Clinical trial results:
A Phase 3, Randomized, Double-Blind Study of Trilaciclib or Placebo in Patients Receiving First- or Second-Line Gemcitabine and Carboplatin Chemotherapy for Locally Advanced Unresectable or Metastatic Triple-Negative Breast Cancer (PRESERVE 2)

Summary

EudraCT number	2020-004930-39
Trial protocol	FR BG PL ES
Global end of trial date	24 May 2024

Results information

Result version number	v1 (current)
This version publication date	19 March 2025
First version publication date	19 March 2025

Trial information

Trial identification

Sponsor protocol code	G1T28-208

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04799249
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	G1 Therapeutics, Inc.
Sponsor organisation address	700 Park Offices Dr. Suite 200 PO Box 110341 Research Triangle Park, North Carolina, United States, 27709
Public contact	Clinical Trial Information, G1 Therapeutics, Inc., 000 1919 213 9835, clinicalinfo@g1therapeutics.com
Scientific contact	Clinical Trial Information, G1 Therapeutics, Inc., 000 1919 213 9835, 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	13 June 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 May 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Cohort 1: First-Line, programmed cell death protein 1 (PD-1)/ programmed death-ligand 1(PD-L1) Inhibitor-Naïve Population:
To evaluate the effect of trilaciclib on overall survival (OS) compared with placebo

Cohort 2: Second-line, Previously Treated with a PD-1/PD-L1 Inhibitor Population:
To evaluate the effect of trilaciclib on OS compared with placebo

Protection of trial subjects:

This study was conducted in accordance with the ethical principles of Good Clinical Practice (GCP), including archiving of essential documents, and according to the International Council for Harmonisation (ICH) Harmonised Tripartite Guideline.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 May 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 22
Country: Number of subjects enrolled	Spain: 15
Country: Number of subjects enrolled	Bulgaria: 2
Country: Number of subjects enrolled	France: 13
Country: Number of subjects enrolled	United States: 22
Country: Number of subjects enrolled	Ukraine: 13
Country: Number of subjects enrolled	Russian Federation: 7
Country: Number of subjects enrolled	Moldova, Republic of: 4
Country: Number of subjects enrolled	Georgia: 43
Country: Number of subjects enrolled	China: 37
Country: Number of subjects enrolled	Australia: 9
Worldwide total number of subjects	187
EEA total number of subjects	52

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)	132
From 65 to 84 years	55
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 80 sites in Australia, Bulgaria, China, France, Georgia, Moldova, Poland, Russia, Spain, Ukraine, and the US, from 08 June 2021 (first subject enrolled) to 24 May 2024 (last subject last visit).

Pre-assignment

Screening details:

Subjects who met the inclusion criteria and none of the exclusion criteria were enrolled to the study. All study assessments were performed as per the schedule of assessment.
Of the 252 subjects screened, 65 were screen failures and 187 subjects were randomized to treatment.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo + Gemcitabine + Carboplatin

Arm description:

Subjects received placebo matching with Trilaciclib prior to chemotherapy on Day 1 and Day 8 of each 21-day cycles.

Arm type	Placebo
Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	Chemotherapy
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Gemcitabine 1000 mg/m2 was administered intravenously (IV) on Day 1 and Day 8 of each 21-day cycle.

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

Dosage and administration details:

Placebo matching with Trilaciclib was administered IV over 30 minutes prior to chemotherapy on Day 1 and Day 8 of each 21-day cycle.

Investigational medicinal product name	Carboplatin
Investigational medicinal product code	
Other name	Chemotherapy
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Carboplatin with a target area under the curve (AUC)=2 was administered IV on Day 1 and Day 8 of each 21-day cycle.

Arm title	Trilaciclib + Gemcitabine + Carboplatin

Arm description:	
Subjects received Trilaciclib prior to chemotherapy on Day 1 and Day 8 of each 21-day cycle.	
Arm type	Experimental
Investigational medicinal product name	Trilaciclib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intravenous use
Dosage and administration details:	
Trilaciclib 240 mg/m2 was administered IV over 30 minutes prior to chemotherapy on Day 1 and Day 8 of each 21-day cycle.	
Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	Chemotherapy
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Gemcitabine 1000 mg/m2 was administered IV on Day 1 and Day 8 of each 21-day cycle.	
Investigational medicinal product name	Carboplatin
Investigational medicinal product code	
Other name	Chemotherapy
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Carboplatin with a target area under the curve (AUC)=2 was administered IV on Day 1 and Day 8 of each 21-day cycle.	

Number of subjects in period 1	Placebo + Gemcitabine + Carboplatin	Trilaciclib + Gemcitabine + Carboplatin
Started	91	96
Completed	0	0
Not completed	91	96
Consent withdrawn by subject	11	16
Death	54	50
Other	-	1
Study Terminated by Sponsor	23	25
Lost to follow-up	3	4

Baseline characteristics

Reporting groups	
Reporting group title	Placebo + Gemcitabine + Carboplatin
Reporting group description:	
Subjects received placebo matching with Trilaciclib prior to chemotherapy on Day 1 and Day 8 of each 21-day cycles.	
Reporting group title	Trilaciclib + Gemcitabine + Carboplatin
Reporting group description:	
Subjects received Trilaciclib prior to chemotherapy on Day 1 and Day 8 of each 21-day cycle.	

Reporting group values	Placebo + Gemcitabine + Carboplatin	Trilaciclib + Gemcitabine + Carboplatin	Total
Number of subjects	91	96	187
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	65	67	132
From 65-84 years	26	29	55
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	57.1	58.6	
standard deviation	± 11.40	± 11.10	-
Gender categorical Units: Subjects			
Female	90	95	185
Male	1	1	2

End points

End points reporting groups

Reporting group title	Placebo + Gemcitabine + Carboplatin
Reporting group description:	
Subjects received placebo matching with Trilaciclib prior to chemotherapy on Day 1 and Day 8 of each 21-day cycles.	
Reporting group title	Trilaciclib + Gemcitabine + Carboplatin
Reporting group description:	
Subjects received Trilaciclib prior to chemotherapy on Day 1 and Day 8 of each 21-day cycle.	

Primary: Overall Survival (OS)

End point title	Overall Survival (OS)
End point description:	
The OS defined as time from randomization to death due to any cause for those who died; or time to last contact known as alive for those who survived in the study (censored cases). The effect of Trilaciclib on OS compared with placebo was evaluated. The intent-to-treat (ITT) population included all randomized subjects.	
End point type	Primary
End point timeframe:	
From the first dose of study drug (Day 1) up to 30 days after the last dose of study drug, approximately 32.5 months	

End point values	Placebo + Gemcitabine + Carboplatin	Trilaciclib + Gemcitabine + Carboplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	96		
Units: Months				
median (confidence interval 95%)	17.8 (13.3 to 22.5)	17.4 (12.4 to 21.3)		

Statistical analyses

Statistical analysis title	Trilaciclib vs Placebo
Statistical analysis description:	
The hazard ratio (HR) and its confidence interval (CI) were generated using the Cox regression model accounting for stratification factors of PD-L1 status, disease-free interval, and region.	
Comparison groups	Placebo + Gemcitabine + Carboplatin v Trilaciclib + Gemcitabine + Carboplatin

Number of subjects included in analysis	187
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	1.33

Statistical analysis title	Trilaciclib vs Placebo

Statistical analysis description:

The HR and its CI were generated using the Cox regression model without accounting for stratification factors of PD-L1 status, disease-free interval, and region.

Comparison groups	Placebo + Gemcitabine + Carboplatin v Trilaciclib + Gemcitabine + Carboplatin
Number of subjects included in analysis	187
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	1.38

Secondary: OS in PD-L1-positive subgroup

End point title	OS in PD-L1-positive subgroup

End point description:

The OS defined as time from randomization to death due to any cause for those who died; or time to last contact known as alive for those who survived in the study (censored cases).
The effect of Trilaciclib on OS as compared with placebo in the PD-L1-positive subgroup was assessed.
The ITT population included all randomized subjects. Only subjects with PD-L1-positive were analyzed.
Here, 99999 indicates that the upper limit of 95% CI was not estimable due to small number of events.

End point type	Secondary

End point timeframe:

From the first dose of study drug (Day 1) up to 30 days after the last dose of study drug, approximately 32.5 months

End point values	Placebo + Gemcitabine + Carboplatin	Trilaciclib + Gemcitabine + Carboplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	37		
Units: Months				
median (confidence interval 95%)	21.8 (14.9 to 26.0)	23.1 (9.1 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: OS in PD-L1-negative subgroup

End point title	OS in PD-L1-negative subgroup

End point description:

The OS defined as time from randomization to death due to any cause for those who died; or time to last contact known as alive for those who survived in the study (censored cases).
The effect of Trilaciclib on OS as compared with placebo in the PD-L1-negative subgroup was assessed.
The ITT population included all randomized subjects. Only subjects with PD-L1-negative were analyzed.

End point type	Secondary

End point timeframe:

From the first dose of study drug (Day 1) up to 30 days after the last dose of study drug, approximately 32.5 months

End point values	Placebo + Gemcitabine + Carboplatin	Trilaciclib + Gemcitabine + Carboplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54	59		
Units: Months				
median (confidence interval 95%)	14.9 (9.9 to 22.4)	15.7 (11.9 to 20.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)

End point description:

The PFS using Response Evaluation Criteria in Solid Tumors (RECIST 1.1), defined as time from randomization to disease progression or death due to any cause, whichever occurred first.
The effect of Trilaciclib on PFS as compared with placebo was assessed.
The ITT population included all randomized subjects. Only subjects with PFS event were analyzed.

End point type	Secondary

End point timeframe:

Up to 32.5 months

End point values	Placebo + Gemcitabine + Carboplatin	Trilaciclib + Gemcitabine + Carboplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	58		
Units: Months				
median (confidence interval 95%)	6.4 (5.2 to 8.1)	6.3 (4.4 to 8.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)

End point description:

Confirmed ORR [confirmed complete response (CR) or partial response (PR)] is defined as the percentage of subjects who achieved confirmed objective response based on the Response evaluable population.
The anti-tumor activity of Trilaciclib as compared with placebo was assessed.
The Response evaluable population included those subjects in the ITT population and had measurable (target) tumor lesion(s) at the baseline tumor assessment.

End point type	Secondary

End point timeframe:

Up to 32.5 months

End point values	Placebo + Gemcitabine + Carboplatin	Trilaciclib + Gemcitabine + Carboplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	95		
Units: Percentage of subjects				
number (confidence interval 95%)	38.2 (28.1 to 49.1)	29.5 (20.6 to 39.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Benefit Rate (CBR)

End point title	Clinical Benefit Rate (CBR)

End point description:

The CBR is defined as the percentage of subjects with best overall response of confirmed CR, confirmed PR, or stable disease lasting 24 weeks or longer, based on the Response evaluable population.

The anti-tumor activity of trilaciclib as compared with placebo was assessed.
The Response evaluable population included those subjects in the ITT population and had measurable (target) tumor lesion(s) at the baseline tumor assessment.

End point type	Secondary

End point timeframe:

Up to 32.5 months

End point values	Placebo + Gemcitabine + Carboplatin	Trilaciclib + Gemcitabine + Carboplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	95		
Units: Percentage of subjects				
number (confidence interval 95%)	52.8 (41.9 to 63.5)	42.1 (32.0 to 52.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of objective response (DOR)

End point title	Duration of objective response (DOR)

End point description:

The DoR is defined as the time from the date when the objective response of CR or PR was first documented to the date that radiographic progressive disease is documented, or death, whichever comes first.
The anti-tumor activity of Trilaciclib as compared with placebo was assessed.
The Response evaluable population included those subjects in the ITT population and had measurable (target) tumor lesion(s) at the baseline tumor assessment.

End point type	Secondary

End point timeframe:

Up to 32.5 months

End point values	Placebo + Gemcitabine + Carboplatin	Trilaciclib + Gemcitabine + Carboplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	95		
Units: Months				
median (confidence interval 95%)	8.3 (4.5 to 12.8)	7.6 (6.2 to 17.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Number of subjects with Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point description:

An AE is any unwanted medical occurrence that happens during or after the use of a treatment, regardless of its relation to the treatment. AEs can include side effects, abnormal test results, or other health issues. These events can vary in severity, from mild symptoms to more serious conditions.
An SAE is a specific, more severe type of AE. It includes events that result in death, life-threatening situations, hospitalization, significant disability, or birth defects. An SAE may also involve events that require intervention to prevent these outcomes.
The safety and tolerability of Trilaciclib compared with placebo were assessed.
The safety population included all randomized subjects in the ITT population who received at least 1 dose of study drug.
Common terminology criteria for adverse events = CTCAE; Discontinuation = DC; Adverse event of special interest = AESI; Trilaciclib/Placebo = t/p

End point type	Secondary

End point timeframe:

From Day 1 (first dose administration) through last dose + 30 days (Safety Follow-up Visit) (approximately 32.5 months)

End point values	Placebo + Gemcitabine + Carboplatin	Trilaciclib + Gemcitabine + Carboplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	93		
Units: Subjects				
Any AE	82	86		
Any AE of CTCAE Grade ≥3	73	70		
Any AE of CTCAE Grade ≥4	28	14		
Any study drug-related AE	78	81		
Trilaciclib/placebo (t/p)-related AE	53	56		
Gemcitabine-related AE	78	78		
Carboplatin-related AE	77	80		
Any serious adverse event (SAE)	12	16		
Any t/p-related SAE	3	6		
Any gemcitabine-related SAE	8	10		
Any carboplatin-related SAE	7	10		
AE leading to DC of any study drug	23	21		
AE leading to t/p DC	8	15		
AE leading to gemcitabine DC	11	18		
AE leading to carboplatin DC	20	18		
T/p-related AE leading to DC of t/p	5	5		
AE leading to death	1	0		
AESI for trilaciclib	10	12		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with Trilaciclib infusion interruptions

End point title	Number of subjects with Trilaciclib infusion interruptions

End point description:

The safety and tolerability of Trilaciclib compared with placebo were assessed.
The safety population included all randomized subjects in the ITT population who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

From Day 1 (first dose administration) up to 32.5 months

End point values	Placebo + Gemcitabine + Carboplatin	Trilaciclib + Gemcitabine + Carboplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	93		
Units: Subjects	0	7		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with chemotherapy dose modifications

End point title	Number of subjects with chemotherapy dose modifications

End point description:

The safety and tolerability of Trilaciclib compared with placebo was assessed.
The safety population included all randomized subjects in the ITT population who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

From Day 1 (first dose administration) up to 32.5 months

End point values	Placebo + Gemcitabine + Carboplatin	Trilaciclib + Gemcitabine + Carboplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	93		
Units: Subjects				
Overall (any chemotherapy)	57	46		
Gemcitabine	57	46		
Carboplatin	53	42		

Statistical analyses

No statistical analyses for this end point

Secondary: Relative dose intensity for gemcitabine and carboplatin

End point title	Relative dose intensity for gemcitabine and carboplatin

End point description:

The safety and tolerability of Trilaciclib compared with placebo was assessed.
The safety population included all randomized subjects in the ITT population who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

From Day 1 (first dose administration) up to 32.5 months

End point values	Placebo + Gemcitabine + Carboplatin	Trilaciclib + Gemcitabine + Carboplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	93		
Units: Percentage				
median (full range (min-max))				
Gemcitabine	71.84 (27.10 to 99.55)	75.50 (27.79 to 109.87)		
Carboplatin	73.86 (23.32 to 119.47)	76.75 (31.36 to 106.31)		

Statistical analyses

No statistical analyses for this end point

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

End point title	Duration of severe (Grade 4) neutropenia in Cycle 1

End point description:

The effects of trilaciclib on the neutrophil lineage compared with placebo was assessed.
The ITT population included all randomized subjects.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1 (each cycle was 21 days)

End point values	Placebo + Gemcitabine + Carboplatin	Trilaciclib + Gemcitabine + Carboplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	96		
Units: Days				
arithmetic mean (standard deviation)	0.9 (± 2.74)	0.4 (± 1.91)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with severe (Grade 4) neutropenia

End point title	Number of subjects with severe (Grade 4) neutropenia

End point description:

The effects of trilaciclib on the neutrophil lineage compared with placebo was assessed.
The ITT population included all randomized subjects.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1 (each cycle is 21 days) up to 14 months

End point values	Placebo + Gemcitabine + Carboplatin	Trilaciclib + Gemcitabine + Carboplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	96		
Units: Subjects	26	8		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with febrile neutropenia AEs

End point title	Number of subjects with febrile neutropenia AEs

End point description:

The effects of trilaciclib on the neutrophil lineage compared with placebo was assessed.
The ITT population included all randomized subjects.

End point type	Secondary

End point timeframe:

From Day 1 (first dose administration) up to 32.5 months

End point values	Placebo + Gemcitabine + Carboplatin	Trilaciclib + Gemcitabine + Carboplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	96		
Units: Subjects	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with granulocyte-colony stimulating factor (G-CSF) administration

End point title	Number of subjects with granulocyte-colony stimulating factor (G-CSF) administration

End point description:

The effects of trilaciclib on the neutrophil lineage compared with placebo was assessed.
The ITT population included all randomized subjects.

End point type	Secondary

End point timeframe:

From Day 1 (first dose administration) up to 32.5 months

End point values	Placebo + Gemcitabine + Carboplatin	Trilaciclib + Gemcitabine + Carboplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	96		
Units: Subjects	56	56		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with Grade 3 or 4 decreased hemoglobin laboratory values

End point title	Number of subjects with Grade 3 or 4 decreased hemoglobin laboratory values

End point description:

The effects of trilaciclib on the red blood cell (RBC) lineage compared with placebo was assessed.
The ITT population included all randomized subjects.

End point type	Secondary

End point timeframe:

From Day 1 (first dose administration) up to 32.5 months

End point values	Placebo + Gemcitabine + Carboplatin	Trilaciclib + Gemcitabine + Carboplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	96		
Units: Subjects	21	17		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with red blood cell (RBC) transfusions

End point title	Number of subjects with red blood cell (RBC) transfusions

End point description:

The effects of Trilaciclib on the RBC lineage compared with placebo was assessed.
The ITT population included all randomized subjects.

End point type	Secondary

End point timeframe:

On or after Week 5 up to 32.5 months

End point values	Placebo + Gemcitabine + Carboplatin	Trilaciclib + Gemcitabine + Carboplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	96		
Units: Subjects	12	9		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with erythropoiesis stimulating agent (ESA) administration

End point title	Number of subjects with erythropoiesis stimulating agent (ESA) administration

End point description:

The effects of Trilaciclib on the RBC lineage compared with placebo were assessed.
The ITT population included all randomized subjects.

End point type	Secondary

End point timeframe:

From Day 1 (first dose administration) up to 32.5 months

End point values	Placebo + Gemcitabine + Carboplatin	Trilaciclib + Gemcitabine + Carboplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	96		
Units: Subjects	6	9		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with Grade 3 or 4 decreased platelet count laboratory values

End point title	Number of subjects with Grade 3 or 4 decreased platelet count laboratory values

End point description:

The effects of trilaciclib on the platelet lineage compared with placebo were assessed.
The ITT population included all randomized subjects.

End point type	Secondary

End point timeframe:

From Day 1 (first dose administration) up to 32.5 months

End point values	Placebo + Gemcitabine + Carboplatin	Trilaciclib + Gemcitabine + Carboplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	96		
Units: Subjects	15	14		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with platelet transfusions

End point title	Number of subjects with platelet transfusions

End point description:

The effects of trilaciclib on the platelet lineage compared with placebo were assessed.
The ITT population included all randomized subjects.

End point type	Secondary

End point timeframe:

From Day 1 (first dose administration) up to 32.5 months

End point values	Placebo + Gemcitabine + Carboplatin	Trilaciclib + Gemcitabine + Carboplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	96		
Units: Subjects	3	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with at least one hospitalization due to chemotherapy-induced myelosuppression

End point title	Number of subjects with at least one hospitalization due to chemotherapy-induced myelosuppression

End point description:

The effects of trilaciclib on hospitalizations due to chemotherapy-induced myelosuppression compared with placebo were assessed.
The ITT population included all randomized subjects.

End point type	Secondary

End point timeframe:

From Day 1 (first dose administration) up to 32.5 months

End point values	Placebo + Gemcitabine + Carboplatin	Trilaciclib + Gemcitabine + Carboplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	96		
Units: Subjects	5	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with all-cause dose reductions

End point title	Number of subjects with all-cause dose reductions

End point description:

The effects of trilaciclib on chemotherapy dosing compared with placebo were assessed.
The ITT population included all randomized subjects.

End point type	Secondary

End point timeframe:

From Day 1 (first dose administration) up to 32.5 months

End point values	Placebo + Gemcitabine + Carboplatin	Trilaciclib + Gemcitabine + Carboplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	96		
Units: Subjects	57	46		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with all-cause cycle delays

End point title	Number of subjects with all-cause cycle delays

End point description:

The effects of trilaciclib on chemotherapy dosing compared with placebo were assessed.
The ITT population included all randomized subjects.

End point type	Secondary

End point timeframe:

From Day 1 (first dose administration) up to 32.5 months

End point values	Placebo + Gemcitabine + Carboplatin	Trilaciclib + Gemcitabine + Carboplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	96		
Units: Subjects	56	49		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Confirmed Deterioration of Fatigue (TTCD-fatigue)

End point title	Time to First Confirmed Deterioration of Fatigue (TTCD-fatigue)

End point description:

The effect of trilaciclib on subjects' quality of life as measured by time to first confirmed deterioration of fatigue compared with placebo as measured by the functional assessment of chronic illness therapy - fatigue (FACIT-F) was planned to be assessed.
Data was not collected due to insufficient subjects at the end of the study.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1 (each cycle is 21 days) up to 14 months

End point values	Placebo + Gemcitabine + Carboplatin	Trilaciclib + Gemcitabine + Carboplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[1]	0[2]		
Units: Months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[1] - Data was not collected due to insufficient subjects at the end of the study

[2] - Data was not collected due to insufficient subjects at the end of the study

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Quality of Life, Fatigue, and Patient-Reported Outcomes

End point title	Change in Quality of Life, Fatigue, and Patient-Reported Outcomes

End point description:

The effect of Trilaciclib on chemotherapy-induced myelosuppression-related symptoms and functional limitations compared with placebo was planned to be assessed.
Data was not collected due to insufficient subjects at the end of the study

End point type	Secondary

End point timeframe:

Cycle 1 Day 1 (each cycle is 21 days) up to 14 months

End point values	Placebo + Gemcitabine + Carboplatin	Trilaciclib + Gemcitabine + Carboplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[3]	0[4]		
Units: Score				
number (not applicable)				

Notes:

[3] - Data was not collected due to insufficient subjects at the end of the study

[4] - Data was not collected due to insufficient subjects at the end of the study

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs are collected starting from the first dose of study drug (Day 1) up to 30 days after the last dose of study drug, approximately 32.5 months

Adverse event reporting additional description:

The safety population included all randomized subjects in the ITT population who received at least 1 dose of study drug.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.1

Reporting groups

Reporting group title	Placebo + Gemcitabine + Carboplatin

Reporting group description:

Subjects received placebo matching with Trilaciclib prior to chemotherapy on Day 1 and Day 8 of each 21-day cycles.

Reporting group title	Trilaciclib + Gemcitabine + Carboplatin

Reporting group description:

Subjects received Trilaciclib prior to chemotherapy on Day 1 and Day 8 of each 21-day cycle.

Serious adverse events	Placebo + Gemcitabine + Carboplatin	Trilaciclib + Gemcitabine + Carboplatin	
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 93 (13.98%)	17 / 96 (17.71%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	1	0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 93 (0.00%)	2 / 96 (2.08%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	2 / 93 (2.15%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			

subjects affected / exposed	1 / 93 (1.08%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 93 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 93 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Superior vena cava syndrome			
subjects affected / exposed	1 / 93 (1.08%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac disorders			
Cardiac failure congestive			
subjects affected / exposed	0 / 93 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular failure			
subjects affected / exposed	0 / 93 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Seizure			
subjects affected / exposed	0 / 93 (0.00%)	2 / 96 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	2 / 93 (2.15%)	4 / 96 (4.17%)	
occurrences causally related to treatment / all	0 / 2	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 93 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 93 (1.08%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 93 (1.08%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 93 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 93 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 93 (1.08%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			

subjects affected / exposed	1 / 93 (1.08%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary thrombosis			
subjects affected / exposed	1 / 93 (1.08%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Drug-induced liver injury			
subjects affected / exposed	1 / 93 (1.08%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 93 (1.08%)	2 / 96 (2.08%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	0 / 93 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mastitis			
subjects affected / exposed	0 / 93 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	0 / 93 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 93 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			

Dehydration			
subjects affected / exposed	0 / 93 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 93 (1.08%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo + Gemcitabine + Carboplatin	Trilaciclib + Gemcitabine + Carboplatin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	86 / 93 (92.47%)	88 / 96 (91.67%)	
Investigations			
Neutrophil count decreased			
subjects affected / exposed	37 / 93 (39.78%)	41 / 96 (42.71%)	
occurrences (all)	172	166	
Alanine aminotransferase increased			
subjects affected / exposed	38 / 93 (40.86%)	23 / 96 (23.96%)	
occurrences (all)	104	51	
White blood cell count decreased			
subjects affected / exposed	24 / 93 (25.81%)	33 / 96 (34.38%)	
occurrences (all)	113	190	
Aspartate aminotransferase increased			
subjects affected / exposed	34 / 93 (36.56%)	22 / 96 (22.92%)	
occurrences (all)	84	51	
Platelet count decreased			
subjects affected / exposed	26 / 93 (27.96%)	25 / 96 (26.04%)	
occurrences (all)	83	88	
Lymphocyte count decreased			
subjects affected / exposed	10 / 93 (10.75%)	9 / 96 (9.38%)	
occurrences (all)	41	40	
Blood alkaline phosphatase increased			

subjects affected / exposed	9 / 93 (9.68%)	9 / 96 (9.38%)	
occurrences (all)	15	22	
Gamma-glutamyltransferase increased			
subjects affected / exposed	10 / 93 (10.75%)	8 / 96 (8.33%)	
occurrences (all)	17	13	
Weight decreased			
subjects affected / exposed	5 / 93 (5.38%)	1 / 96 (1.04%)	
occurrences (all)	9	1	
Vascular disorders			
Hypertension			
subjects affected / exposed	5 / 93 (5.38%)	0 / 96 (0.00%)	
occurrences (all)	5	0	
Nervous system disorders			
Headache			
subjects affected / exposed	15 / 93 (16.13%)	7 / 96 (7.29%)	
occurrences (all)	16	14	
Dizziness			
subjects affected / exposed	7 / 93 (7.53%)	6 / 96 (6.25%)	
occurrences (all)	8	8	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	59 / 93 (63.44%)	57 / 96 (59.38%)	
occurrences (all)	211	203	
Neutropenia			
subjects affected / exposed	30 / 93 (32.26%)	33 / 96 (34.38%)	
occurrences (all)	94	109	
Thrombocytopenia			
subjects affected / exposed	27 / 93 (29.03%)	16 / 96 (16.67%)	
occurrences (all)	81	47	
Leukopenia			
subjects affected / exposed	11 / 93 (11.83%)	3 / 96 (3.13%)	
occurrences (all)	62	3	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	19 / 93 (20.43%)	24 / 96 (25.00%)	
occurrences (all)	27	41	

Asthenia			
subjects affected / exposed	18 / 93 (19.35%)	20 / 96 (20.83%)	
occurrences (all)	39	42	
Pyrexia			
subjects affected / exposed	12 / 93 (12.90%)	3 / 96 (3.13%)	
occurrences (all)	16	5	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	33 / 93 (35.48%)	26 / 96 (27.08%)	
occurrences (all)	47	64	
Constipation			
subjects affected / exposed	13 / 93 (13.98%)	17 / 96 (17.71%)	
occurrences (all)	16	24	
Vomiting			
subjects affected / exposed	14 / 93 (15.05%)	15 / 96 (15.63%)	
occurrences (all)	24	33	
Diarrhoea			
subjects affected / exposed	11 / 93 (11.83%)	17 / 96 (17.71%)	
occurrences (all)	19	19	
Stomatitis			
subjects affected / exposed	2 / 93 (2.15%)	5 / 96 (5.21%)	
occurrences (all)	3	5	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	13 / 93 (13.98%)	6 / 96 (6.25%)	
occurrences (all)	15	9	
Dyspnoea			
subjects affected / exposed	7 / 93 (7.53%)	9 / 96 (9.38%)	
occurrences (all)	7	11	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	8 / 93 (8.60%)	15 / 96 (15.63%)	
occurrences (all)	10	15	
Rash			
subjects affected / exposed	4 / 93 (4.30%)	12 / 96 (12.50%)	
occurrences (all)	4	12	

Psychiatric disorders			
Insomnia			
subjects affected / exposed	5 / 93 (5.38%)	3 / 96 (3.13%)	
occurrences (all)	7	3	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 93 (5.38%)	6 / 96 (6.25%)	
occurrences (all)	7	13	
Pain in extremity			
subjects affected / exposed	4 / 93 (4.30%)	6 / 96 (6.25%)	
occurrences (all)	4	6	
Bone pain			
subjects affected / exposed	7 / 93 (7.53%)	1 / 96 (1.04%)	
occurrences (all)	7	1	
Spinal pain			
subjects affected / exposed	5 / 93 (5.38%)	0 / 96 (0.00%)	
occurrences (all)	5	0	
Infections and infestations			
COVID-19			
subjects affected / exposed	10 / 93 (10.75%)	9 / 96 (9.38%)	
occurrences (all)	10	9	
Upper respiratory tract infection			
subjects affected / exposed	9 / 93 (9.68%)	7 / 96 (7.29%)	
occurrences (all)	13	8	
Urinary tract infection			
subjects affected / exposed	3 / 93 (3.23%)	5 / 96 (5.21%)	
occurrences (all)	3	7	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	8 / 93 (8.60%)	10 / 96 (10.42%)	
occurrences (all)	10	12	
Hypokalaemia			
subjects affected / exposed	5 / 93 (5.38%)	11 / 96 (11.46%)	
occurrences (all)	11	16	
Hypomagnesaemia			

subjects affected / exposed	4 / 93 (4.30%)	6 / 96 (6.25%)	
occurrences (all)	4	8	
Hyperglycaemia			
subjects affected / exposed	4 / 93 (4.30%)	5 / 96 (5.21%)	
occurrences (all)	9	11	
Hypoalbuminaemia			
subjects affected / exposed	1 / 93 (1.08%)	6 / 96 (6.25%)	
occurrences (all)	2	6	
Hypocalcaemia			
subjects affected / exposed	0 / 93 (0.00%)	6 / 96 (6.25%)	
occurrences (all)	0	16	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 January 2021	Amendment 2 v3.0 – Revised disease-free interval to ≥6 months and <12 months.
02 March 2021	Amendment 3 v4.0 – Updated language regarding regions to include China and account for regional differences in other countries such as in Eastern Europe, Russia, and China. – Updated Inclusion criterion to include language regarding red blood cell transfusion or erythropoiesis stimulating agent administration. – Changed gemcitabine/carboplatin dose calculation form “adjusted” to actual body weight. – Added language to Section 'Measures to Minimize Bias' to provide clarity on the definition of disease-free interval. – Added language to Section 'Definitions of Tumor Response and Disease Progression' to provide clarification for the use of PET scans in this study.

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.

Due to change in treatment landscape for the second-line TNBC patients, planned analyses for Cohort 2 was not conducted and data of few selective efficacy parameters for Cohort 1 were collected and analyzed.

Notes: