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^2 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:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	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
Arm title	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^2 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^2. 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).

Arm title	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^2 and carboplatin AUC 2 (maximum 300 mg) administered IV.
In Group 2, trilaciclib (240 mg/m^2) was administered as an IV infusion over 30 (±5) minutes prior to each GC treatment (on Days 1 and 8).

There were no intrapatient 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^2 (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.

Arm title	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 of 21-day cycles, plus Gemcitabine and Carboplatin therapy (Days 2 and 9 of 21-day cycles).
Gemcitabine 1000 mg/m^2 and carboplatin AUC 2 (maximum 300 mg) administered IV.
In Group 3, trilaciclib (240 mg/m^2) 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 intrapatient 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[1]	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^2 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^2 and carboplatin AUC 2 (maximum 300 mg) administered IV.
In Group 2, trilaciclib (240 mg/m^2) was administered as an IV infusion over 30 (±5) minutes prior to each GC treatment (on Days 1 and 8).

There were no intrapatient 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 of 21-day cycles, plus Gemcitabine and Carboplatin therapy (Days 2 and 9 of 21-day cycles).
Gemcitabine 1000 mg/m^2 and carboplatin AUC 2 (maximum 300 mg) administered IV.
In Group 3, trilaciclib (240 mg/m^2) 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 intrapatient 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 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 Units: years			
arithmetic mean	55	56	58
standard deviation	± 13.6	± 12.1	± 9.5
Gender categorical 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 [weight (kg)]/ [height (m)]^2.			
Units: kg/m^2			
arithmetic mean	28.97	27.07	27.47
standard deviation	± 5.962	± 5.708	± 5.028
Body Surface Area			
BSA is computed using DuBois-DuBois formula as 0.20247 × [height (m)]^0.725 x [weight (kg)]^0.425			
Units: m^2			
arithmetic mean	1.81	1.77	1.77
standard deviation	± 0.199	± 0.194	± 0.202

Reporting group values	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 [weight (kg)]/ [height (m)]^2.			
Units: kg/m^2 arithmetic mean standard deviation	- -		
Body Surface Area			
BSA is computed using DuBois-DuBois formula as 0.20247 × [height (m)]^0.725 x [weight (kg)]^0.425			
Units: m^2 arithmetic mean standard deviation	- -		

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^2 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^2 and carboplatin AUC 2 (maximum 300 mg) administered IV.
In Group 2, trilaciclib (240 mg/m^2) was administered as an IV infusion over 30 (±5) minutes prior to each GC treatment (on Days 1 and 8).

There were no intrapatient 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 of 21-day cycles, plus Gemcitabine and Carboplatin therapy (Days 2 and 9 of 21-day cycles).
Gemcitabine 1000 mg/m^2 and carboplatin AUC 2 (maximum 300 mg) administered IV.
In Group 3, trilaciclib (240 mg/m^2) 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 intrapatient 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 × 10^9 cells/L observed between Day 1 Cycle X and the end of Cycle X to the date of the first ANC value ≥0.5 × 10^9/L that met the following: (1) occurred after the ANC value of <0.5 × 10^9 cells/L and (2) no other ANC values <0.5 × 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

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: days				
arithmetic mean (standard deviation)				
Duration of severe neutropenia in Cycle 1 (days)	1 (± 2.2)	2 (± 3.5)	1 (± 2.6)	

Statistical analyses

Statistical analysis title	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 [1]
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.

Statistical analysis title	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:

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.

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:

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	= 0.2382 [2]
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.

Statistical analysis title	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

Statistical analysis title	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

Statistical analysis title	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)

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)	

Statistical analyses

No statistical analyses for this end point

Secondary: Relative dose intensity of gemcitabine and carboplatin

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/m2) administered to a patient in the duration of exposure, i.e. total number of cycles received [(mg/m2)]

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^2				
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/m2) 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 [3]
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.

Statistical analysis title	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 ≥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 ≥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 [4]
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.

Statistical analysis title	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 [5]
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 ≥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

Statistical analysis title	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 [6]
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.

Statistical analysis title	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 [7]
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 ≥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 ≥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

Statistical analysis title	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 [8]
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.

Statistical analysis title	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)

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	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)

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	12	11	8	

Statistical analyses

Statistical analysis title	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 [9]
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

Statistical analysis title	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 [10]
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/m2) 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 ≥3	27	29	29	
Number of patients with any TEAE of Grade ≥4	13	14	12	
Number of TEAE Grade ≥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^2 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^2 and carboplatin AUC 2 administered IV.
In Group 2, trilaciclib (240 mg/m2) was administered as an IV infusion over 30 (±5) minutes prior to each GC treatment (on Days 1 and 8).

There were no intrapatient 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 of 21-day cycles, plus Gemcitabine and Carboplatin therapy (Days 2 and 9 of 21-day cycles).
Gemcitabine 1000 mg/m^2 and carboplatin AUC 2 (maximum 300 mg) administered IV.
In Group 3, trilaciclib (240 mg/m^2) 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 intrapatient 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
Vascular disorders			
Embolism			
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
Hypertension			
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
Hypotension			
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
General disorders and administration site conditions			
Non-cardiac chest 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 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
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
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
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
Pleural effusion			
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
Pulmonary embolism			

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
Hypercalcaemia			
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 %

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

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			
subjects affected / exposed	3 / 30 (10.00%)	9 / 33 (27.27%)	6 / 35 (17.14%)
occurrences (all)	3	10	7
Cough			
subjects affected / exposed	2 / 30 (6.67%)	8 / 33 (24.24%)	7 / 35 (20.00%)
occurrences (all)	2	8	9
Nasal congestion			
subjects affected / exposed	1 / 30 (3.33%)	2 / 33 (6.06%)	4 / 35 (11.43%)
occurrences (all)	1	4	4
Oropharyngeal pain			
subjects affected / exposed	1 / 30 (3.33%)	1 / 33 (3.03%)	2 / 35 (5.71%)
occurrences (all)	1	1	2
Pleural effusion			
subjects affected / exposed	0 / 30 (0.00%)	3 / 33 (9.09%)	0 / 35 (0.00%)
occurrences (all)	0	4	0
Upper-airway cough syndrome			
subjects affected / exposed	1 / 30 (3.33%)	2 / 33 (6.06%)	1 / 35 (2.86%)
occurrences (all)	1	2	1
Psychiatric disorders			
Anxiety			
subjects affected / exposed	3 / 30 (10.00%)	2 / 33 (6.06%)	4 / 35 (11.43%)
occurrences (all)	3	2	4
Depression			
subjects affected / exposed	3 / 30 (10.00%)	5 / 33 (15.15%)	1 / 35 (2.86%)
occurrences (all)	3	5	1
Insomnia			
subjects affected / exposed	4 / 30 (13.33%)	1 / 33 (3.03%)	4 / 35 (11.43%)
occurrences (all)	4	1	4
Investigations			
Neutrophil count decreased			
subjects affected / exposed	8 / 30 (26.67%)	12 / 33 (36.36%)	11 / 35 (31.43%)
occurrences (all)	20	50	30
Platelet count decreased			
subjects affected / exposed	8 / 30 (26.67%)	8 / 33 (24.24%)	12 / 35 (34.29%)
occurrences (all)	38	13	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	1 / 30 (3.33%)	2 / 33 (6.06%)	1 / 35 (2.86%)
occurrences (all)	1	2	1
Restless legs syndrome			
subjects affected / exposed	0 / 30 (0.00%)	2 / 33 (6.06%)	1 / 35 (2.86%)
occurrences (all)	0	2	1
Burning sensation			
subjects affected / exposed	0 / 30 (0.00%)	0 / 33 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	0	2
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	22 / 30 (73.33%)	16 / 33 (48.48%)	15 / 35 (42.86%)
occurrences (all)	61	46	35
Neutropenia			
subjects affected / exposed	13 / 30 (43.33%)	15 / 33 (45.45%)	12 / 35 (34.29%)
occurrences (all)	49	79	31
Thrombocytopenia			
subjects affected / exposed	13 / 30 (43.33%)	13 / 33 (39.39%)	11 / 35 (31.43%)
occurrences (all)	68	55	55
Leukopenia			
subjects affected / exposed	5 / 30 (16.67%)	3 / 33 (9.09%)	1 / 35 (2.86%)
occurrences (all)	9	12	3
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 30 (0.00%)	2 / 33 (6.06%)	0 / 35 (0.00%)
occurrences (all)	0	2	0
Eye disorders			
Lacrimation increased			
subjects affected / exposed	1 / 30 (3.33%)	0 / 33 (0.00%)	2 / 35 (5.71%)
occurrences (all)	1	0	2
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	7 / 30 (23.33%)	14 / 33 (42.42%)	17 / 35 (48.57%)
occurrences (all)	8	19	31
Vomiting			
subjects affected / exposed	8 / 30 (26.67%)	8 / 33 (24.24%)	11 / 35 (31.43%)
occurrences (all)	9	23	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			
subjects affected / exposed	1 / 30 (3.33%)	2 / 33 (6.06%)	1 / 35 (2.86%)
occurrences (all)	4	4	1
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	0 / 30 (0.00%)	1 / 33 (3.03%)	2 / 35 (5.71%)
occurrences (all)	0	1	2
Acute kidney injury			
subjects affected / exposed	0 / 30 (0.00%)	2 / 33 (6.06%)	0 / 35 (0.00%)
occurrences (all)	0	4	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	3 / 30 (10.00%)	7 / 33 (21.21%)	3 / 35 (8.57%)
occurrences (all)	3	15	5
Arthralgia			
subjects affected / exposed	3 / 30 (10.00%)	6 / 33 (18.18%)	3 / 35 (8.57%)
occurrences (all)	4	7	4
Pain in extremity			
subjects affected / exposed	2 / 30 (6.67%)	4 / 33 (12.12%)	3 / 35 (8.57%)
occurrences (all)	3	6	4
Bone pain			
subjects affected / exposed	4 / 30 (13.33%)	2 / 33 (6.06%)	2 / 35 (5.71%)
occurrences (all)	5	2	3
Myalgia			
subjects affected / exposed	5 / 30 (16.67%)	2 / 33 (6.06%)	1 / 35 (2.86%)
occurrences (all)	5	2	1
Musculoskeletal chest pain			
subjects affected / exposed	1 / 30 (3.33%)	2 / 33 (6.06%)	3 / 35 (8.57%)
occurrences (all)	1	3	3
Musculoskeletal pain			
subjects affected / exposed	1 / 30 (3.33%)	1 / 33 (3.03%)	4 / 35 (11.43%)
occurrences (all)	1	1	6
Flank pain			
subjects affected / exposed	0 / 30 (0.00%)	3 / 33 (9.09%)	1 / 35 (2.86%)
occurrences (all)	0	6	2
Muscular weakness			

subjects affected / exposed	0 / 30 (0.00%)	3 / 33 (9.09%)	0 / 35 (0.00%)
occurrences (all)	0	3	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	• 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. • 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. • 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.
20 March 2017	• 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. • 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. • 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). • A specification was added that on chemotherapy dosing days, trilaciclib was always to be administered first. • 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. • 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.

31 August 2017	•Inclusion criterion 1 modified to change the requirement from "measurable" disease to "evaluable" disease at baseline •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 •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 •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 •An allowance for a second dose modification of gemcitabine and carboplatin for hematologic toxicity or for Grade ≥3 nonhematologic toxicities was added, whereby gemcitabine or carboplatin was permitted to be discontinued while the other drug was continued at the previously reduced dose •Therapeutic use of growth factors in Cycle 1 was allowed per the ASCO guidelines for neutropenia and package inserts •Stratification for randomization was changed from ECOG performance status (0 or 1) to previous systemic anti-cancer therapy (none or prior therapy) •Added baseline brain scan with contrast (by CT or MRI) to be performed at screening for all patients •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 •Clarification that malignant lymph nodes were considered an organ • Clarification that patients who withdrew consent from further study treatment/procedures could agree to be followed for survival

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: