



Clinical trial results:

Phase 2 Study of Carboplatin, Etoposide, and Atezolizumab With or Without Trilaciclib (G1T28) in Patients with Untreated Extensive-Stage Small Cell Lung Cancer

Summary

EudraCT number	2017-000358-20
Trial protocol	EE LV BG ES FR
Global end of trial date	29 October 2020

Results information

Result version number	v1 (current)
This version publication date	14 November 2021
First version publication date	14 November 2021
Summary attachment (see zip file)	G1T28-05_CSR Synopsis (Synopsis G1T28-05_Clinical_Study_Report_v1.0_30_Mar_2020.docx (002).pdf)

Trial information

Trial identification

Sponsor protocol code	G1T28-05
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03041311
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, 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	11 December 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 August 2018
Global end of trial reached?	Yes
Global end of trial date	29 October 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the potential of trilaciclib, compared with placebo, to reduce chemotherapy-induced myelosuppression in patients with small cell lung cancer (SCLC) undergoing treatment with etoposide, carboplatin, and atezolizumab

Protection of trial subjects:

This study is being conducted in full conformance with the 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. The investigator ensured adherence to the basic principles of Good Clinical Practice (GCP), as outlined in the current version of 21 Code of Federal Regulations, Part 312, Subpart D (Responsibilities of Sponsors and Investigators), Part 50 (Protection of Human Subjects), Part 54 (Financial Disclosure by Clinical Investigators), and Part 56 (IRBs), and International Council for Harmonisation (ICH) E6 GCP. The investigator followed all national, state, and local laws of the pertinent regulatory authorities.

Written informed consent was obtained from each patient participating in this study, after adequate explanation of the goals, methods, potential benefits, and hazards of the study.

An external data monitoring committee (DMC) was used to evaluate safety of the study in an ongoing manner. The DMC performed an initial review after approximately 12 patients were enrolled and completed at least 1 cycle to assess the initial safety data from the 2 groups; subsequent reviews were completed approximately every 4 months depending on the enrollment rate. Additional reviews could occur based on DMC requests. At no time did the DMC indicate that the study needed to be modified or stopped.

Background therapy:

The combination of etoposide and carboplatin is a standard SCLC treatment and, at the time of protocol initiation, was under investigation with atezolizumab for the treatment of SCLC. Atezolizumab (Tecentriq®) is a monoclonal antibody that binds to programmed death-ligand 1 (PD-L1), inhibiting its interaction with the programmed cell death protein 1 (PD-1) receptor and releasing the PD-L1/PD-1-mediated inhibition of the immune response. On March 18, 2019, the Food and Drug Administration approved atezolizumab (TECENTRIQ, Genentech Inc.) in combination with carboplatin and etoposide, for the first-line treatment of adult patients with extensive-stage SCLC. All patients in this study underwent treatment with etoposide, carboplatin, and atezolizumab.

Evidence for comparator: -

Actual start date of recruitment	29 June 2017
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	United States: 42
Country: Number of subjects enrolled	Georgia: 16

Country: Number of subjects enrolled	Ukraine: 19
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	Bulgaria: 13
Country: Number of subjects enrolled	Estonia: 5
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Latvia: 6
Worldwide total number of subjects	107
EEA total number of subjects	30

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)	54
From 65 to 84 years	53
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 37 sites enrolled patients in the United States, Spain, France, Bulgaria, Estonia, Latvia, Ukraine, and Georgia.

Pre-assignment

Screening details:

A total of 125 patients were enrolled in this study; 18 were reported as screen failures (15 failed to meet the eligibility criteria, 2 withdrew consent, and 1 had the Screening Phase expire and was later rescreened). Thus, 107 patients were randomized to a treatment group. However, 2 patients were randomized in error and received no study drug.

Period 1

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

Blinding implementation details:

Because the active drug product trilaciclib has a faint yellow color when reconstituted and diluted, an unblinded pharmacist/designee and unblinded infusion nurse were identified to prepare the drug and the infusion sets that included placement of an amber bag over the infusion bag and amber sleeves to cover the IV tubing to hide the color of the infusate. This infusion apparatus was handed off to the blinded infusion nurse for administration.

Arms

Are arms mutually exclusive?	Yes
Arm title	Trilaciclib

Arm description:

Induction Period: Patients received trilaciclib 240 mg/m² administered intravenously (IV) once daily prior to chemotherapy on Days 1 to 3 of each 21-day therapy cycle (up to 4 cycles in total). Etoposide 100 mg/m² was administered as an IV infusion over 60 minutes on Days 1, 2, and 3 of each 21-day cycle. The carboplatin dose was to be calculated using the Calvert formula with a target AUC of 5 mg·min/mL (maximum 750 mg) IV over approximately 30 minutes on Day 1 of each 21-day cycle. Atezolizumab 1200 mg was administered as an IV infusion on Day 1 of each 21-day cycle. Maintenance Period: Patients received atezolizumab monotherapy once every 21 days.

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

Dosage and administration details:

240 mg/m² administered IV once daily on Days 1 to 3 of each 21-day therapy cycle during the Induction Period

Arm title	Placebo
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Arm description:

Induction Period: Patients received placebo administered IV once daily prior to chemotherapy on Days 1 to 3 of each 21-day therapy cycle (up to 4 cycles in total). Etoposide 100 mg/m² was administered as an IV infusion over 60 minutes on Days 1, 2, and 3 of each 21-day cycle. The carboplatin dose was to be calculated using the Calvert formula with a target AUC of 5 mg·min/mL (maximum 750 mg) IV over approximately 30 minutes on Day 1 of each 21-day cycle. Atezolizumab 1200 mg was administered as an IV infusion on Day 1 of each 21-day cycle. Maintenance Period: Patients received atezolizumab monotherapy once every 21 days.

Arm type	Placebo
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Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

250 mL of dextrose 5% in water or sodium chloride solution 0.9% administered IV once daily on Days 1 to 3 of each 21-day therapy cycle during the Induction Period

Number of subjects in period 1	Trilaciclib	Placebo
Started	54	53
Completed	0	0
Not completed	54	53
Consent withdrawn by subject	8	5
Death	39	42
Progressive disease	3	1
Lost to follow-up	-	1
Randomized in error; did not receive drug	2	-
Sponsor terminated study	2	4

Baseline characteristics

Reporting groups

Reporting group title	Trilaciclib
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Reporting group description:

Induction Period: Patients received trilaciclib 240 mg/m² administered intravenously (IV) once daily prior to chemotherapy on Days 1 to 3 of each 21-day therapy cycle (up to 4 cycles in total). Etoposide 100 mg/m² was administered as an IV infusion over 60 minutes on Days 1, 2, and 3 of each 21-day cycle. The carboplatin dose was to be calculated using the Calvert formula with a target AUC of 5 mg·min/mL (maximum 750 mg) IV over approximately 30 minutes on Day 1 of each 21-day cycle. Atezolizumab 1200 mg was administered as an IV infusion on Day 1 of each 21-day cycle. Maintenance Period: Patients received atezolizumab monotherapy once every 21 days.

Reporting group title	Placebo
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Reporting group description:

Induction Period: Patients received placebo administered IV once daily prior to chemotherapy on Days 1 to 3 of each 21-day therapy cycle (up to 4 cycles in total). Etoposide 100 mg/m² was administered as an IV infusion over 60 minutes on Days 1, 2, and 3 of each 21-day cycle. The carboplatin dose was to be calculated using the Calvert formula with a target AUC of 5 mg·min/mL (maximum 750 mg) IV over approximately 30 minutes on Day 1 of each 21-day cycle. Atezolizumab 1200 mg was administered as an IV infusion on Day 1 of each 21-day cycle. Maintenance Period: Patients received atezolizumab monotherapy once every 21 days.

Reporting group values	Trilaciclib	Placebo	Total
Number of subjects	54	53	107
Age categorical			
Units: Subjects			
Adults (18-64 years)	27	27	54
Adults (65-75 years)	24	21	45
Adults (>75 years)	3	5	8
Age continuous			
Units: years			
arithmetic mean	63	64	
standard deviation	± 8.4	± 8.3	-
Gender categorical			
Units: Subjects			
Female	13	19	32
Male	41	34	75
Race			
Units: Subjects			
White	53	51	104
Black or African American	0	1	1
Native Hawaiian or Other Pacific Islander	1	0	1
Other	0	1	1
Ethnicity			
Units: Subjects			
Hispanic or Latino	0	1	1
Not Hispanic or Latino	54	51	105
Unknown	0	1	1
Country			
Units: Subjects			
USA	20	22	42

Non-USA	34	31	65
Eastern Cooperative Oncology Group (ECOG) Performance Status Units: Subjects			
Status: 0-1	46	46	92
Status: 2	8	7	15
Smoking history Units: Subjects			
Never smoked	4	6	10
Former smokers	26	29	55
Current smokers	23	18	41
Missing	1	0	1
Presence of brain metastases Units: Subjects			
Yes	15	15	30
No	39	38	77
Body Weight at Screening Units: kg			
arithmetic mean	79.2	72.4	
standard deviation	± 17.32	± 14.42	-
Height at Screening Units: cm			
arithmetic mean	171.1	168.6	
standard deviation	± 7.62	± 10.21	-
Body Mass Index Units: kg/m ²			
arithmetic mean	27.10	25.45	
standard deviation	± 5.907	± 4.618	-
Body Surface Area Units: m ²			
arithmetic mean	1.91	1.82	
standard deviation	± 0.198	± 0.205	-

End points

End points reporting groups

Reporting group title	Trilaciclib
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Reporting group description:

Induction Period: Patients received trilaciclib 240 mg/m² administered intravenously (IV) once daily prior to chemotherapy on Days 1 to 3 of each 21-day therapy cycle (up to 4 cycles in total). Etoposide 100 mg/m² was administered as an IV infusion over 60 minutes on Days 1, 2, and 3 of each 21-day cycle. The carboplatin dose was to be calculated using the Calvert formula with a target AUC of 5 mg·min/mL (maximum 750 mg) IV over approximately 30 minutes on Day 1 of each 21-day cycle. Atezolizumab 1200 mg was administered as an IV infusion on Day 1 of each 21-day cycle. Maintenance Period: Patients received atezolizumab monotherapy once every 21 days.

Reporting group title	Placebo
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Reporting group description:

Induction Period: Patients received placebo administered IV once daily prior to chemotherapy on Days 1 to 3 of each 21-day therapy cycle (up to 4 cycles in total). Etoposide 100 mg/m² was administered as an IV infusion over 60 minutes on Days 1, 2, and 3 of each 21-day cycle. The carboplatin dose was to be calculated using the Calvert formula with a target AUC of 5 mg·min/mL (maximum 750 mg) IV over approximately 30 minutes on Day 1 of each 21-day cycle. Atezolizumab 1200 mg was administered as an IV infusion on Day 1 of each 21-day cycle. Maintenance Period: Patients received atezolizumab monotherapy once every 21 days.

Primary: Co-primary Endpoint: Duration of severe (Grade 4) neutropenia in Cycle 1

End point title	Co-primary Endpoint: Duration of severe (Grade 4) neutropenia in Cycle 1
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End point description:

Duration of severe neutropenia (DSN; days) was defined as the number of days from the date of the first absolute neutrophil count (ANC) value of $<0.5 \times 10^9/L$ observed between start of cycle and end of cycle to the date of the first ANC value $\geq 0.5 \times 10^9/L$ that met the following criteria: (1) occurred after the ANC value of $<0.5 \times 10^9/L$ and (2) no other ANC values $<0.5 \times 10^9/L$ occurred between this day and end of cycle. DSN was set to 0 for patients who did not experience severe neutropenia in a cycle, including those that were randomized and not treated. Data from unscheduled visits and the actual assessment date (rather than visit date) were included in the derivation. This endpoint was analyzed using the intent-to-treat (ITT) analysis set, which included all randomized patients.

End point type	Primary
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End point timeframe:

Evaluated for Cycle 1 of the Induction Period (i.e., from the date of randomization to the end of Cycle 1). Results presented are based on data collected through Database Lock 1 (17 Aug 2018).

End point values	Trilaciclib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54	53		
Units: days				
arithmetic mean (standard deviation)	0 ($\pm$ 1.0)	4 ($\pm$ 4.7)		

Statistical analyses

Statistical analysis title	Duration of severe neutropenia in Cycle 1
Statistical analysis description:	
Treatment difference was evaluated using a nonparametric analysis of covariance (ANCOVA). The nonparametric ANCOVA included study baseline ANC value as covariate, stratification factors of ECOG performance status (0 to 1 versus 2) and brain metastases (Yes versus No), and treatment as a fixed effect.	
Comparison groups	Trilaciclib v Placebo
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[1]
Method	Nonparametric ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-3.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.9
upper limit	-2.3
Variability estimate	Standard error of the mean
Dispersion value	0.65

Notes:

[1] - A Hochberg-based gatekeeping procedure was used to control the global familywise error rate across the multiple null hypotheses (for 2 primary and 8 secondary myelosuppression endpoints) in a strong sense at a 1-sided 0.025 level.

Primary: Co-primary Endpoint: Occurrence of severe (Grade 4) neutropenia

End point title	Co-primary Endpoint: Occurrence of severe (Grade 4) neutropenia
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End point description:

The occurrence of severe (Grade 4) neutropenia (SN) was a binary variable. If a patient had at least 1 absolute neutrophil count value $<0.5 \times 10^9/L$ during the Induction Period, the patient was assigned as Yes to the occurrence of SN; otherwise, it was No. This endpoint was analyzed using the intent-to-treat (ITT) analysis set, which included all randomized patients.

End point type	Primary
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End point timeframe:

Evaluated for the Induction Period (i.e., from the date of randomization to the end of the last Induction cycle). Results presented are based on data collected through Database Lock 1 (17 August 2018).

End point values	Trilaciclib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54 ^[2]	53 ^[3]		
Units: Patients with severe neutropenia	1	26		

Notes:

[2] - Percentage with severe neutropenia: 1.9%

[3] - Percentage with severe neutropenia: 49.1%

Statistical analyses

Statistical analysis title	Occurrence of severe neutropenia
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Statistical analysis description:

Treatment group difference was analyzed using a modified Poisson regression model to account for the variable duration of the Induction Period for each patient. The model included baseline absolute neutrophil count as a covariate, the stratification factors of ECOG performance status (0 to 1 versus 2) and brain metastases (Yes versus No), and treatment as a fixed effect. The logarithm transformation of number of Induction cycles was included as an offset variable in the modeling.

Comparison groups	Trilaciclib v Placebo
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[4]
Method	Modified Poisson regression
Parameter estimate	Adjusted rate ratio
Point estimate	0.038
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.008
upper limit	0.195
Variability estimate	Standard error of the mean
Dispersion value	0.0319

Notes:

[4] - A Hochberg-based gatekeeping procedure was used to control the global familywise error rate across the multiple null hypotheses (for 2 primary and 8 secondary myelosuppression endpoints) in a strong sense at a 1-sided 0.025 level.

Secondary: Key Secondary Endpoint: Occurrence of red blood cell transfusions on/after Week 5 (proportion of patients)

End point title	Key Secondary Endpoint: Occurrence of red blood cell transfusions on/after Week 5 (proportion of patients)
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End point description:

For this endpoint, the occurrence during the Induction 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, a value of 0 was assigned to that patient. Each red blood cell transfusion with a unique start date on/after Week 5 on study during the Induction was defined as a separate event.

End point type	Secondary
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End point timeframe:

Evaluated for the Induction Period starting at Week 5. Results presented are based on data collected through Database Lock 1 (17 August 2018).

End point values	Trilaciclib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54 ^[5]	53 ^[6]		
Units: Patients with transfusion on/after Wk 5	7	11		

Notes:

[5] - Percentage with red blood cell transfusion on/after Week 5: 13.0%

[6] - Percentage with red blood cell transfusion on/after Week 5: 20.8%

Statistical analyses

Statistical analysis title	Occurrence of RBC transfusion on/after Week 5
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Statistical analysis description:

Treatment group difference was analyzed using a modified Poisson regression model to account for the variable duration of the Induction Period for each patient. The model included baseline hemoglobin level as a covariate, the stratification factors of ECOG performance status (0 to 1 versus 2) and brain metastases (Yes versus No), and treatment as a fixed effect. The logarithm transformation of duration of Induction Period in weeks was included as an offset variable in the modeling.

Comparison groups	Trilaciclib v Placebo
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2003 ^[7]
Method	Modified Poisson regression
Parameter estimate	Adjusted rate ratio
Point estimate	0.642
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.294
upper limit	1.404
Variability estimate	Standard error of the mean
Dispersion value	0.2564

Notes:

[7] - A Hochberg-based gatekeeping procedure was used to control the global familywise error rate across the multiple null hypotheses (for 2 primary and 8 secondary myelosuppression endpoints) in a strong sense at a 1-sided 0.025 level.

Secondary: Key Secondary Endpoint: Occurrence of granulocyte colony-stimulating factor (G-CSF) administration (proportion of patients)

End point title	Key Secondary Endpoint: Occurrence of granulocyte colony-stimulating factor (G-CSF) administration (proportion of patients)
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End point description:

For this endpoint, the occurrence during the Induction 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, a value of 0 was assigned to that patient. Any G-CSF administration in a cycle during the Induction Period was defined as a separate event. A patient with at least 1 cycle with G-CSF administration during an induction cycle or the Induction Period was considered to have occurrence of G-CSF administration.

End point type	Secondary
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End point timeframe:

Evaluated for the Induction Period (i.e., from the date of randomization to the end of the last Induction cycle). Results presented are based on data collected through Database Lock 1 (17 August 2018).

End point values	Trilaciclib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54 ^[8]	53 ^[9]		
Units: Patients with G-CSF administration	16	25		

Notes:

[8] - Percentage of patients with G-CSF administration: 29.6%

[9] - Percentage of patients with G-CSF administration: 47.2%

Statistical analyses

Statistical analysis title	Occurrence of G-CSF administration
Statistical analysis description:	
Treatment group difference was analyzed using a modified Poisson regression model to account for the variable duration of the Induction Period for each patient. The model included baseline absolute neutrophil count as a covariate, the stratification factors of ECOG performance status (0 to 1 versus 2) and brain metastases (Yes versus No), and treatment as a fixed effect. The logarithm transformation of number of Induction cycles was included as an offset variable in the modeling.	
Comparison groups	Trilaciclib v Placebo
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0823 ^[10]
Method	Modified Poisson regression
Parameter estimate	Adjusted rate ratio
Point estimate	0.646
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.403
upper limit	1.034
Variability estimate	Standard error of the mean
Dispersion value	0.1551

Notes:

[10] - A Hochberg-based gatekeeping procedure was used to control the global familywise error rate across the multiple null hypotheses (for 2 primary and 8 secondary myelosuppression endpoints) in a strong sense at a 1-sided 0.025 level.

Secondary: Key Secondary Endpoint: Major Adverse Hematologic Events (MAHE) (Composite endpoint)

End point title	Key Secondary Endpoint: Major Adverse Hematologic Events (MAHE) (Composite endpoint)
End point description:	
The composite endpoint "major adverse hematologic events" (MAHE) included the following aspects of myelosuppression:	
All-cause hospitalizations - Each recorded preferred term (PT) with a unique start date was counted as an event.	
All-cause dose reductions - Dose reductions were permitted for E/P but not for trilaciclib or atezolizumab. No more than 2 dose reductions were allowed. Each dose reduction was counted as a separate event.	
Febrile neutropenia-Each febrile neutropenia event with a unique start date during the Induction Period was defined as a separate event.	
Prolonged severe neutropenia (SN)-Each cycle with a severe neutropenia duration greater than 5 days was counted as an event, with the date of the first Grade 4 laboratory value defined as the start date for the time-to-first event analysis.	
Red blood cell (RBC) transfusion on/after Week 5-Each RBC transfusion with a unique start date on/after Week 5 on study during the Induction Period was defined as a separate event.	
End point type	Secondary

End point timeframe:

Evaluated for the Induction Period. Results presented are based on data collected through Database Lock 1 (17 August 2018).

End point values	Trilaciclib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54	53		
Units: Event rate				
number (not applicable)				
Composite: MAHE (per week)	0.058	0.132		
Component: All-cause hospitalization (per week)	0.032	0.030		
Component: All-cause dose reductions (per cycle)	0.021	0.085		
Component: Febrile neutropenia TEAEs (per week)	0.002	0.004		
Component: RBC transfusions on/after Wk 5 (per wk)	0.017	0.026		
Component: Prolonged SN (>5 days) (per cycle)	0.005	0.170		

Statistical analyses

Statistical analysis title	Composite: MAHE (per week)
Statistical analysis description:	
Total number of MAHEs was analyzed using a negative binomial regression model. The model included the stratification factors of ECOG performance status (0 to 1 versus 2) and brain metastases (Yes versus No) and treatment as a fixed effect. The logarithm transformation of duration of Induction Period in weeks was included as an offset variable in the modeling.	
Comparison groups	Trilaciclib v Placebo
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0044 ^[11]
Method	Negative binomial regression
Parameter estimate	Adjusted rate ratio
Point estimate	0.437
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.253
upper limit	0.754
Variability estimate	Standard error of the mean
Dispersion value	0.1216

Notes:

[11] - A Hochberg-based gatekeeping procedure was used to control the global familywise error rate across the multiple null hypotheses (for 2 primary and 8 secondary myelosuppression endpoints) in a strong sense at a 1-sided 0.025 level.

Secondary: Best Overall Response

End point title	Best Overall Response
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End point description:

For all patients, the RECIST v1.1 tumor response data were used to determine each patient's visit response (TPR = time point response) according to RECIST v1.1 and the best overall response (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. Results shown here are from the programmatically derived assessments.

End point type	Secondary
End point timeframe:	
Evaluated for the full Treatment Phase (Induction and Maintenance Periods). Results presented are based on data collected through Database Lock 2 (28 June 2019).	

End point values	Trilaciclib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	52		
Units: Subjects				
Complete response (CR)	0	1		
Partial response (PR)	28	32		
Stable disease (SD)	20	14		
Progressive disease (PD)	2	2		
Not evaluable (NE)	0	2		
Missing	0	1		
Unconfirmed CR	0	1		
Unconfirmed PR	11	6		
Objective response (CR+PR)	28	33		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of objective response (complete response or partial response)

End point title	Duration of objective response (complete response or partial response)
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.	
End point type	Secondary
End point timeframe:	
Evaluated for the full Treatment Phase (Induction Period and Maintenance Period). Results presented are based on data collected through Database Lock 2 (28 June 2019).	

End point values	Trilaciclib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	33		
Units: Months				
number (confidence interval 95%)				
25%	4.4 (2.9 to 4.7)	3.0 (2.7 to 4.1)		
Median	5.6 (4.4 to 7.0)	4.3 (3.4 to 4.7)		
75%	8.3 (5.8 to 13.2)	5.0 (4.6 to 10.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival

End point title	Progression-free survival
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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.

End point type	Secondary
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End point timeframe:

Evaluated for the full Treatment Phase (Induction and Maintenance Periods). Results presented are based on data collected through Database Lock 2 (28 June 2019).

End point values	Trilaciclib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54 ^[12]	53 ^[13]		
Units: Months				
number (confidence interval 95%)				
25%	3.7 (2.7 to 4.2)	4.0 (3.1 to 4.3)		
Median	5.9 (4.2 to 7.1)	5.4 (4.3 to 5.7)		
75%	8.5 (7.1 to 10.4)	6.4 (5.7 to 8.9)		

Notes:

[12] - (death without progressive disease: n=6, disease progression: n=42, censored: n=6)

[13] - (death without progressive disease: n=6, disease progression: n=43, censored: n=4)

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival
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End point description:

Overall survival was calculated as the time (months) from date of randomization to the date of death due to any cause. Patients who did not die during the study were censored at the date last known to be alive. Patients lacking data beyond the date of randomization had their survival time censored at date of randomization. Overall survival was not censored if a patient received other anti-tumor treatments after the study drugs. Overall survival was calculated using the Kaplan-Meier method.

End point type	Secondary
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End point timeframe:

Evaluated for the full duration of the study (i.e., from randomization through the Survival Follow-up Phase). Results presented are based on data collected through Final Database Lock (11 December 2020).

End point values	Trilaciclib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54 ^[14]	53 ^[15]		
Units: Months				
number (confidence interval 95%)				
25%	7.2 (4.9 to 10.2)	6.7 (3.6 to 8.1)		
Median	12.0 (9.6 to 16.2)	12.8 (7.9 to 15.5)		
75%	20.6 (14.5 to 23.2)	22.4 (15.5 to 30.0)		

Notes:

[14] - (deaths: n=42, censored: n=12)

[15] - (deaths: n=44, censored: n=9)

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence of febrile neutropenia

End point title	Occurrence of febrile neutropenia
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End point description:

The criterion for identifying febrile neutropenia was if the preferred term for an adverse event was "FEBRILE NEUTROPENIA." Any occurrence of a febrile neutropenia event during the induction treatment period is defined as a binary variable (Yes or No); Yes if total number of febrile neutropenia events ≥ 1 is observed, No for other scenarios. Each febrile neutropenia event with a unique start date during the induction treatment period was defined as a separate event.

End point type	Secondary
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End point timeframe:

Evaluated for the Induction Period. Results presented are based on data collected through Database Lock 1 (17 August 2018).

End point values	Trilaciclib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54	53		
Units: Subjects	1	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence of erythropoiesis stimulating agent (ESA) administrations

End point title	Occurrence of erythropoiesis stimulating agent (ESA) administrations
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End point description:

Any ESA administration in a cycle during the Induction Period was defined as a separate event. A patient with at least 1 cycle with ESA administration during an induction cycle or the Induction Period was considered to have occurrence of ESA administration. The criterion to select proper records was as follows: If the chemical subgroup from WHO-DD Version September 2017 (ie TEXT4 for CODE4) takes the value "OTHER ANTIANEMIC PREPARATIONS," the medication was classified as ESAs.

End point type	Secondary
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End point timeframe:

Evaluated for the Induction Period. Results presented are based on data collected through Database Lock 1 (17 August 2018).

End point values	Trilaciclib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54 ^[16]	53 ^[17]		
Units: Subjects	3	6		

Notes:

[16] - (cycles with ESA administered: 5/195 cycles; event rate: 0.026)

[17] - (cycles with ESA administered: 12/200 cycles; event rate: 0.060)

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence of platelet transfusion

End point title	Occurrence of platelet transfusion
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End point description:

Any occurrence of a platelet transfusion during the induction treatment period was defined as a binary variable (Yes or No); Yes if total number of febrile neutropenia events ≥ 1 is observed, No for other scenarios. If the patient did not have an event, the value of 0 was assigned to that patient. Each platelet transfusion event with a unique start date during the induction treatment period was defined as a separate event.

End point type	Secondary
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End point timeframe:

Evaluated for the Induction Period. Results presented are based on data collected through Database Lock 1 (17 August 2018).

End point values	Trilaciclib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54 ^[18]	53 ^[19]		
Units: Subjects	1	2		

Notes:

[18] - (platelet transfusion rate over time: 1/652 weeks; event rate: 0.002)

[19] - (platelet transfusion rate over time: 5/703 weeks; event rate: 0.007)

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence of Grade 3 or 4 hematologic laboratory abnormalities

End point title	Occurrence of Grade 3 or 4 hematologic laboratory abnormalities
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 1 Grade 3 or 4 hematologic toxicities during the Induction 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: Evaluated for the Induction Period. Results presented are based on data collected through Database Lock 1 (17 August 2018).	

End point values	Trilaciclib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54 ^[20]	53 ^[21]		
Units: Subjects	23	43		

Notes:

[20] - (# of cycles with Grade 3/4 hematologic laboratory abnormalities: 34/195 cycles; event rate: 0.174)

[21] - (# of cycles with Grade 3/4 hematologic laboratory abnormalities: 107/200 cycles; event rate: 0.535)

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence of infection serious adverse events (SAEs)

End point title	Occurrence of infection serious adverse events (SAEs)
End point description: Any occurrence of an infection SAE during the induction treatment period was defined as a binary variable (Yes or No); Yes if total number of febrile neutropenia events ≥ 1 is observed, No for other scenarios. If the 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) Version 20.1 takes value "INFECTIONS AND INFESTATIONS," and the AE was a serious event.	
End point type	Secondary
End point timeframe: Evaluated for the Induction Period. Results presented are based on data collected through Database Lock 1 (17 August 2018).	

End point values	Trilaciclib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54 ^[22]	53 ^[23]		
Units: Subjects	3	7		

Notes:

[22] - (# of infection SAEs: 4/652 weeks; event rate: 0.006 per week)

[23] - (# of infection SAEs: 7/703 weeks; event rate: 0.010 per week)

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence of pulmonary infection serious adverse events (SAEs)

End point title	Occurrence of pulmonary infection serious adverse events (SAEs)
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End point description:

Any occurrence of a pulmonary SAE during the induction treatment period was defined as a binary variable (Yes or No); Yes if total number of febrile neutropenia events ≥ 1 is observed, No for other scenarios. If the patient did not have an event, the value of 0 was assigned to that patient. Each pulmonary infection SAE with a unique start date during the induction treatment period was defined as separate event. The criterion for identifying the proper pulmonary infection SAE records was as follows: The SOC from MedDRA Version 20.1 took the value "INFECTIONS AND INFESTATIONS," the adverse event was a serious event, and the PT took values from the following list of PTs under the category of pulmonary infection adverse events: bronchiolitis, bronchitis, infectious pleural effusion, influenza, pneumonia, pneumonia bacterial, respiratory tract infection, upper respiratory tract infection, and viral upper respiratory tract infection.

End point type	Secondary
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End point timeframe:

Evaluated for the Induction Period. Results presented are based on data collected through Database Lock 1 (17 August 2018).

End point values	Trilaciclib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54 ^[24]	53 ^[25]		
Units: Subjects	2	5		

Notes:

[24] - (# of pulmonary infection SAEs: 3/652 weeks; event rate: 0.005 per week)

[25] - (# of pulmonary infection SAEs: 5/703 weeks; event rate: 0.007 per week)

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence of intravenous (IV) antibiotic use

End point title	Occurrence of intravenous (IV) antibiotic use
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End point description:

Occurrence of an IV antibiotics administration during the induction treatment period is defined as a binary variable (Yes or No); Yes if total number of IV antibiotics administration ≥ 1 is observed, No for other scenarios. Each IV antibiotic with a unique start date during the induction treatment period will be defined as a separate event. 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 the value "ANTIBACTERIALS FOR SYSTEMIC USE," and (2) the route of medication was "intravenous" or the route was "other" with the detailed specification as "IVPB."

End point type	Secondary
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End point timeframe:

Evaluated for the Induction Period. Results presented are based on data collected through Database Lock 1 (17 August 2018).

End point values	Trilaciclib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54 ^[26]	53 ^[27]		
Units: Subjects	10	12		

Notes:

[26] - (# of IV antibiotic administrations: 13/652 weeks; event rate: 0.020 per week)

[27] - (# of IV antibiotic administrations: 17/703 weeks; event rate: 0.024 per week)

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of study drug exposure (Induction Period and Maintenance Period)

End point title	Duration of study drug exposure (Induction Period and Maintenance Period)
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End point description:

Induction period duration of exposure (days) = Day 1 of last induction cycle – Cycle 1 Day 1 of induction phase + 21. Maintenance period duration of exposure (days) = Day 1 of the last maintenance cycle – Cycle 1 Day 1 of maintenance phase + 21.

End point type	Secondary
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End point timeframe:

Evaluated for the Induction Period and Maintenance Period (data collected through Final Database Lock - 11 December 2020).

End point values	Trilaciclib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: Days				
arithmetic mean (standard deviation)				
Induction Period	83 (± 15.6)	88 (± 20.5)		
Maintenance Period	223 (± 253.3)	232 (± 271.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of cycles completed (Induction Period and Maintenance Period)

End point title	Number of cycles completed (Induction Period and Maintenance Period)
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End point description:

Patients were considered to have started a cycle if they have received at least one dose of any study drug (carboplatin, etoposide, atezolizumab or trilaciclib).

End point type	Secondary
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End point timeframe:

Evaluated for the Induction Period and Maintenance Period (data collected through Final Database Lock - 11 December 2020).

End point values	Trilaciclib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: Cycles				
arithmetic mean (standard deviation)				
Induction Period	4 (± 0.6)	4 (± 0.8)		
Maintenance Period	10 (± 11.9)	10 (± 11.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Relative dose intensity of Trilaciclib/Placebo, Carboplatin, Etoposide, Atezolizumab (Induction Period) and Atezolizumab (Maintenance Period)

End point title	Relative dose intensity of Trilaciclib/Placebo, Carboplatin, Etoposide, Atezolizumab (Induction Period) and Atezolizumab (Maintenance Period)
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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
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End point timeframe:

Induction Period: Results presented are based on data collected through Database Lock 1 (17 August 2018). Maintenance Period: Results presented are based on data collected through Database Lock 2 (28 June 2019).

End point values	Trilaciclib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: Percent				
arithmetic mean (standard deviation)				
Trilaciclib/placebo	94.6 (± 7.65)	91.1 (± 10.68)		
Carboplatin	95.3 (± 7.26)	89.1 (± 12.25)		
Etoposide	93.4 (± 9.59)	87.7 (± 13.92)		
Atezolizumab (Induction)	94.1 (± 9.54)	91.0 (± 11.26)		
Atezolizumab (Maintenance)	93.5 (± 11.45)	94.2 (± 10.19)		

Statistical analyses

No statistical analyses for this end point

Secondary: Dose modifications - Cycle delays (Induction Period)

End point title	Dose modifications - Cycle delays (Induction Period)
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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. A "Cycle Day Status" page asks if the cycle was delayed. If the start of the current cycle was delayed (the site answers "Yes"), this will be counted as a delay. Cycle delays could occur for management of toxicity (hematologic or non-hematologic) or for administrative/logistic reasons. The reason for each cycle delay was captured in the eCRF if it was related to AEs. Reasons other than AEs were not captured.

End point type	Secondary
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End point timeframe:

Evaluated for the Induction Period. Results presented are based on data collected through Final Database Lock (11 December 2020).

End point values	Trilaciclib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	31		
Units: Number of patients with any cycle delays				
0 cycles	34	22		
1 cycle	14	18		
2 cycles	2	10		
3 or more cycles	2	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Dose modifications - Cycle delays (Maintenance Period)

End point title	Dose modifications - Cycle delays (Maintenance Period)
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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. A "Cycle Day Status" page asks if the cycle was delayed. If the start of the current cycle was delayed (the site answers "Yes"), this will be counted as a delay. Cycle delays could occur for management of toxicity (hematologic or non-hematologic) or for administrative/logistic reasons. The reason for each cycle delay was captured in the eCRF if it was related to AEs. Reasons other than AEs were not captured.

End point type	Secondary
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End point timeframe:

Evaluated for the Maintenance Period. Results presented are based on data collected through Final Database Lock (11 December 2020).

End point values	Trilaciclib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	26		
Units: Number of patients with any cycle delays				
0 cycles	20	21		
1 cycle	10	12		
2 cycles	6	6		
3 or more cycles	5	8		

Statistical analyses

No statistical analyses for this end point

Secondary: Dose modifications - Trilaciclib/Placebo, Carboplatin and Etoposide Missed Doses (Induction Period)

End point title	Dose modifications - Trilaciclib/Placebo, Carboplatin and Etoposide Missed Doses (Induction Period)
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End point description:

Missed doses are identified on the dosing page of each study drug based on the question "Was the dose given?". The missed dose information will be obtained for each study drug. For a study drug, if the last record of response to question "Was the dose given?" is No, it will not be considered as a missed dose but instead considered to be end of treatment if both criteria below are met: (1) No other study drugs are given on the same day, and (2) No study drugs are given subsequently.

End point type	Secondary
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End point timeframe:

Evaluated for the Induction Period. Results presented are based on data collected through Final Database Lock (11 December 2020).

End point values	Trilaciclib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: Patients with missed doses				
Trilaciclib/Placebo	3	0		
Carboplatin	1	0		
Etoposide	3	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Dose modifications - Atezolizumab Missed Doses (Overall Treatment Period)

End point title	Dose modifications - Atezolizumab Missed Doses (Overall Treatment Period)
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End point description:

Missed doses are identified on the dosing page of each study drug based on the question "Was the dose given?". The missed dose information will be obtained for each study drug. For a study drug, if the last record of response to question "Was the dose given?" is No, it will not be considered as a missed dose but instead considered to be end of treatment if both criteria below are met: (1) No other study drugs are given on the same day, and (2) No study drugs are given subsequently.

End point type	Secondary
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End point timeframe:

Evaluated for the full duration of the study (i.e., from randomization through the Survival Follow-up Phase). Results presented are based on data collected through Final Database Lock (11 December 2020).

End point values	Trilaciclib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: Patients with missed doses	3	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Dose modifications - Trilaciclib/Placebo, Carboplatin and Etoposide Dose Interruptions (Induction Period)

End point title	Dose modifications - Trilaciclib/Placebo, Carboplatin and Etoposide Dose Interruptions (Induction Period)
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End point description:

Dose interruptions were defined as interruption of infusion, regardless of whether the study drug was continued after the interruption.

End point type	Secondary
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End point timeframe:

Evaluated for the Induction Period. Results presented are based on data collected through Final Database Lock (11 December 2020).

End point values	Trilaciclib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: Patients with dose interruptions				
Trilaciclib/Placebo	3	0		
Carboplatin	0	1		
Etoposide	2	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Dose modifications - Atezolizumab Dose Interruptions (Overall Treatment Period)

End point title	Dose modifications - Atezolizumab Dose Interruptions (Overall Treatment Period)
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End point description:

Dose interruptions were defined as interruption of infusion, regardless of whether the study drug was continued after the interruption.

End point type	Secondary
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End point timeframe:

Evaluated for the full duration of the study (i.e., from randomization through the Survival Follow-up Phase). Results presented are based on data collected through Final Database Lock (11 December 2020).

End point values	Trilaciclib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: Patients with dose interruptions	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Dose modifications - Carboplatin and Etoposide Dose Reductions (Induction Period)

End point title	Dose modifications - Carboplatin and Etoposide Dose Reductions (Induction Period)
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End point description:

No dose reductions were allowed for trilaciclib or atezolizumab during the study. As of Database Lock 1, all patients had completed the Induction Period or had withdrawn from treatment; therefore, no additional dose reductions were reported as of Final Database Lock.

End point type	Secondary
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End point timeframe:

Evaluated for the Induction Period. Results presented are based on data collected through Database Lock 1 (17 August 2018).

End point values	Trilaciclib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: Patients with Dose Reductions				
Etoposide	3	14		
Carboplatin	1	13		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events collected through 30 days after last dose of study drug. Treatment-emergent serious adverse events collected through 90 days after last dose of study drug. Results presented are based on Final Database Lock (11 Dec 2020).

Adverse event reporting additional description:

Adverse events were assessed using the safety analysis set, which included all randomized patients who received at least 1 dose of any study drug (etoposide, carboplatin, atezolizumab, or trilaciclib). Analyses using the safety analysis set were conducted based on the actual treatment received.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Trilaciclib
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Reporting group description:

Induction Period: Patients received trilaciclib 240 mg/m² administered IV once daily on Days 1 to 3 of each 21-day therapy cycle (up to 4 cycles in total). Etoposide 100 mg/m² was administered as an IV infusion over 60 minutes on Days 1, 2, and 3 of each 21-day cycle. The carboplatin dose was to be calculated using the Calvert formula with a target AUC of 5 mg·min/mL (maximum 750 mg) IV over approximately 30 minutes on Day 1, and 100 mg/m² etoposide was administered IV over approximately 60 minutes daily on Days 1, 2, and 3 of each 21-day cycle. Atezolizumab 1200 mg was administered as an IV infusion on Day 1 of each 21-day cycle.

Maintenance Period: Patients received atezolizumab monotherapy once every 21 days.

Reporting group title	Placebo
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Reporting group description:

Induction Period: Patients received placebo administered IV once daily on Days 1 to 3 of each 21-day therapy cycle (up to 4 cycles in total). Etoposide 100 mg/m² was administered as an IV infusion over 60 minutes on Days 1, 2, and 3 of each 21-day cycle. The carboplatin dose was to be calculated using the Calvert formula with a target AUC of 5 mg·min/mL (maximum 750 mg) IV over approximately 30 minutes on Day 1, and 100 mg/m² etoposide was administered IV over approximately 60 minutes daily on Days 1, 2, and 3 of each 21-day cycle. Atezolizumab 1200 mg was administered as an IV infusion on Day 1 of each 21-day cycle.

Maintenance Period: Patients received atezolizumab monotherapy once every 21 days.

Serious adverse events	Trilaciclib	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 52 (32.69%)	25 / 53 (47.17%)	
number of deaths (all causes)	42	44	
number of deaths resulting from adverse events	2	5	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 52 (1.92%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			

subjects affected / exposed	1 / 52 (1.92%)	0 / 53 (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			
Non-cardiac chest pain			
subjects affected / exposed	1 / 52 (1.92%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	0 / 52 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 52 (1.92%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 52 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 52 (3.85%)	2 / 53 (3.77%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 52 (1.92%)	2 / 53 (3.77%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			

subjects affected / exposed	1 / 52 (1.92%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	1 / 52 (1.92%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypoxia			
subjects affected / exposed	0 / 52 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 52 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	1 / 52 (1.92%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 52 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Platelet count decreased			
subjects affected / exposed	0 / 52 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 52 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hip fracture			
subjects affected / exposed	1 / 52 (1.92%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 52 (1.92%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 52 (1.92%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 52 (1.92%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Balance disorder			
subjects affected / exposed	0 / 52 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cognitive disorder			
subjects affected / exposed	0 / 52 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised tonic-clonic seizure			
subjects affected / exposed	0 / 52 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 52 (1.92%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Paraneoplastic neurological syndrome			
subjects affected / exposed	0 / 52 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	0 / 52 (0.00%)	4 / 53 (7.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 52 (0.00%)	3 / 53 (5.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	1 / 52 (1.92%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	1 / 52 (1.92%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Retroperitoneal haemorrhage			
subjects affected / exposed	1 / 52 (1.92%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	1 / 52 (1.92%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Inappropriate antidiuretic hormone secretion			

subjects affected / exposed	1 / 52 (1.92%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 52 (1.92%)	2 / 53 (3.77%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	3 / 52 (5.77%)	8 / 53 (15.09%)	
occurrences causally related to treatment / all	0 / 5	0 / 8	
deaths causally related to treatment / all	0 / 1	0 / 1	
Sepsis			
subjects affected / exposed	0 / 52 (0.00%)	2 / 53 (3.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Urinary tract infection			
subjects affected / exposed	1 / 52 (1.92%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiolitis			
subjects affected / exposed	0 / 52 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 52 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 52 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Empyema			
subjects affected / exposed	0 / 52 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Meningoencephalitis herpetic			
subjects affected / exposed	0 / 52 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 52 (0.00%)	2 / 53 (3.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			
subjects affected / exposed	0 / 52 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

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

Non-serious adverse events	Trilaciclib	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	49 / 52 (94.23%)	52 / 53 (98.11%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 52 (5.77%)	3 / 53 (5.66%)	
occurrences (all)	6	4	
Flushing			
subjects affected / exposed	3 / 52 (5.77%)	2 / 53 (3.77%)	
occurrences (all)	4	2	
Hypotension			
subjects affected / exposed	1 / 52 (1.92%)	3 / 53 (5.66%)	
occurrences (all)	1	4	
Phlebitis			

subjects affected / exposed occurrences (all)	3 / 52 (5.77%) 4	0 / 53 (0.00%) 0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	16 / 52 (30.77%)	20 / 53 (37.74%)	
occurrences (all)	24	32	
Asthenia			
subjects affected / exposed	8 / 52 (15.38%)	9 / 53 (16.98%)	
occurrences (all)	17	21	
Non-cardiac chest pain			
subjects affected / exposed	5 / 52 (9.62%)	7 / 53 (13.21%)	
occurrences (all)	5	7	
Pyrexia			
subjects affected / exposed	8 / 52 (15.38%)	4 / 53 (7.55%)	
occurrences (all)	8	5	
oedema periph			
subjects affected / exposed	4 / 52 (7.69%)	4 / 53 (7.55%)	
occurrences (all)	4	4	
Chills			
subjects affected / exposed	2 / 52 (3.85%)	4 / 53 (7.55%)	
occurrences (all)	2	5	
Gait disturbance			
subjects affected / exposed	1 / 52 (1.92%)	3 / 53 (5.66%)	
occurrences (all)	1	3	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	8 / 52 (15.38%)	13 / 53 (24.53%)	
occurrences (all)	13	20	
Cough			
subjects affected / exposed	8 / 52 (15.38%)	8 / 53 (15.09%)	
occurrences (all)	8	12	
Haemoptysis			
subjects affected / exposed	3 / 52 (5.77%)	5 / 53 (9.43%)	
occurrences (all)	3	7	
Oropharyngeal pain			

subjects affected / exposed occurrences (all)	2 / 52 (3.85%) 2	3 / 53 (5.66%) 4	
Productive cough subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1	4 / 53 (7.55%) 4	
Wheezing subjects affected / exposed occurrences (all)	3 / 52 (5.77%) 3	2 / 53 (3.77%) 2	
Dysphonia subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1	3 / 53 (5.66%) 3	
Epistaxis subjects affected / exposed occurrences (all)	0 / 52 (0.00%) 0	3 / 53 (5.66%) 3	
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	3 / 52 (5.77%) 8	5 / 53 (9.43%) 5	
Confusional state subjects affected / exposed occurrences (all)	2 / 52 (3.85%) 2	4 / 53 (7.55%) 5	
Insomnia subjects affected / exposed occurrences (all)	0 / 52 (0.00%) 0	4 / 53 (7.55%) 4	
Investigations Platelet count decreased subjects affected / exposed occurrences (all)	5 / 52 (9.62%) 10	13 / 53 (24.53%) 63	
Neutrophil count decreased subjects affected / exposed occurrences (all)	3 / 52 (5.77%) 11	11 / 53 (20.75%) 50	
White blood cell count decreased subjects affected / exposed occurrences (all)	7 / 52 (13.46%) 20	6 / 53 (11.32%) 25	
Aspartate aminotransferase increased			

subjects affected / exposed	6 / 52 (11.54%)	2 / 53 (3.77%)	
occurrences (all)	11	4	
Alanine aminotransferase increased			
subjects affected / exposed	5 / 52 (9.62%)	2 / 53 (3.77%)	
occurrences (all)	10	4	
Blood alkaline phosphatase increased			
subjects affected / exposed	4 / 52 (7.69%)	3 / 53 (5.66%)	
occurrences (all)	5	6	
Blood creatinine increased			
subjects affected / exposed	3 / 52 (5.77%)	4 / 53 (7.55%)	
occurrences (all)	4	5	
Blood lactate dehydrogenase increased			
subjects affected / exposed	3 / 52 (5.77%)	4 / 53 (7.55%)	
occurrences (all)	5	8	
weight dec			
subjects affected / exposed	4 / 52 (7.69%)	3 / 53 (5.66%)	
occurrences (all)	5	3	
Lipase increased			
subjects affected / exposed	1 / 52 (1.92%)	5 / 53 (9.43%)	
occurrences (all)	2	10	
Weight increased			
subjects affected / exposed	3 / 52 (5.77%)	0 / 53 (0.00%)	
occurrences (all)	3	0	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	5 / 52 (9.62%)	2 / 53 (3.77%)	
occurrences (all)	11	2	
Fall			
subjects affected / exposed	2 / 52 (3.85%)	4 / 53 (7.55%)	
occurrences (all)	3	6	
Nervous system disorders			
Dizziness			
subjects affected / exposed	9 / 52 (17.31%)	9 / 53 (16.98%)	
occurrences (all)	11	13	
Headache			

subjects affected / exposed occurrences (all)	9 / 52 (17.31%) 13	6 / 53 (11.32%) 9	
Tremor subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1	3 / 53 (5.66%) 3	
dysgeusia subjects affected / exposed occurrences (all)	0 / 52 (0.00%) 0	3 / 53 (5.66%) 3	
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	19 / 52 (36.54%) 60	32 / 53 (60.38%) 122	
Neutropenia subjects affected / exposed occurrences (all)	19 / 52 (36.54%) 35	28 / 53 (52.83%) 85	
Thrombocytopenia subjects affected / exposed occurrences (all)	7 / 52 (13.46%) 14	21 / 53 (39.62%) 44	
Leukopenia subjects affected / exposed occurrences (all)	4 / 52 (7.69%) 5	14 / 53 (26.42%) 38	
Gastrointestinal disorders			
Nausea subjects affected / exposed occurrences (all)	20 / 52 (38.46%) 36	18 / 53 (33.96%) 30	
Constipation subjects affected / exposed occurrences (all)	5 / 52 (9.62%) 6	12 / 53 (22.64%) 15	
Diarrhoea subjects affected / exposed occurrences (all)	9 / 52 (17.31%) 13	6 / 53 (11.32%) 10	
Vomiting subjects affected / exposed occurrences (all)	6 / 52 (11.54%) 10	5 / 53 (9.43%) 6	
Stomatitis			

subjects affected / exposed occurrences (all)	3 / 52 (5.77%) 3	3 / 53 (5.66%) 5	
Abdominal pain subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1	4 / 53 (7.55%) 5	
Dyspepsia subjects affected / exposed occurrences (all)	4 / 52 (7.69%) 4	0 / 53 (0.00%) 0	
Skin and subcutaneous tissue disorders			
Alopecia subjects affected / exposed occurrences (all)	7 / 52 (13.46%) 8	18 / 53 (33.96%) 21	
Pruritus subjects affected / exposed occurrences (all)	8 / 52 (15.38%) 9	3 / 53 (5.66%) 3	
Rash subjects affected / exposed occurrences (all)	5 / 52 (9.62%) 10	4 / 53 (7.55%) 5	
Rash maculo-papular subjects affected / exposed occurrences (all)	0 / 52 (0.00%) 0	3 / 53 (5.66%) 11	
Renal and urinary disorders			
Urinary incontinence subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 4	3 / 53 (5.66%) 5	
Endocrine disorders			
Hypothyroidism subjects affected / exposed occurrences (all)	3 / 52 (5.77%) 3	7 / 53 (13.21%) 7	
Hyperthyroidism subjects affected / exposed occurrences (all)	2 / 52 (3.85%) 3	6 / 53 (11.32%) 6	
Musculoskeletal and connective tissue disorders			
Back pain subjects affected / exposed occurrences (all)	5 / 52 (9.62%) 10	3 / 53 (5.66%) 3	

Arthralgia subjects affected / exposed occurrences (all)	5 / 52 (9.62%) 5	2 / 53 (3.77%) 2	
Muscular weakness subjects affected / exposed occurrences (all)	3 / 52 (5.77%) 3	3 / 53 (5.66%) 3	
Muscle spasms subjects affected / exposed occurrences (all)	2 / 52 (3.85%) 2	3 / 53 (5.66%) 4	
Pain in extremity subjects affected / exposed occurrences (all)	2 / 52 (3.85%) 2	3 / 53 (5.66%) 3	
Infections and infestations			
Urinary tract infection subjects affected / exposed occurrences (all)	5 / 52 (9.62%) 7	3 / 53 (5.66%) 4	
Pneumonia subjects affected / exposed occurrences (all)	4 / 52 (7.69%) 4	3 / 53 (5.66%) 4	
Upper respiratory tract infection subjects affected / exposed occurrences (all)	3 / 52 (5.77%) 4	3 / 53 (5.66%) 5	
Bronchitis subjects affected / exposed occurrences (all)	3 / 52 (5.77%) 4	2 / 53 (3.77%) 2	
Metabolism and nutrition disorders			
Dehydration subjects affected / exposed occurrences (all)	5 / 52 (9.62%) 6	9 / 53 (16.98%) 11	
Decreased appetite subjects affected / exposed occurrences (all)	4 / 52 (7.69%) 5	9 / 53 (16.98%) 10	
Hyperglycaemia subjects affected / exposed occurrences (all)	5 / 52 (9.62%) 11	3 / 53 (5.66%) 3	
Hyponatraemia			

subjects affected / exposed	4 / 52 (7.69%)	4 / 53 (7.55%)	
occurrences (all)	13	4	
Hypokalaemia			
subjects affected / exposed	4 / 52 (7.69%)	2 / 53 (3.77%)	
occurrences (all)	6	2	
Hyperkalaemia			
subjects affected / exposed	3 / 52 (5.77%)	1 / 53 (1.89%)	
occurrences (all)	7	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 May 2017	• An additional risk (hypophysitis) with atezolizumab was added. • Assessments to be made after the last dose of study drug were changed from 30 and 120 days after the last dose to 30 and 90 days after the last dose. • Specification was added that the weight used for calculation of glomerular filtration rate using the Cockcroft-Gault equation should be the actual body weight (and not ideal body weight). • It was clarified that concomitant medications like bisphosphonates and denosumab, which are used to prevent skeletal-related events in patients with bony metastases, are allowed as long as the patient has been on stable doses for at least 4 weeks. • An allowance was added that such that the timing and number of samples collected for pharmacokinetic, immunologic markers and anti-atezolizumab antibody testing can be altered based on emerging data without requiring an amendment if the blood volume/day or overall does not increase and the patient is not required to have additional clinic visits or prolongation of a clinic visit, ie, the risk-benefit profile for the patient does not worsen. Specification was added that the investigators and institutional review boards (IRBs) or Independent Ethics Committees (IECs) will be notified if the frequency is reduced. • A provision was added that any ECG with a QTc value of > 500 should be repeated every 5 minutes for a total of 3 ECGs to confirm this finding, and that the QTc value should also be confirmed via manual read. • Clarifications were made to the secondary objectives and inclusion criteria. • Descriptions regarding the timing of vital sign assessments and infusion duration for both trilaciclib and placebo were modified slightly.
14 September 2018	• Additional rationale describing the mechanism of action of trilaciclib and the potential myelopreservation benefit to patients receiving cytotoxic chemotherapy has been added. • Statistics has been updated to further define the modified Primary and Secondary endpoints. • Objectives and endpoints were updated to evaluate the potential of trilaciclib to reduce chemotherapy-induced myelosuppression • Modification of sample size justification; the sample size calculation is now based on demonstrating the superiority of trilaciclib + E/P/A versus placebo + E/P/A with respect to at least one of the primary efficacy endpoints. No adjustment to the sample size was determined to be needed; therefore, this amendment does not impact patient accrual. • Clarification of Final Analysis as well as an End of Study Analysis where the Final Analysis will include the final myelopreservation and ORR analysis and interim PFS and OS, and the End of Study Analysis would be performed when at least 70% of the patients have died. The timing of the Final Analysis was chosen to occur at a time point when all patients will have completed the randomized Induction Period of the study and will have discontinued trilaciclib or placebo treatment. • Modification of the planned statistical methods. A composite is proposed as either a Key Secondary endpoint (Region 1) or a supportive secondary endpoint (Region 2). Myelosuppression is an example of a serious disease for which more than one clinical outcome is important, and trilaciclib is expected to elicit an effect on more than one of these clinically relevant endpoints. Therefore, analysis of a composite endpoint presents an opportunity to evaluate multiple aspects of clinically relevant effectiveness in a single analysis. • Text describing multiplicity adjustments for the myelosuppression endpoints has been added. • Details of the analysis of supportive secondary efficacy endpoints (anti-tumor and myelosuppression) have been added.

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.

Small sample size may have reduced the ability to observe statistically significant treatment effects on secondary myelopreservation measures (i.e. occurrence of FN AEs, infections and antibiotics usage). Only able to detect large differences in OS.

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/33895103>

<http://www.ncbi.nlm.nih.gov/pubmed/33348420>