |
| Ear and labyrinth disorders  |                        |                        |                        |
| Tinnitus<br>subjects affected / exposed<br>occurrences (all)               | 0 / 30 (0.00%)<br>0    | 2 / 33 (6.06%)<br>2    | 0 / 35 (0.00%)<br>0    |
| Eye disorders  |                        |                        |                        |
| Lacrimation increased<br>subjects affected / exposed<br>occurrences (all)  | 1 / 30 (3.33%)<br>1    | 0 / 33 (0.00%)<br>0    | 2 / 35 (5.71%)<br>2    |
| Gastrointestinal disorders   |                        |                        |                        |
| Nausea<br>subjects affected / exposed<br>occurrences (all)                 | 7 / 30 (23.33%)<br>8   | 14 / 33 (42.42%)<br>19 | 17 / 35 (48.57%)<br>31 |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)               | 8 / 30 (26.67%)<br>9   | 8 / 33 (24.24%)<br>23  | 11 / 35 (31.43%)<br>18 |
| Constipation   |                        |                        |                        |



|  |                 |                 |                 |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed            | 5 / 30 (16.67%) | 9 / 33 (27.27%) | 9 / 35 (25.71%) |
| occurrences (all)                      | 6               | 16              | 11              |
| Diarrhoea                              |                 |                 |                 |
| subjects affected / exposed            | 4 / 30 (13.33%) | 9 / 33 (27.27%) | 5 / 35 (14.29%) |
| occurrences (all)                      | 4               | 15              | 6               |
| Gastrooesophageal reflux disease       |                 |                 |                 |
| subjects affected / exposed            | 3 / 30 (10.00%) | 5 / 33 (15.15%) | 1 / 35 (2.86%)  |
| occurrences (all)                      | 3               | 5               | 1               |
| Abdominal pain                         |                 |                 |                 |
| subjects affected / exposed            | 1 / 30 (3.33%)  | 4 / 33 (12.12%) | 2 / 35 (5.71%)  |
| occurrences (all)                      | 1               | 6               | 3               |
| Abdominal pain upper                   |                 |                 |                 |
| subjects affected / exposed            | 1 / 30 (3.33%)  | 3 / 33 (9.09%)  | 3 / 35 (8.57%)  |
| occurrences (all)                      | 1               | 3               | 3               |
| Stomatitis                             |                 |                 |                 |
| subjects affected / exposed            | 2 / 30 (6.67%)  | 1 / 33 (3.03%)  | 2 / 35 (5.71%)  |
| occurrences (all)                      | 5               | 1               | 3               |
| Abdominal distension                   |                 |                 |                 |
| subjects affected / exposed            | 0 / 30 (0.00%)  | 3 / 33 (9.09%)  | 1 / 35 (2.86%)  |
| occurrences (all)                      | 0               | 3               | 1               |
| Flatulence                             |                 |                 |                 |
| subjects affected / exposed            | 0 / 30 (0.00%)  | 2 / 33 (6.06%)  | 0 / 35 (0.00%)  |
| occurrences (all)                      | 0               | 2               | 0               |
| Skin and subcutaneous tissue disorders |                 |                 |                 |
| Alopecia                               |                 |                 |                 |
| subjects affected / exposed            | 1 / 30 (3.33%)  | 5 / 33 (15.15%) | 6 / 35 (17.14%) |
| occurrences (all)                      | 1               | 5               | 6               |
| Pruritus                               |                 |                 |                 |
| subjects affected / exposed            | 1 / 30 (3.33%)  | 3 / 33 (9.09%)  | 4 / 35 (11.43%) |
| occurrences (all)                      | 1               | 3               | 5               |
| Erythema                               |                 |                 |                 |
| subjects affected / exposed            | 0 / 30 (0.00%)  | 4 / 33 (12.12%) | 3 / 35 (8.57%)  |
| occurrences (all)                      | 0               | 21              | 4               |
| Rash                                   |                 |                 |                 |
| subjects affected / exposed            | 1 / 30 (3.33%)  | 3 / 33 (9.09%)  | 3 / 35 (8.57%)  |
| occurrences (all)                      | 1               | 3               | 4               |

|  |                      |                       |                      |
|--|----------------------|-----------------------|----------------------|
| Rash maculo-papular<br>subjects affected / exposed<br>occurrences (all)        | 1 / 30 (3.33%)<br>4  | 2 / 33 (6.06%)<br>4   | 1 / 35 (2.86%)<br>1  |
| Renal and urinary disorders  |                      |                       |                      |
| Pollakiuria<br>subjects affected / exposed<br>occurrences (all)                | 0 / 30 (0.00%)<br>0  | 1 / 33 (3.03%)<br>1   | 2 / 35 (5.71%)<br>2  |
| Acute kidney injury<br>subjects affected / exposed<br>occurrences (all)        | 0 / 30 (0.00%)<br>0  | 2 / 33 (6.06%)<br>4   | 0 / 35 (0.00%)<br>0  |
| Musculoskeletal and connective tissue disorders                                |                      |                       |                      |
| Back pain<br>subjects affected / exposed<br>occurrences (all)                  | 3 / 30 (10.00%)<br>3 | 7 / 33 (21.21%)<br>15 | 3 / 35 (8.57%)<br>5  |
| Arthralgia<br>subjects affected / exposed<br>occurrences (all)                 | 3 / 30 (10.00%)<br>4 | 6 / 33 (18.18%)<br>7  | 3 / 35 (8.57%)<br>4  |
| Pain in extremity<br>subjects affected / exposed<br>occurrences (all)          | 2 / 30 (6.67%)<br>3  | 4 / 33 (12.12%)<br>6  | 3 / 35 (8.57%)<br>4  |
| Bone pain<br>subjects affected / exposed<br>occurrences (all)                  | 4 / 30 (13.33%)<br>5 | 2 / 33 (6.06%)<br>2   | 2 / 35 (5.71%)<br>3  |
| Myalgia<br>subjects affected / exposed<br>occurrences (all)                    | 5 / 30 (16.67%)<br>5 | 2 / 33 (6.06%)<br>2   | 1 / 35 (2.86%)<br>1  |
| Musculoskeletal chest pain<br>subjects affected / exposed<br>occurrences (all) | 1 / 30 (3.33%)<br>1  | 2 / 33 (6.06%)<br>3   | 3 / 35 (8.57%)<br>3  |
| Musculoskeletal pain<br>subjects affected / exposed<br>occurrences (all)       | 1 / 30 (3.33%)<br>1  | 1 / 33 (3.03%)<br>1   | 4 / 35 (11.43%)<br>6 |
| Flank pain<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 30 (0.00%)<br>0  | 3 / 33 (9.09%)<br>6   | 1 / 35 (2.86%)<br>2  |
| Muscular weakness  |                      |                       |                      |

|  |                     |                     |                     |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all) | 0 / 30 (0.00%)<br>0 | 3 / 33 (9.09%)<br>3 | 0 / 35 (0.00%)<br>0 |
| Infections and infestations                      |                     |                     |                     |
| Urinary tract infection                          |                     |                     |                     |
| subjects affected / exposed                      | 5 / 30 (16.67%)     | 4 / 33 (12.12%)     | 3 / 35 (8.57%)      |
| occurrences (all)                                | 5                   | 4                   | 4                   |
| Pneumonia  |                     |                     |                     |
| subjects affected / exposed                      | 1 / 30 (3.33%)      | 3 / 33 (9.09%)      | 0 / 35 (0.00%)      |
| occurrences (all)                                | 1                   | 3                   | 0                   |
| Sinusitis  |                     |                     |                     |
| subjects affected / exposed                      | 1 / 30 (3.33%)      | 1 / 33 (3.03%)      | 2 / 35 (5.71%)      |
| occurrences (all)                                | 1                   | 1                   | 3                   |
| Upper respiratory tract infection                |                     |                     |                     |
| subjects affected / exposed                      | 1 / 30 (3.33%)      | 2 / 33 (6.06%)      | 0 / 35 (0.00%)      |
| occurrences (all)                                | 1                   | 3                   | 0                   |
| Nasopharyngitis                                  |                     |                     |                     |
| subjects affected / exposed                      | 2 / 30 (6.67%)      | 0 / 33 (0.00%)      | 0 / 35 (0.00%)      |
| occurrences (all)                                | 2                   | 0                   | 0                   |
| Metabolism and nutrition disorders               |                     |                     |                     |
| Hypokalaemia                                     |                     |                     |                     |
| subjects affected / exposed                      | 3 / 30 (10.00%)     | 4 / 33 (12.12%)     | 5 / 35 (14.29%)     |
| occurrences (all)                                | 3                   | 5                   | 5                   |
| Decreased appetite                               |                     |                     |                     |
| subjects affected / exposed                      | 2 / 30 (6.67%)      | 5 / 33 (15.15%)     | 4 / 35 (11.43%)     |
| occurrences (all)                                | 2                   | 6                   | 7                   |
| Hypophosphataemia                                |                     |                     |                     |
| subjects affected / exposed                      | 0 / 30 (0.00%)      | 3 / 33 (9.09%)      | 3 / 35 (8.57%)      |
| occurrences (all)                                | 0                   | 4                   | 7                   |
| Dehydration                                      |                     |                     |                     |
| subjects affected / exposed                      | 4 / 30 (13.33%)     | 0 / 33 (0.00%)      | 1 / 35 (2.86%)      |
| occurrences (all)                                | 4                   | 0                   | 1                   |
| Hypomagnesaemia                                  |                     |                     |                     |
| subjects affected / exposed                      | 2 / 30 (6.67%)      | 1 / 33 (3.03%)      | 2 / 35 (5.71%)      |
| occurrences (all)                                | 2                   | 1                   | 2                   |
| Hyponatraemia                                    |                     |                     |                     |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 30 (3.33%) | 2 / 33 (6.06%) | 2 / 35 (5.71%) |
| occurrences (all)           | 3              | 2              | 2              |
| Hypoalbuminaemia            |                |                |                |
| subjects affected / exposed | 1 / 30 (3.33%) | 1 / 33 (3.03%) | 2 / 35 (5.71%) |
| occurrences (all)           | 1              | 2              | 2              |
| Hypocalcaemia               |                |                |                |
| subjects affected / exposed | 1 / 30 (3.33%) | 2 / 33 (6.06%) | 0 / 35 (0.00%) |
| occurrences (all)           | 3              | 2              | 0              |
| Hyperlipidaemia             |                |                |                |
| subjects affected / exposed | 2 / 30 (6.67%) | 0 / 33 (0.00%) | 0 / 35 (0.00%) |
| occurrences (all)           | 2              | 0              | 0              |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment  |
|------------------|--|
| 08 December 2016 | <ul style="list-style-type: none"><li>• Text was added to allow the protocol to enroll patients in Europe and North America and to make the protocol compliant with the safety reporting standards for Europe.</li><li>• The immunologic marker blood sample collection schedule was simplified to allow all groups to have samples collected on Day 1 of each odd cycle prior to any study therapy.</li><li>• The schedule of assessments for patients randomized to Group 3 was revised. All assessments completed on Days 2 and 9 (excluding G1T28 infusion, GC infusion, associated vitals, and optional PK sampling and associated ECGs) were transitioned from Days 2 and 9 to Days 1 and 8. These assessments were aligned with assessments completed on Days 1 and 8 for patients in Groups 1 and 2. This change simplified the schedule of assessments for all groups.</li></ul>  |
