USING AN EXPLORATORY COMPOSITE ENDPOINT TO EVALUATE THE MYELOPRESERVATION BENEFITS OF TRILACICLIB IN PATIENTS WITH SMALL CELL LUNG CANCER

JANAKIRAMAN SUBRAMANIAN[1]; JANA JAAL[2]; IVETA KUDABA[3]; KRASIMIR NIKOLOV[4]; DAVORIN RADOSAVLJEVIC[5]; TIBOR CSŐSZI[6]; JIE XIAO[7]; JANET HORTON[7]; RAJESH K. MALIK[7]; MANUEL DÓMINE GÓMEZ[8]

[1]Saint Luke's Cancer Institute/University of Missouri, Kansas City, MO; [2]University of Tartu, Tartu, Estonia; [3]Riga East Clinical University-Latvian Oncology Center, Riga, Latvia; [4]Complex Oncology Center, Burgas, Bulgaria; [5]Institute for Oncology and Radiology of Serbia, Belgrade, Serbia; [6]Hetenyi Geza Korhaz, Szolnok, Hungary; [7]G1 Therapeutics, Inc., Research Triangle Park, NC; [8]Instituto de Investigacion Sanitaria-Fundación Jimenez Diaz (IIS-FJD), Madrid, Spain

INTRODUCTION

- Chemotherapy-induced myelosuppression (CIM) is an acute, dose-limiting complication of standard-of-care chemotherapy regimens used in the treatment of extensive stage small cell lung cancer (ES-SCLC) and other cancers[1]
- CIM can manifest as neutropenia, anemia, and/or thrombocytopenia and can lead to serious complications, which frequently require dose modification, hospitalization, growth factor support (granulocyte colony-stimulating factor [G-CSF] and erythropoiesis-stimulating agents [ESAs]), and red blood cell (RBC) transfusions[1,2]
  - Current supportive care interventions are specific to individual hematopoietic cell lineages, reactively administered, and impart their own set of risks for adverse reactions[1]
- Trilaciclib is a transient CDK4/6 inhibitor that is administered intravenously prior to chemotherapy to reduce the occurrence of CIM[3–7]
  - Trilaciclib transiently arrests hematopoietic stem and progenitor cells in the G1 phase of the cell cycle during chemotherapy exposure to preserve bone marrow and immune system function from chemotherapy-induced damage (myelopreservation)[3–7]
- The effects of administering trilaciclib prior to chemotherapy have been investigated in three randomized, placebo-controlled, double-blind, phase 2 clinical studies in patients with ES-SCLC[4–7]
- Across all studies, myelopreservation of blood cell lineages resulted in less hematologic toxicity, reduced the use of supportive care interventions, and improved quality of life[7,8]
- The aim of this analysis was to use pooled data from these studies to assess the totality of benefit with trilaciclib across several clinically meaningful components of myelopreservation, using the prospectively defined, exploratory composite endpoint of major adverse hematologic events (MAHE)

METHODS

- The MAHE endpoint comprised five individual components:
  - All-cause hospitalizations
  - All-cause chemotherapy dose reductions
  - Febrile neutropenia (FN)
  - Prolonged severe (grade 4; absolute neutrophil count <0.5 × 10^9 cells/L) neutropenia (SN; duration >5 days)
  - RBC transfusions on/after week 5
    - RBC transfusions before week 5 were excluded to ensure that analyses of potential benefit were not confounded by the residual effect of previous treatment
- The cumulative incidence of MAHE and its individual components was assessed using data pooled from patients enrolled in the studies outlined in **Table 1**
- Primary prophylaxis with G-CSF and use of ESA was prohibited in cycle 1, although therapeutic G-CSF was allowed; after cycle 1, supportive care, including G-CSF and ESAs, was allowed as needed. RBC and platelet transfusions were allowed per investigator discretion throughout the entire treatment period

TABLE 1. OVERVIEW OF TRILACICLIB CLINICAL STUDIES INCLUDED IN POOLED ANALYSIS

Study	Patient Population	Treatment Schedule
G1T28-02 (NCT02499770)	Newly diagnosed (first-line) ES-SCLC	Trilaciclib 240 mg/m^2 IV QD or placebo IV QD prior to chemotherapy on days 1–3 of each 21-day E/P IV cycle[a]
G1T28-05 (NCT03041311)	Newly diagnosed (first-line) ES-SCLC	Trilaciclib 240 mg/m^2 IV QD or placebo IV QD prior to chemotherapy on days 1–3 of each 21-day E/P/A IV cycle[b] for up to four cycles followed by atezolizumab monotherapy (without trilaciclib or placebo) Q21D
G1T28-03 (NCT02514447)	Previously treated (second-/third-line) ES-SCLC	Trilaciclib 240 mg/m^2 IV QD or placebo IV QD prior to topotecan 1.5 mg/m^2 IV QD on days 1–5 of each 21-day cycle

[a] E/P therapy comprised standard-of-care etoposide (100 mg/m^2) IV on days 1, 2, and 3 and carboplatin AUC 5 on day 1 of each 21-day cycle.
[b] E/P/A therapy comprised standard-of-care etoposide (100 mg/m^2) IV on days 1, 2, and 3, carboplatin AUC 5 on day 1, with the addition of atezolizumab (1200 mg) IV on day 1 of each 21-day chemotherapy cycle. Maintenance treatment comprised atezolizumab (1200 mg) IV on day 1 of each 21-day cycle; trilaciclib and placebo were not administered during maintenance.
AUC, area under the plasma concentration-time curve; E/P, etoposide/carboplatin; E/P/A, etoposide/carboplatin/atezolizumab; ES-SCLC, extensive-stage small cell lung cancer; IV, intravenous(ly); QD, once daily; Q21D, every 21 days.

- For each component of MAHE, the number of events was counted as the number of events (all-cause hospitalizations; FN; RBC transfusions on/after week 5) or cycles (all-cause chemotherapy dose reductions; prolonged SN) with a unique start date during the treatment period
- The cumulative incidence of MAHE was obtained by summing the total number of events across the prespecified components

RESULTS

Patient disposition and baseline characteristics

- The pooled efficacy analysis set comprised 123 and 119 patients who received trilaciclib or placebo prior to chemotherapy, respectively
- As previously reported, patient demographics and baseline disease characteristics were generally comparable between treatment groups[7]

Impact of trilaciclib on the cumulative incidence of major adverse hematologic events

- Compared with placebo, administration of trilaciclib prior to chemotherapy resulted in a statistically significant reduction in the cumulative incidence of MAHE (**Table 2**)
  - Cumulative incidence of MAHE was statistically significantly lower in the trilaciclib group than in the placebo group by week 3 and remained significantly lower throughout the treatment period (up to week 36; **Figure 1A**)
- Statistically significant reductions in the cumulative incidence of all-cause chemotherapy dose reductions, FN, prolonged severe (grade 4) neutropenia and RBC transfusions on/after week 5 were also observed with trilaciclib versus placebo (**Table 2**; **Figure 1C–1F**)
- While all-cause hospitalizations were not significantly different for trilaciclib versus placebo in the pooled analysis (**Table 2**; **Figure 1B**), a separate ad hoc analysis of hospitalization due to CIM or sepsis showed that significantly fewer patients receiving trilaciclib (4.1%) were hospitalized compared with placebo (13.6%, P = 0.0088; **Table 3**)

TABLE 2. CUMULATIVE INCIDENCE OF MAJOR ADVERSE HEMATOLOGIC EVENTS AND ITS INDIVIDUAL COMPONENTS

Event Rate[a]	Trilaciclib Prior to Chemotherapy (n = 123)	Placebo Prior to Chemotherapy (n = 119)	Adjusted Rate Ratio (95% CI)[b]	P Value
MAHE composite endpoint (per week)	0.054	0.139	0.355 (0.245, 0.513)	<0.0001
All-cause hospitalizations (per week)	0.024	0.028	0.786 (0.427, 1.448)	0.4403
All-cause chemotherapy dose reductions (per cycle)	0.028	0.093	0.263 (0.136, 0.507)	<0.0001
FN (per week)	0.002	0.008	0.278 (0.078, 0.991)	0.0485
Prolonged SN (per cycle)	0.020	0.171	0.097 (0.047, 0.202)	<0.0001
RBC transfusions on/after week 5 (per week)	0.015	0.031	0.411 (0.230, 0.734)	0.0027

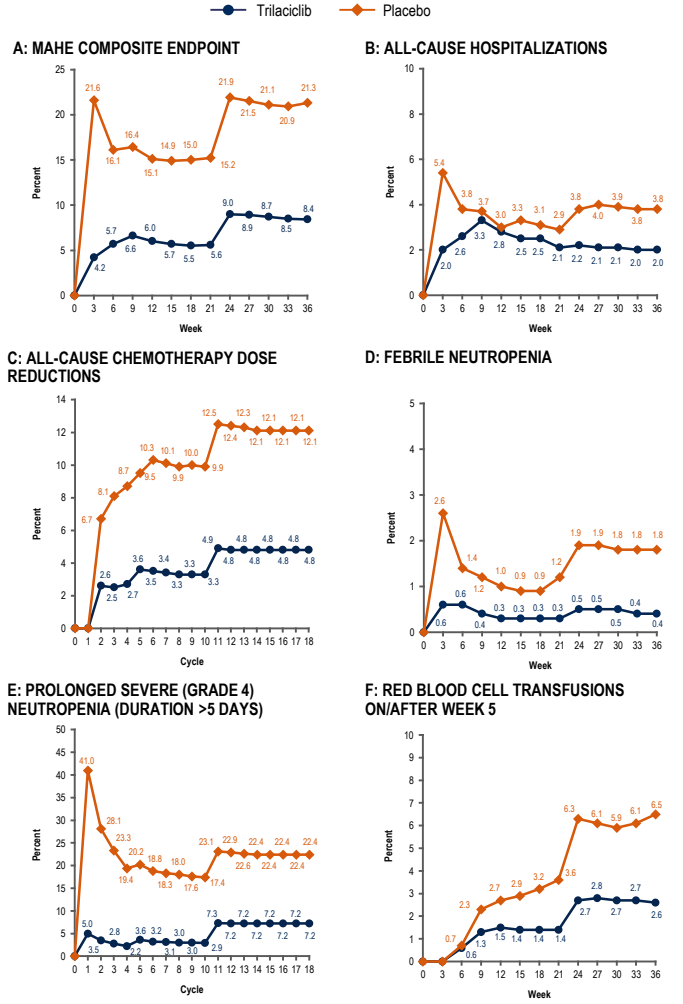
[a] Calculated as the total number of events divided by the total weeks of duration, or total number of cycles with an event divided by the total number of cycles.
[b] Calculated using the negative binomial method, adjusting for duration of treatment in weeks or number of cycles.
Three stratification factors: Eastern Cooperative Oncology Group performance status (0/1 vs 2), presence of brain metastases (yes/no), and study were included as fixed effects.
CI, confidence interval; FN, febrile neutropenia; MAHE, major adverse hematologic events; RBC, red blood cell; SN, severe (grade 4) neutropenia.

TABLE 3. POOLED ANALYSIS OF HOSPITALIZATION DUE TO CIM OR SEPSIS

	n (%)			Total Number of Events (Incidence Rate per 100 Cycles)		
Preferred Term	Trilaciclib (n = 122)	Placebo (n = 118)	P Value[a]	Trilaciclib (n = 122)	Placebo (n = 118)	P Value[b]
Any hospitalization due to CIM or sepsis	5 (4.1)	16 (13.6)	0.0088	5 (0.94)	29 (5.70)	0.0055
CIM	5 (4.1)	15 (12.7)	0.0145	5 (0.94)	25 (4.91)	0.0085
Neutropenia[c]	3 (2.5)	11 (9.3)	-	3 (0.56)	14 (2.75)	-
Anemia[d]	1 (0.8)	6 (5.1)	-	1 (0.19)	7 (1.38)	-
Thrombocytopenia[e]	1 (0.8)	4 (3.4)	-	1 (0.19)	4 (0.79)	-
Sepsis	0	4 (3.4)	-	0	4 (0.79)	-

Data were pooled from patients who were randomized and received at least one dose of study drug.
[a] Calculated using stratified exact Cochran-Mantel-Haenszel method to account for stratification factors of ECOG performance status (0 to 1 versus 2), presence of brain metastases (yes versus no), and study (G1T28-02, G1T28-03 and G1T28-05).
[b] Calculated using negative binomial method adjusting for number of cycles, stratification factors of ECOG performance status (0 to 1 versus 2), presence of brain metastases (yes versus no), and study (G1T28-02, G1T28-03 and G1T28-05) as fixed effects.
[c] Includes AEs coded with PT as neutropenia and febrile neutropenia.
[d] Includes AEs coded with PT as anemia, anemia macrocytic, and pancytopenia (based on ICD10 coding).
[e] Included AEs coded with PT as thrombocytopenia and platelet count decreased.
AE, adverse event; CIM, chemotherapy-induced myelosuppression; ECOG, Eastern Cooperative Oncology Group; ICD, International Classification of Diseases; PT, preferred term.

FIGURE 1. CUMULATIVE INCIDENCE OF MAJOR ADVERSE HEMATOLOGIC EVENTS AND ITS INDIVIDUAL COMPONENTS



CONCLUSIONS

- Improvements in the exploratory MAHE composite endpoint further support the myelopreservation benefits of trilaciclib, its ability to reduce health care utilization through the reduced need for RBC transfusions and hospitalizations due to CIM or sepsis, and its ability to improve the overall safety profile of chemotherapy regimens used to treat patients with ES-SCLC

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