CLINICAL STUDY REPORT

G1T28-05

PHASE 2 STUDY OF CARBOPLATIN, ETOPOSIDE, AND ATEZOLIZUMAB WITH OR WITHOUT TRILACICLIB (G1T28) IN PATIENTS WITH UNTREATED EXTENSIVE-STAGE SMALL CELL LUNG CANCER

Indication studied:	Prevention or mitigation of chemotherapy-induced myelosuppression
Investigational product:	Trilaciclib (G1T28)
Developmental phase of study:	2
ClinicalTrials.gov identifier:	NCT03041311
EudraCT number:	2017-000358-20
First patient enrolled (signed informed consent):	29 June 2017
Last patient observation for this report:	28 June 2019
Release date of report:	30 March 2020
Company/sponsor signatory:	Shannon R. Morris, MD, PhD Vice President, Clinical Development G1 Therapeutics, Inc. Email: smorris@g1therapeutics.com
Coordinating investigator:	Davey Daniel, MD Sarah Cannon Research Institute Chattanooga, TN Email: ddaniel@tnonc.com

This study was conducted in accordance with the ethical principles of Good Clinical Practice, including archiving of essential documents, according to the ICH Harmonized Tripartite Guideline.

2. SYNOPSIS

<table>
<tr><td>Name of Sponsor/Company:
G1 Therapeutics, Inc.</td><td rowspan="3">Individual Study Table Referring to Part of the Dossier:
Volume:
Page:</td><td rowspan="3">(For National Authority Use Only)</td></tr>
<tr><td>Name of Finished Product:
Trilaciclib (G1T28)</td></tr>
<tr><td>Name of Active Ingredient:
Trilaciclib (G1T28)</td></tr>
<tr><td colspan="3">Title of Study: Phase 2 Study of Carboplatin, Etoposide, and Atezolizumab with or without Trilaciclib (G1T28) in Patients with Untreated Extensive-Stage Small Cell Lung Cancer</td></tr>
<tr><td colspan="3">Coordinating Investigator: Davey Daniel, MD</td></tr>
<tr><td colspan="3">Study Sites: The study is being conducted at 56 study sites in the United States, Spain, France, Bulgaria, Estonia, Latvia, Ukraine, and Georgia.</td></tr>
<tr><td colspan="3">Publications:
Daniel, D., Kuchava, V., Bondarenko, I., et al. Trilaciclib decreases myelosuppression in extensive-stage small cell lung cancer (ES-SCLC) patients receiving first-line chemotherapy plus atezolizumab. Abstract: ESMO 2019 Congress Poster; September 2019; Barcelona, Spain.
Weiss J., Skaltsa, K., Gwaltney, C., et al. Positive effects of trilaciclib on patient myelosuppression-related symptoms and functioning: results from 3 phase 2 randomized, double-blind, placebo-controlled small cell lung cancer trials. Oral Presentation: MASCC; June 2019; San Francisco, CA
Weiss, J., Positive effects of trilaciclib on patient myelosuppression-related symptoms and functioning: results from 3 phase 2 randomized, double-blind, placebo-controlled small cell lung cancer trials. Abstract: MASCC; June 2019; San Francisco, CA</td></tr>
<tr><td colspan="2">Studied Period (years): ~2 years
Date first patient enrolled: 29 June 2017
Date last patient observed for this report: 28 June 2019</td><td>Phase of Development: 2</td></tr>
</table>

Objectives and Endpoints:

Note that the key secondary endpoints are described by geographic region (Region 1 [EU] and Region 2 [US]), reflecting the advice received from regulatory authorities in the respective regions and with reference to ICH E17: General Principles for Planning and Design of Multiregional Clinical Trials (ICH E17). To enable statistical analyses that control for multiplicity among primary endpoints and key secondary endpoints for 2 different sets of key secondary endpoints, 2 corresponding SAPs (Region 1 and Region 2) were developed. The two SAPs are identical in contents except for the section where the statistical algorithm for multiplicity adjustment was described. The SAPs were finalized prior to database lock and analysis of the data.

The primary, key secondary, supportive secondary, and exploratory objectives and endpoints of this study are as follows:

<table>
<tr><th>Primary Objective</th><th colspan="2">Primary Endpoints</th></tr>
<tr><td rowspan="2">To evaluate the potential of trilaciclib, compared with placebo, to reduce chemotherapy-induced myelosuppression in patients with SCLC undergoing treatment with etoposide, carboplatin, and atezolizumab (E/P/A)</td><td colspan="2">All Regions</td></tr>
<tr><td colspan="2">• Duration of severe (Grade 4) neutropenia in Cycle 1
• Occurrence of severe (Grade 4) neutropenia</td></tr>
<tr><th>Key Secondary Objectives</th><th colspan="2">Key Secondary Endpoints</th></tr>
<tr><td rowspan="2">To evaluate the potential of trilaciclib, compared with placebo, to reduce chemotherapy-induced myelosuppression and its consequences in patients with SCLC undergoing treatment with E/P/A</td><th>Region 1 (EU)</th><th>Region 2 (US)</th></tr>
<tr><td>• Occurrence of RBC transfusions on/after Week 5 (proportion of patients)
• Occurrence of G-CSF administration (proportion of patients)
• A composite endpoint (MAHE; number of events for all components) defined to include the following:
  • All-cause hospitalizations
  • All-cause dose reductions
  • Febrile neutropenia
  • RBC transfusions on/after Week 5</td><td>• OS (was not factored into multiplicity adjustment)
• All-cause dose reductions (number of events)
• Occurrence of RBC transfusions on/after Week 5 (proportion of patients)
• Occurrence of G-CSF administration (proportion of patients)</td></tr>
</table>

	• Prolonged severe (Grade 4) neutropenia (duration >5 days)	
Supportive Secondary Objectives	**Supportive Secondary Endpoints**	

To evaluate the potential of trilaciclib, compared with placebo, to reduce chemotherapy-induced myelosuppression and its consequences in patients with SCLC undergoing treatment with E/P/A	• (**Region 1 ONLY**) OS
	• (**Region 2 ONLY**) A composite endpoint (MAHE; number of events for all components) defined to include the following:
	  • All-cause hospitalizations
	  • All-cause dose reductions
	  • Febrile neutropenia
	  • RBC transfusions on/after Week 5
	  • Prolonged severe neutropenia (duration >5 days)	

To evaluate the anti-tumor activity of trilaciclib or placebo administered in combination with E/P/A to patients with SCLC	• Occurrence of objective response (CR or PR per RECIST v1.1 as assessed by investigator) • Duration of objective response (CR or PR per RECIST v1.1 as assessed by investigator) • PFS (per RECIST v1.1 as assessed by investigator)	
To determine the safety and tolerability of trilaciclib or placebo administered in combination with E/P/A in patients with SCLC	• Occurrence and severity of AEs by NCI-CTCAE v4.03 • Occurrence and severity of AESIs for atezolizumab by NCI-CTCAE v4.03 • Changes in laboratory parameters (hematology, chemistry, and urinalysis), vital signs, and ECG parameters • Grade 3 and 4 abnormalities in laboratory parameters (hematology and chemistry) • Occurrence and severity of infusion-related reactions • Occurrence of trilaciclib dose delays and interruptions • Occurrence of chemotherapy dose reductions • Occurrence of chemotherapy dose delays and interruptions • Occurrence of atezolizumab dose delays and interruptions • RDI of carboplatin and etoposide • Occurrence of patients that discontinue study treatment because of AEs	

To evaluate the potential of trilaciclib to reduce chemotherapy-induced myelosuppression by assessing effects on multiple lineages and current standard-of-care interventions to treat myelosuppression (neutrophils, RBC, platelets, lymphocytes)	• All-cause hospitalizations • Febrile neutropenia • G-CSF administration • Occurrence of Grade 3 and 4 hematologic laboratory values • ANC nadir by cycle • Prolonged severe neutropenia (duration >5 days) • Platelet transfusions • RBC transfusions • ANC, hemoglobin, platelet counts, and lymphocyte counts over time • Occurrence of ESA administration • Occurrence of systemic antimicrobial administration
To describe the PK of trilaciclib, carboplatin, and etoposide in a subset of patients; and atezolizumab in all patients	PK parameters to be calculated (as data permit) for trilaciclib, carboplatin, etoposide, and atezolizumab: C_{max}, C_{min}, T_{max}, AUC_{0-t}, AUC_{inf}, $t_{1/2}$, CL, and V_z
Exploratory Objectives	**Exploratory Endpoints (as data warrant)**
To evaluate the effects of trilaciclib on PROs for patients with SCLC treated with E/P/A	Assess change from baseline in the following: • FACT QOL instrument total scale score (general) • FACT domain scores (physical, social/family, emotional, and FWB) • FACT-L total scale score • FACT-L lung cancer subscale score • FACT-L trial outcome index score • FACT-An total scale score • FACT-An anemia subscale score • FACT-An trial outcome index score
To evaluate the anti-tumor activity of trilaciclib or placebo administered in combination with E/P/A to patients with SCLC, as assessed by irRECIST	• Occurrence of objective response (CR or PR) per irRECIST • Duration of response (CR or PR) per irRECIST • PFS per irRECIST
To evaluate the ability of patients with SCLC to continue receiving subsequent anti-cancer therapy after discontinuing study drug	• Characterize number of patients who receive systemic anti-cancer therapy after discontinuing study drug • Characterize types and number of lines of treatments patients receive after discontinuing study drug
To explore the changes in peripheral blood immune subsets by immunophenotyping in	• Summary of change from baseline of immune cell subsets

patients with SCLC administered trilaciclib or placebo in combination with E/P/A	• Relationship between immune subsets and biological/clinical endpoints
To evaluate tumor biomarkers potentially predictive of response to trilaciclib in combination with E/P/A	Relationship between tumor biomarkers (including but not limited to PD-L1 and PD-1) and biological/clinical endpoints
To evaluate the effect of ATA on atezolizumab PK, safety, and efficacy (ORR, PFS, and OS)	Relationships between presence of ATA in the blood and atezolizumab PK, safety, and efficacy (ORR, PFS, and OS)

AE=adverse event; AESI=adverse event of special interest; ANC=absolute neutrophil count; ATA=anti-atezolizumab therapeutic antibodies; AUC_{0-t}=area under the plasma concentration-time curve from 0 to t hours after dosing; AUC_{inf}=area under the plasma concentration-time curve from time zero extrapolated to infinity; CL=clearance; C_{max}=maximum concentration; C_{min}=minimum concentration; CR=complete response; ECG=electrocardiogram; ESA=erythropoiesis-stimulating agent; E/P/A=etoposide, carboplatin, and atezolizumab; ESA=erythropoiesis-stimulating agent; FACT=Functional Assessment of Cancer Therapy; FACT-An=Functional Assessment of Cancer Therapy–Anemia quality of life instrument; FACT-L=-Functional Assessment of Cancer Therapy Lung quality of life instrument;- FWB=Functional Well-Being; G-CSF=-granulocyte colony stimulating factor; irRECIST=immune-related Response Evaluation Criteria in Solid Tumors; MAHE=major adverse hematologic events; NCI CTCAE v4.03=National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.03; ORR=objective response rate; OS=overall survival; PD-1=program cell death protein 1; PDL1=programmed death ligand 1; PK=pharmacokinetics; PFS=progression-free survival; PR=partial response; PRO=patient reported outcome; QOL=quality of life; RBC=red blood cell; RDI=relative dose intensity; RECIST v1.1=Response Evaluation Criteria in Solid Tumors, Version 1.1; SCLC=small cell lung cancer; $t_{1/2}$=terminal phase half-life; T_{max}=Time of maximum observed concentration; Vz=apparent volume of distribution during terminal elimination phase after extravascular administration.

Methodology:

This Phase 2, randomized, double-blind, placebo-controlled, global, multicenter study assessed the efficacy and safety of trilaciclib or placebo in patients being treated with etoposide, carboplatin, and atezolizumab (E/P/A) for newly diagnosed extensive-stage SCLC. Approximately 100 patients were planned to be randomly assigned in a 1:1 fashion to trilaciclib 240 mg/m^2 or placebo administered intravenously once daily on Days 1 to 3, with E/P/A therapy for up to four 21-day cycles (Induction). Randomization was stratified by Eastern Cooperative Oncology Group (ECOG) performance status (0 to 1 versus 2) and presence of brain metastases (Yes versus No).

Following the completion of up to a maximum of 4 chemotherapy-containing (trilaciclib or placebo + E/P/A) cycles, patients proceeded to Maintenance and received atezolizumab monotherapy on Day 1 of every 21-day cycle until disease progression, unacceptable toxicity, withdrawal of consent, or discontinuation by the investigator. Study drug refers to trilaciclib or placebo + E/P/A during Induction and to atezolizumab during Maintenance. The study included 3 phases: Screening Phase, Treatment Period (Induction + Maintenance), and Survival Follow-up Phase. For each patient, the Treatment Period began on the day of first dose with any study drug and was completed after the last Post-Treatment Visit.

The initial diagnosis of SCLC was based on standard pathological examination, preferably including immunohistochemical staining for neuroendocrine features. Archived tumor samples were to be available for banking for assessment of relevant deoxyribonucleic acid, ribonucleic acid, and protein markers, such as programmed death-ligand 1 (PD-L1) or those involved in the cyclin-dependent kinase 4/6 (CDK4/6) pathway.

Based on its mechanism of action (MOA), the administration of trilaciclib prior to chemotherapy is predicted to prevent chemotherapy-induced myelosuppression. Therefore, the endpoints measuring trilaciclib myelopreservation efficacy are the same measures one would use to measure the safety of

chemotherapy. This concept is critical to understanding how the trilaciclib myelopreservation efficacy was evaluated in this study. Trilaciclib also has the potential to improve anti-tumor efficacy by allowing chemotherapy to be delivered on time and at standard-of-care doses while simultaneously facilitating a more favorable, and less damaged, immune system.

Number of patients (planned and analyzed):

Planned: Approximately 100 patients were planned to be enrolled in the study and randomly assigned (1:1) to 1 of 2 groups.

Analyzed:

Category	Number (%) of Patients		
	Placebo (N = 53)	**Trilaciclib 240 mg/m^2 (N = 54)**	**Total (N = 107)**
ITT analysis set	53 (100.0)	54 (100.0)	107 (100.0)
mITT analysis set	53 (100.0)	52 (96.3)	105 (98.1)
PP analysis set	48 (90.6)	48 (88.9)	96 (89.7)
Safety analysis set	53 (100.0)	52 (96.3)	105 (98.1)
RE analysis set	52 (98.1)	50 (96.2)	102 (97.1)

ITT=intent-to-treat; mITT=modified intent-to-treat; PP=per-protocol; RE=response evaluable.

Diagnosis and main criteria for inclusion:

In order to be eligible, female or male patients ≥18 years of age with confirmed diagnosis of SCLC by histology or cytology must have had all of the following:

- At least 1 target lesion that was measurable by Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1).
- Hemoglobin ≥9.0 g/dL;
- Absolute neutrophil count (ANC) ≥1.5 × 10^9/L;
- Platelet count ≥100 × 10^9/L;
- Creatinine ≤1.5 mg/dL or glomerular filtration rate of ≥60 mL/minute;
- Total bilirubin ≤1.5× upper limit of normal (ULN);
- Aspartate aminotransferase and alanine transaminase ≤2.5× ULN;
- An ECOG performance status of 0 to 2; and
- A predicted life expectancy of ≥3 months.

Patients were not eligible if they had:

- Limited-stage SCLC or prior chemotherapy for limited or extensive-stage SCLC;
- Prior treatment with immunotherapies, the presence of symptomatic brain metastases requiring immediate treatment, and malignancies other than SCLC within 3 years prior to randomization;
- History of idiopathic pulmonary fibrosis, organizing pneumonia, drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computed tomography scan;
- Active, known, or suspected autoimmune, uncontrolled ischemic heart disease or uncontrolled symptomatic congestive heart failure, known history of stroke or cerebrovascular accident, serious active infection at the time of enrollment, psychiatric illness/social situations that would

limit study compliance, other uncontrolled serious chronic disease or conditions, or known human immunodeficiency virus, known active hepatitis B or hepatitis C;

- Radiotherapy to any site within 2 weeks prior to enrollment, or receipt of any investigational medication or administration of a live attenuated vaccine within 4 weeks before enrollment;
- A condition requiring systemic treatment with either corticosteroids or other immunosuppressive medications within 14 days of study drug administration;
- Hypersensitivity to any of the components of the formulation of etoposide or etoposide phosphate, carboplatin or other platinum-containing compounds, or mannitol; or
- Were pregnant or lactating.

Test product, dose and mode of administration, batch number:

A dose of trilaciclib 240 mg/m^2 diluted in 250 mL of dextrose 5% in water or sodium chloride solution 0.9% was administered by intravenous (IV) infusion over approximately 30 (±5) minutes once daily on Days 1 to 3 of each 21-day cycle E/P/A therapy cycle (up to 4 cycles in total).

Batch numbers: 085I1016, 029I0717, 012I0417, and 080I1117.

Duration of treatment: Study drug administration continued until disease progression per RECIST v1.1, unacceptable toxicity, withdrawal of consent, or discontinuation by investigator, whichever occurred first.

Reference therapy, dose and mode of administration:

Placebo:

Placebo formulation of 250 mL of dextrose 5% in water or sodium chloride solution 0.9% administered as an IV infusion over 30 minutes once daily on Days 1 to 3 of each 21-day cycle prior to the dose(s) of chemotherapy.

Chemotherapy treatment:

Patients in both the placebo and trilaciclib group received E/P/A therapy during the Induction Period of the study.

The carboplatin dose calculated using the Calvert formula with a target area under the concentration-time curve (AUC) of 5 mg·min/mL (maximum 750 mg) was administered IV over approximately 30 minutes on Day 1, and 100 mg/m^2 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 IV on Day 1 of each 21-day cycle in both the Induction Period and Maintenance Period. Atezolizumab was administered following the completion of administration of trilaciclib or placebo + E/P during Induction.

Criteria for evaluation:

Efficacy: The myelopreservation efficacy of trilaciclib (compared with placebo) was evaluated using myelosuppression endpoints measuring abnormal hematologic laboratory parameters (eg, complete blood counts [CBCs]) and their derivatives. The primary myelosuppression endpoints were duration of severe (Grade 4) neutropenia (DSN) in Cycle 1 (Strategy 1) and occurrence of severe (Grade 4) neutropenia (SN). The treatment effect of trilaciclib was also evaluated by measuring standard-of-care interventions used to manage chemotherapy-induced myelosuppression. In contrast, investigator reported hematologic treatment-emergent adverse events (TEAEs) were considered safety parameters. Although somewhat artificial, this approach has been taken to clearly differentiate between the myelopreservation efficacy of trilaciclib and parameters used to describe the safety of patients enrolled in this study.

More specifically, myelopreservation efficacy assessments were based on the following: CBCs; hematologic toxicities, including the occurrence of febrile neutropenia (FN) TEAEs and infection

serious adverse events (SAEs); occurrence of red blood cell (RBC) and platelet transfusions; hematopoietic growth factor utilization including the occurrence of granulocyte colony-stimulating factor (G-CSF) and erythropoiesis-stimulating agent (ESA) administration; systemic antibiotic use; hospitalizations, and chemotherapy dose modifications including dose reductions. Exploratory assessments of myelopreservation efficacy effects on patients were based on patient-reported outcomes (PROs) (ie, Functional Assessment of Cancer Therapy–Anemia quality of life instrument [FACT-An], Functional Assessment of Cancer Therapy–General [FACT-G], and Functional Assessment of Cancer Therapy–Lung quality of life instrument [FACT-L]).

Anti-tumor efficacy evaluation was based on tumor response using Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1), including objective response rate (ORR), progression-free survival (PFS), and overall survival (OS).

Pharmacokinetics: For those patients that agreed to participate, serial blood samples were collected for the measurement of trilaciclib, etoposide, and carboplatin concentrations in plasma on Day 1 of Cycles 1 and 3. The time points for collection were as follows: predose, end of trilaciclib or placebo infusion, end of carboplatin infusion, end of etoposide infusion, 4 hours after start of trilaciclib or placebo infusion, 6 hours after start of trilaciclib or placebo infusion, and on Day 2 immediately prior to start of trilaciclib or placebo infusion.

Blood samples were collected for PK analysis of atezolizumab from all patients on Day 1 of Induction Cycles 1, 2, 3, and 4; Maintenance Cycles 4, 8, 12, and every eighth cycle thereafter; and at 30 and 90 days after the last dose of study drug. On each of these days, samples were to be drawn predose and 30 minutes after the infusion of atezolizumab.

Immunologic Markers: To evaluate the impact of trilaciclib administration on chemotherapy-induced changes of the immune system, peripheral blood immune subsets were evaluated.

Safety: Safety was assessed by the evaluation of AEs, vital signs measurements, physical examinations, electrocardiograms (ECGs), clinical laboratory data, and infusion-related reactions. Chemotherapy exposure, dose reductions, and dose interruptions were also evaluated as part of the safety assessments.

Statistical Methods: The final myelopreservation analysis was conducted after all patients been on study for at least 12 weeks or discontinued study drug prior to Week 12, which corresponds to the first database lock (DBL1) with a data cutoff date of 17 August 2018. All patients' data collected through this date were included in the final myelopreservation efficacy analysis even if a patient discontinued study treatment or the study itself prior to the minimum 12-week time point. These analyses included but were not limited to the final myelopreservation efficacy analysis, final PRO analyses, interim safety analysis, interim tumor response analysis, and interim PFS/OS analysis. The results of the final myelopreservation efficacy analysis are presented in this report.

Since patients continued to receive single agent atezolizumab as maintenance therapy at the time of the DCO for DBL1, a second database lock with cutoff date 28 June 2019 (database lock 2; DBL2) was done. The results from DBL2 are also presented in this report and are comprised of relevant results for safety and anti-tumor efficacy analysis. These results are included to provide an updated summary of the overall safety and anti-tumor efficacy evaluation.

As described in the SAP, the end-of-study analysis will be conducted when at least 70% of the patients have died. Anti-tumor efficacy analyses and safety analyses, which include all data collected during the entire study, will be the focus of the end-of-study analysis. There is no plan to re-run myelopreservation efficacy endpoint analyses in this final analysis. Additional PFS/OS analyses may be conducted during the time period between the final myelopreservation analysis and the End-of-Study analysis.

The intent-to-treat (ITT) analysis set included all randomized patients and was the primary population used to analyze myelopreservation efficacy endpoints, anti-tumor efficacy endpoints (PFS and OS), and PRO endpoints. ITT analyses were conducted on the basis of the randomly assigned treatment. A modified intent-to-treat (mITT) analysis set included the patients from the ITT analysis set who received at least 1 dose of any study drug and was used to assess sensitivity of selected efficacy analyses. A per-protocol analysis set, which was a subset of the mITT analysis set and included patients who had no key protocol deviations and who received the treatment to which they were randomized, was used to analyze selected efficacy analyses to test the robustness of results. The response evaluable (RE) analysis set included all patients who were in the mITT and met 1 of the following conditions: (1) had at least 1 post-baseline tumor assessment, (2) discontinued treatment because of clinical progression, or (3) died due to disease progression before their first post-baseline tumor scan. The RE analysis set was used for analyses of tumor response. The safety analysis set included all randomized patients who received at least 1 dose of any study drug and was used for the analysis of safety endpoints. The analyses using the safety analysis set were conducted on the basis of the actual treatment received.

Data were summarized by treatment group. The descriptive summary for the categorical variables included frequencies and percentages. The descriptive summary for the continuous variables included means, medians, standard deviations, and minimum and maximum values. For a time-to-event endpoint, the Kaplan-Meier method was used to estimate its median and 25% and 75% percentiles, along with their 95% confidence intervals (CIs) based on the Brookmeyer-Crowley method, if applicable.

Treatment effects were evaluated at a 2-sided significance level of 0.05. Where appropriate, model-based point estimates, together with their 95% CIs, were presented along with the 2-sided p-values for the tests, unless otherwise specified.

Myelopreservation Efficacy Analysis

There were 2 primary myelosuppression endpoints, DSN in Cycle 1 based on Strategy 1 and occurrence of SN during Induction.

DSN in Cycle 1 (Strategy 1) was analyzed with a nonparametric analysis of covariance (ANCOVA) (Stokes 2012). The nonparametric ANCOVA included the study baseline ANC value as a covariate, with the stratification factors of ECOG performance status (0 or 1 versus 2) and brain metastases (Yes versus No) at baseline, and treatment as fixed effects.

The binary response variable of occurrence of SN (Yes, No) during Induction was analyzed using a modified Poisson regression to account for the variable duration of the Treatment Period for each patient (Zou 2004). This model contained the stratification factors of ECOG performance status (0 to 1 versus 2) and brain metastases (Yes versus No) at baseline and treatment as fixed effects with baseline ANC value included as a covariate. The logarithm transformation of number of induction cycles in Induction for each patient was used as an offset to account for the variability of duration among patients. The binary response variables listed below were analyzed using the same method as described for occurrence of SN with the following caveats: (1) depending on the variable, the model included the appropriate baseline laboratory value (ANC or hemoglobin) as a covariate and (2) depending on the variable, the offset variable was either the logarithm transformation of the number of cycles or the number of weeks:

- Occurrence of RBC transfusion on/after Week 5
- Occurrence of G-CSF administration
- Occurrence of platelet transfusion
- Occurrence of Grade 3 or 4 hematologic laboratory values
- Occurrence of an ESA administration

- Occurrence of chemotherapy dose reductions
- Occurrence of FN
- Occurrence of IV antibiotic administration
- Occurrence of oral antibiotic administration
- Occurrence of oral or IV antibiotic administration
- Occurrence of an infection SAE
- Occurrent of pulmonary infection SAEs
- Occurrence of Grade 3 or 4 decreased hemoglobin laboratory values
- Occurrence of Grade 3 or 4 decreased platelet count laboratory values

In addition to assessing treatment effects on the occurrence, the number of events (eg, RBC transfusions on/after week 5, the number of all-cause chemotherapy dose reductions) was analyzed using a negative binomial regression model with the two stratification factors as the fixed terms and the log-transformed weeks (or cycles; depending on the endpoint) in Induction for each patient as offset variable. Event rate either per week or per cycle was presented. The number of events related to hematologic toxicity were also analyzed as a composite endpoint, denoted as major adverse hematologic events (MAHEs). The total number of MAHEs and the total number of events for each individual MAHE component were analyzed using the similar negative binomial regression model as described above.

There were 2 primary and multiple key secondary myelosuppression endpoints. A Hochberg-based gatekeeping procedure was utilized to control the global familywise type I error rate across the analyses for the primary and key secondary efficacy endpoints in the strong sense at a 1-sided α=0.025 level. To accommodate two different sets of key secondary endpoints (Region 1 and Region 2), two Hochberg-based gatekeeping procedures were conducted.

Anti-Tumor Efficacy Analysis

Tumor response endpoints, including best overall response (BOR), overall response rate (ORR), duration of overall response (DOR), and clinical benefit rate (CBR), were analyzed based on the response-evaluable analysis set.

The number and percentage of patients in each category of BOR (confirmed complete response [CR], confirmed partial response [PR], stable disease [SD], progressive disease [PD], or not evaluable [NE]), ORR, $ORR_{UNCONFIRMED}$, and CBR according to the investigator tumor assessment were summarized. Similar analyses were repeated based on the response status according to RECIST v1.1 derived from investigator tumor assessment data entered into the electronic case report form. Estimates of response rate, along with the associated exact 2-sided 95% CIs, were computed using the Clopper-Pearson method for ORR and CBR within each treatment group. The treatment effect on ORR was analyzed using a stratum-adjusted method to account for the stratification factors. The adjusted proportion difference (trilaciclib versus GC only) and its 95% CIs were calculated using the Cochran-Mantel-Haenszel (CMH) weight. The 2-sided p-value was calculated using a stratified exact CMH method.

PFS was defined as the time (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. For PFS, the derived endpoint based on only radiologic progression was considered as primary, and the derived endpoint based on both radiologic and clinical progression was considered as supportive. Censoring rules for patients who did not experience PD or death are described in the SAP. OS was calculated as the time (months) from the 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 the date of randomization.

For time-to-event endpoints such as DOR, PFS, and OS, in addition to the quartile summary from the Kaplan-Meier method, Kaplan-Meier estimates were provided for the survival probability at 3, 6, 9, and 12 months post randomization along with their 95% CIs. Treatment group differences in PFS and OS were evaluated using a stratified log-rank test to account for the stratification factors. The hazard ratio between trilaciclib and placebo, together with its 95% CIs, was calculated from a Cox proportional hazard model in which treatment and the stratification factors were included as fixed effects.

Pharmacokinetic Analysis

Pharmacokinetic parameters (eg, C_{max}, time to reach C_{max} [T_{max}], AUC_{0-t}, AUC_{inf}, terminal half-life [$t_{1/2}$], volume of distribution in the terminal elimination phase [V_z], and clearance [CL]) were derived from trilaciclib, etoposide, and carboplatin plasma concentration time data.

Safety Analysis

All safety analyses were based on the safety analysis set. Descriptive statistics were used to summarize the safety outcomes. The continuous safety variables were summarized at each visit, including the end of each cycle (the last non-missing assessment during the cycle), end of treatment (the last non-missing assessment during the applicable treatment period), and end of study (the last non-missing assessment during the whole study), if applicable. No inferential analyses of safety data were planned.

SUMMARY – CONCLUSIONS

Efficacy Results:

The myelopreservation efficacy results indicate that trilaciclib prevents chemotherapy-induced myelosuppression. These benefits manifest as statistically significant, and clinically meaningful, treatment effects observed in both of the primary endpoints, DSN in Cycle 1 and occurrence of SN, with1-sided p values <0.0001 after multiplicity adjustment. The mean (SD) DSN in Cycle 1 (Days) was shorter for patients receiving trilaciclib compared with placebo (0 [1.0] days versus 4 [4.7] days, respectively). The percentage of patients experiencing SN was lower in patients receiving trilaciclib compared with placebo (1.9% versus 49.1%, respectively).

Though most of the key secondary endpoints were found not to be statistically significant after multiplicity adjustment in either Region 1 or Region 2, the results observed for the key secondary and supportive secondary myelosuppression endpoints are clinically meaningful given the consistency in which trilaciclib is favored over placebo. To support this assertion, those endpoints for which trilaciclib was numerically favored over placebo are listed below with those that were statistically significant after multiplicity adjustment indicated in bold:

- DSN for those patients who had SN events (Strategy 2)
- Cumulative incidence (ie, event rate) of SN
- Occurrence and cumulative incidence (ie, event rate) of FN
- Cumulative incidence (ie, event rate) of prolonged SN (>5 days) (**statistically significant after multiplicity adjustment in Region 1**; not adjusted for multiplicity in Region 2)
- Occurrence and cumulative incidence (ie, event rate) of G-CSF administration
- Mean ANC nadir in Cycles 1 through 4
- Occurrence and cumulative incidence (ie, event rate) of RBC transfusions on/after Week 5 and from Day 1
- Occurrence and cumulative incidence (ie, event rate) of ESA administration
- Occurrence of Grade 3 or 4 decreased hemoglobin

- The magnitude of hemoglobin decline over time is less for patients receiving trilaciclib compared with placebo
- Occurrence of Grade 3 or 4 decreased platelet counts
- Occurrence of Grade 4 decreased platelet counts
- Occurrence and cumulative incidence (ie, event rate) of platelet transfusions
- Median number of units of platelets transfused for patients who received transfusions during the Induction Period and Overall Treatment Period
- Occurrence of and cumulative incidence (ie, event rate) of Grade 3 or 4 hematologic laboratory abnormalities.
- Cumulative incidence (ie, event rate) of MAHE (**statistically significant after multiplicity adjustment in Region 1**; not adjusted for multiplicity in Region 2)
- Cumulative incidence (ie, event rate) of all-cause dose reductions (included as part of MAHE and not statistically significant after multiplicity adjustment in Region 1; **a stand-alone key secondary endpoint in Region 2 which was statistically significant after multiplicity adjustment)**
- Occurrence of chemotherapy dose reductions
- Occurrence and cumulative incidence (ie, event rate) of infection SAEs
- Occurrence and cumulative incidence (ie, event rate) of pulmonary infection SAEs
- Occurrence and cumulative incidence (ie, event rate) of IV antibiotic use
- Cumulative incidence (ie, event rate) of oral antibiotic use
- Occurrence and cumulative incidence (ie, event rate) of IV or oral antibiotic use

The only measures of chemotherapy-induced myelosuppression for which trilaciclib did not show numerical improvement over placebo was for the median number of RBC units transfused per patient who received at least one transfusion, the cumulative incidence of all-cause hospitalizations, and occurrence of oral antibiotic use.

Subgroup analyses for patients over 65 years showed similar results to the population as a whole.

Analysis for PRO endpoints indicated that (1) a larger percentage of patients receiving trilaciclib (compared with placebo) had less deterioration in their HRQoL (compared with their baseline HRQoL) while receiving chemotherapy, (2) a larger percentage of patients receiving trilaciclib (compared with placebo) showed an improved HRQoL (compared with their baseline HRQoL) while receiving chemotherapy, and (3) a larger percentage of patients receiving trilaciclib (compared with placebo) had a delay in time to worsening of a variety of HRQoL measures while receiving chemotherapy. These observations, which were made for a variety of subscales and items (especially those associated with anemia and fatigue) suggested that patients on trilaciclib had a more tolerable experience receiving chemotherapy compared with placebo.

No statistically significant differences were observed between trilaciclib and placebo for any measured of anti-tumor efficacy (ORR, DOR, PFS, or OS).

Pharmacokinetic Results:

Trilaciclib:

- Disposition of trilaciclib in patients is comparable to healthy subjects and across different studies.

- Etoposide and carboplatin administration following trilaciclib administration had no effect on trilaciclib PK, as trilaciclib PK in this study was similar to trilaciclib PK observed in healthy subjects.
- There was little to no accumulation observed between cycles.
- No dose adjustment for trilaciclib is needed when trilaciclib is administered in combination with etoposide and/or carboplatin.

Etoposide:

- Etoposide PK parameters when etoposide was administered in combination with carboplatin and trilaciclib were comparable between Induction Cycle 1 Day 1 and Induction Cycle 3 Day 1.
- Etoposide CL and volume of distribution at steady state in this study were comparable to historical values.
- No difference in etoposide PK parameters was observed when administered with or without trilaciclib.

Carboplatin:

- Carboplatin (free and total) PK parameters when administered in combination with etoposide and trilaciclib were comparable between Induction Cycle 1 Day 1 and Induction Cycle 3 Day 1.
- Carboplatin (free and total) clearance and volume in this study were comparable to historical values.
- No difference in carboplatin (free and total) PK parameters was observed when administered with or without trilaciclib.

Safety Results:

Overall, trilaciclib was safe for patients with newly diagnosed extensive-stage SCLC receiving chemotherapy, as evidenced by the following:

- The majority (≥85%) of patients in both groups completed all 4 cycles of induction therapy.
- The mean RDI for carboplatin, etoposide, and atezolizumab was lower for patients in the placebo group compared with trilaciclib, and a lower number of chemotherapy dose delays/reductions were reported in the trilaciclib group compared with the placebo group. This was consistent with trilaciclib preventing chemotherapy-induced myelosuppression.
- During induction, fewer patients receiving trilaciclib experienced TEAEs regardless of grade, TEAEs regardless of grade related to any study drug, TEAEs ≥ Grade 3, TEAEs ≥ Grade 4, and TEAEs ≥ Grade 3 related to any study drug, compared with placebo. This general pattern was also seen for TEAEs reported during maintenance, which suggests that the benefits of trilaciclib on TEAEs may extend beyond when chemotherapy/trilaciclib are discontinued.
- The most common (≥20% of patients) TEAEs reported in the trilaciclib group overall and during induction were nausea, anemia, neutropenia, and fatigue.
- The most common (≥5% of patients) TEAEs considered related to trilaciclib were fatigue, nausea, anemia and infusion related reaction.
- Trilaciclib reduced the percentage of patients experiencing Grade 3 or 4 hematologic TEAEs compared with placebo as would be predicted based on the MOA of trilaciclib to prevent chemotherapy-induced myelosuppression.

- Infusion-related reactions/injection-site reactions or phlebitis TEAEs were more commonly reported for patients in the trilaciclib group as compared with the placebo group. Not all of the events were related to trilaciclib; some events were attributed to chemotherapy alone. All infusion-related reactions/injection-site reactions or phlebitis TEAEs were Grade ≤2.
- A higher percentage of patients had at least 1 atezolizumab AESI in the placebo group compared with the trilaciclib group. In addition, the majority of the AESIs were reported in 1-2 patients.
- Trilaciclib resulted in fewer TEAEs leading to chemotherapy dose reductions and dose delays than placebo.
- The percentage of patients experiencing TEAEs leading to discontinuation of any study drug was comparable for the trilaciclib group compared to placebo for the Overall Treatment Period. Except for asthenia, which was experienced by 2 patients in the trilaciclib group, none of the TEAEs leading to discontinuation of any study drug occurred in >1 patient. Only one patient experienced a TEAE related to trilaciclib that resulted in discontinuation of study drug (Grade 2 injection site reaction).
- The number of patients with SAEs was higher for the placebo group compared with trilaciclib; only 1 SAE was considered related to trilaciclib (deep vein thrombosis).
- SCLC progression was the reason for death for all patients who died, except for 6 patients who died due to fatal TEAEs [failure to thrive, pneumonia (2 patients), sepsis, infectious pleural effusion, and hemoptysis] and 4 patients who died due to "other" reasons (complications of second line therapy and progressive status deterioration for 1 patient each in the placebo group; sepsis/dysphagia and death NOS for 1 patient each in the trilaciclib group). No fatal TEAEs were related to trilaciclib, and only one was related to any study drug: a fatal TEAE of infectious pleural effusion in a patient receiving placebo was related to carboplatin and etoposide.
- There were no trends of clinically meaningful changes in vital signs values, ECOG scores, or ECG parameters during the study.
- No patient met Hy's law criteria. Most reported liver enzyme increases were Grade 1 or Grade 2, none of these were considered related to trilaciclib.
- No patients had a corrected QT interval by Fredericia (QTcF) ≥480 msec or an increase in QTcF ≥60 msec.

Conclusions:

Study G1T28-05 provides statistically significant and clinically meaningful results demonstrating the myelopreservation efficacy of trilaciclib (compared with placebo) administered prior to chemotherapy. The myelopreservation benefits of trilaciclib were demonstrated by the reduction of chemotherapy-induced myelosuppression, the reduction of standard-of-care interventions, and the improved overall safety profile. The following points are supportive of this conclusion:

- Trilaciclib consistently prevented chemotherapy-induced SN in a clinically meaningful and statistically significant manner as measured by the primary endpoints of DSN in Cycle 1 and occurrence of SN.
- Trilaciclib consistently prevented chemotherapy-induced anemia across all RBC endpoints.
- Trilaciclib consistently prevented chemotherapy-induced thrombocytopenia across most platelet endpoints.

- Trilaciclib improves the patient experience of receiving chemotherapy as measured by validated PRO instruments, specifically related to fatigue, which is consistent with the myelopreservation efficacy benefits offered by trilaciclib
- Trilaciclib decreases high grade chemotherapy-related TEAEs associated with chemotherapy-induced myelosuppression without adding significant trilaciclib-related toxicity.
- Trilaciclib does not adversely impact the anti-tumor efficacy of chemotherapy.

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