| 20 March 2017    | <ul style="list-style-type: none"><li>• The secondary PK objective of the study was changed to indicate that the PK profile of gemcitabine and carboplatin was to be assessed when administered with and without trilaciclib. An exploratory objective was added to assess immune cell infiltrates in tumors.</li><li>• Criteria for subsequent study drug cycles were updated to include a provision that if the initiation of the next cycle was delayed due to toxicity, the patient was to have (at least) weekly visits to follow the toxicity.</li><li>• Exclusion criteria were modified to clarify that patients could not receive more than 1 prior chemotherapy regimen for locally recurrent or metastatic TNBC and that noncytotoxic therapies were not considered prior chemotherapy (Exclusion Criterion 1); to clarify that patients with prior treatment of locally recurrent or metastatic breast cancer with gemcitabine, carboplatin, or cisplatin were excluded (Exclusion Criterion 2); to add a provision allowing patients to receive steroids for physiological replacement (as anti-emetics) by inhalation and short course of oral/topical steroids given for allergic reactions or asthma flares (Exclusion Criterion 5); and to remove the prohibition regarding receipt of previous radiotherapy to the target lesion sites (the sites to be followed for determination of response) (Exclusion Criterion 11).</li><li>• A specification was added that on chemotherapy dosing days, trilaciclib was always to be administered first.</li><li>• Specifications were added to instructions for post-Cycle 1 use of colony-stimulating factors, including the allowance of pegfilgrastim 24 to 48 hours after Day 8/9 chemotherapy only.</li><li>• A specification was added that the first Data Monitoring Committee meeting was to occur after approximately the first 20 patients have been enrolled and completed at least 1 cycle.</li></ul> |

|                |   |
|----------------|---|
| 31 August 2017 | <ul style="list-style-type: none"> <li>•Inclusion criterion 1 modified to change the requirement from “measurable” disease to “evaluable” disease at baseline</li> <li>•Exclusion criterion 1 was updated to increase the number of prior lines of therapy allowable in the locally recurrent/metastatic TNBC setting from 1 to 2, as well as to include a specific definition as to how to count lines of prior therapy for locally recurrent/metastatic TNBC</li> <li>•Exclusion criterion 2 was deleted. Since G1T28 was hypothesized to provide clinical benefit through myelopreservation rather than a direct anti-tumor effect, allowing prior gemcitabine and carboplatin would not interfere with the study’s primary objective while expanding the eligible patient population</li> <li>•Exclusion criterion 3 was deleted. Use of chemotherapy doublets in the metastatic TNBC setting is restricted to a subset of patients who need more aggressive therapies, allowing patients with “fast” progression after (neo)adjuvant therapy would expand the eligible patient population</li> <li>•An allowance for a second dose modification of gemcitabine and carboplatin for hematologic toxicity or for Grade <math>\geq 3</math> nonhematologic toxicities was added, whereby gemcitabine or carboplatin was permitted to be discontinued while the other drug was continued at the previously reduced dose</li> <li>•Therapeutic use of growth factors in Cycle 1 was allowed per the ASCO guidelines for neutropenia and package inserts</li> <li>•Stratification for randomization was changed from ECOG performance status (0 or 1) to previous systemic anti-cancer therapy (none or prior therapy)</li> <li>•Added baseline brain scan with contrast (by CT or MRI) to be performed at screening for all patients</li> <li>•Tumor assessments were changed from every other cycle (eg, every 6 weeks) to every 9 weeks through Week 27 and then every 12 weeks thereafter</li> <li>•Clarification that malignant lymph nodes were considered an organ</li> <li>• Clarification that patients who withdrew consent from further study treatment/procedures could agree to be followed for survival</li> </ul> |
|----------------|---|

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Limitations: small sample size and open-label design. Antitumor outcomes not the primary endpoints. Use of doublet chemotherapy backbone may restrict extrapolation to patients receiving single-agent therapy. G1T28 immune effects not fully understood.

Notes: