TRILACICLIB HAS MYELOPRESERVATION BENEFITS IN PATIENTS WITH SMALL CELL LUNG CANCER TREATED WITH CHEMOTHERAPY, IRRESPECTIVE OF AGE

J. THADDEUS BECK[1]; DONALD A. RICHARDS[2]; RICHY AGAJANIAN[3]; DAVID BERZ[4]; HONGBIN CHEN[5]; CHUKWUEMEKA IKPEAZU[6]; MARGARITA MAJEM TARRUELLA[7]; DIDIER VERHOEVEN[8]; YILI PRITCHETT[9]; RAJESH K. MALIK[9]; JOYCE M. ANTAL[9]; MAEN HUSSEIN[10]

[1]Highlands Oncology Group, Fayetteville, AR; [2]Texas Oncology-Tyler, US Oncology Research, Tyler, TX; [3]Innovative Clinical Research Institute (ICRI), Whittier, CA; [4]Beverly Hills Cancer Center, Beverly Hills, CA; [5]Roswell Park Comprehensive Cancer Center, Buffalo, NY; [6]Sylvester Comprehensive Cancer Center, Miami, FL; [7]Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; [8]AZ KLINA, University of Antwerp, Belgium; [9]G1 Therapeutics, Inc., Research Triangle Park, NC; [10]Florida Cancer Specialists, Leesburg, FL

INTRODUCTION

- More than half of patients diagnosed with small cell lung cancer (SCLC) are aged ≥65 years[1]
- Older patients are more vulnerable to chemotherapy-induced myelosuppression (CIM) and its complications, including an increased risk of life-threatening infections, fatigue, and bleeding disorders[2,3]
- CIM is typically managed with chemotherapy dose reductions and/or delays that may limit therapeutic efficacy and negatively impact a cancer patient's prognosis and quality of life (QoL)[2]
  - Current supportive care interventions are specific to individual hematopoietic cell lineages, reactively administered, and impart their own set of risks for adverse reactions[2]
- Trilaciclib is a transient CDK4/6 inhibitor that is administered intravenously prior to chemotherapy to reduce the occurrence of CIM[4–8]
  - Trilaciclib transiently arrests hematopoietic stem and progenitor cells and immune 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)[4–8]
- Consistent findings from 3 randomized, double-blind, placebo-controlled, phase 2 studies of extensive stage SCLC supported pooling of data, which showed that trilaciclib administered prior to chemotherapy resulted in less hematologic toxicity, reduced the use of supportive care interventions, and improved QoL[8,9]
- Here, a subgroup analysis of the pooled data was performed to understand the myelopreservation benefits of trilaciclib among patients aged <65 and ≥65 years

METHODS

- Data were pooled from patients randomized in the studies outlined in **Table 1** (denoted as the intention-to-treat [ITT] population)
- Primary prophylaxis with granulocyte colony-stimulating factor (G-CSF) and use of erythropoiesis-stimulating agents (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. Red blood cell (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 4 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.

- Subgroup analyses of patients aged <65 and ≥65 years were performed to assess the myelopreservation benefits of trilaciclib on:
  - Duration of severe neutropenia (DSN; grade 4; absolute neutrophil count <0.5 × 10^9 cells/L) in cycle 1
  - Percentage of patients with severe neutropenia (SN) during the treatment period
  - Percentage of patients with grade 3/4 decreased hemoglobin levels (anemia)
  - Percentage of patients and number of RBC transfusions on/after week 5
- The treatment-by-age group interaction for these endpoints was also tested
- To understand the impact of the myelopreservation benefits of trilaciclib on patient QoL, subgroup analysis by age group was performed on patient-reported outcome (PRO) measures derived from the Functional Assessment of Cancer Therapy-Anemia (FACT-An) questionnaire: change from study baseline and time to confirmed deterioration (TTCD) were analyzed for physical wellbeing (PWB), functional wellbeing (FWB), fatigue subscale (fatigue), anemia trial outcome index (anemia-TOI), and FACT-An total scores

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
  - 57 (46.3%) and 58 (48.7%) patients who received trilaciclib or placebo prior to chemotherapy, respectively, were aged ≥65 years
    - Compared with the studies in newly diagnosed patients (G1T28-02/05), fewer patients aged ≥65 years were enrolled in the study of trilaciclib/placebo prior to second-/third-line topotecan, possibly due to concern regarding higher susceptibility to treatment toxicity

Myelopreservation efficacy of trilaciclib administered prior to chemotherapy by age

- Administering trilaciclib prior to chemotherapy significantly reduced most measures of CIM in the ITT population (**Table 2**)
- These findings were consistently observed across both age groups (as shown by non-significant treatment-by-age interactions); however, there was a greater magnitude of effect among patients aged ≥65 years who are more susceptible to CIM (**Table 2**)

TABLE 2. MYELOPRESERVATION ENDPOINTS IN THE POOLED EFFICACY ANALYSIS

	Age <65 years		Age ≥65 years		ITT Population	
	Trilaciclib (n = 66)	Placebo (n = 61)	Trilaciclib (n = 57)	Placebo (n = 58)	Trilaciclib (n = 123)	Placebo (n = 119)
Mean DSN in cycle 1, days (SD)[a]	0 (1.7)	3 (4.5)	0 (2.1)	5 (5.6)	0 (1.8)	4 (5.1)
					P < 0.0001	
Patients with SN, n (%)[a]	7 (10.6)	26 (42.6)	7 (12.3)	37 (63.8)	14 (11.4)	63 (52.9)
	Treatment-by-age interaction *P* = 0.3765				*P* < 0.0001	
Patients with grade 3/4 decreased hemoglobin, n (%)	12 (18.2)	16 (26.2)	13 (22.8)	22 (37.9)	25 (20.3)	38 (31.9)
	Treatment-by-age interaction *P* = 0.6957				*P* = 0.0279	
Patients with RBC transfusions on/after week 5, n (%)	8 (12.1)	11 (18.0)	10 (17.5)	20 (34.5)	18 (14.6)	31 (26.1)
	Treatment-by-age interaction *P* = 0.6791				*P* = 0.0252	
Number of RBC transfusions, event rate (per week)	0.011	0.018	0.019	0.045	0.015	0.031
					P = 0.0027	

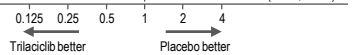
A non significant treatment-by-age interaction indicates that trilaciclib benefits were comparable in both age groups.
[a]Primary endpoints; two-sided *P*-value for treatment effect.
DSN, duration of severe (grade 4) neutropenia; RBC, red blood cell; SD, standard deviation; SN, severe neutropenia.

Impact of myelopreservation benefits of trilaciclib on TTCD in PROs by age

- Myelopreservation benefits extended to improvements in PROs in younger (<65 years) and older (≥65 years) patients receiving trilaciclib
- While the treatment effect was in favor of trilaciclib in both age groups, in the analysis of categorical change from study baseline, significant treatment-by-age group interactions were observed for PWB, fatigue, anemia-TOI and FACT-An total scores, with greater improvements and less deterioration seen for patients aged ≥65 years
- For each of the PRO endpoints, median TTCD for patients receiving trilaciclib was longer than that for patients receiving placebo, with greater improvements (ie, smaller hazard ratios) among older patients who are more susceptible to CIM (**Figure 1**)

FIGURE 1. SUBGROUP ANALYSIS OF TTCD

Subgroup	Events, n / Patients, n: Trilaciclib	Events, n / Patients, n: Placebo	Median TTCD, months: Trilaciclib / Placebo	HR	(95% CI)
Physical wellbeing	32 / 123	51 / 119	NE / 5.16	0.62	(0.396, 0.969)
<65 years	13 / 66	20 / 61	NE / NE	0.66	(0.322, 1.341)
≥65 years	19 / 57	31 / 58	7.20 / 3.38	0.62	(0.344, 1.130)
Functional wellbeing	31 / 123	55 / 119	7.62 / 3.78	0.45	(0.289, 0.709)
<65 years	15 / 66	22 / 61	8.57 / NE	0.57	(0.286, 1.117)
≥65 years	16 / 57	33 / 58	7.20 / 2.79	0.37	(0.196, 0.687)
Fatigue subscale	39 / 123	61 / 119	7.03 / 2.33	0.56	(0.372, 0.850)
<65 years	18 / 66	25 / 61	NE / 6.51	0.63	(0.335, 1.189)
≥65 years	21 / 57	36 / 58	6.21 / 1.48	0.49	(0.269, 0.882)
Anemia TOI	33 / 123	55 / 119	7.20 / 3.78	0.54	(0.349, 0.841)
<65 years	13 / 66	21 / 61	NE / 8.08	0.59	(0.286, 1.208)
≥65 years	20 / 57	34 / 58	6.93 / 1.64	0.52	(0.289, 0.933)
Fact-An total	31 / 123	58 / 119	NE / 3.48	0.47	(0.299, 0.727)
<65 years	12 / 66	22 / 61	NE / 6.90	0.54	(0.257, 1.115)
≥65 years	19 / 57	36 / 58	6.51 / 1.71	0.47	(0.260, 0.840)



Confirmed deterioration was defined as a change from baseline by a clinically meaningful threshold for 2 consecutive visits: ≤–3 points for PWB, FWB, and fatigue; ≤–6 points for anemia TOI points; ≤–7 points for FACT-An total scores.
CI, confidence interval; FACT-An, Functional Assessment of Cancer Therapy-Anemia; FWB, functional wellbeing; HR, hazard ratio; NE, not evaluable; PWB, physical wellbeing; TOI, trial outcome index; TTCD, time to confirmed deterioration.

Safety of trilaciclib by age group

- The percentage of patients with any grade 3 or 4 adverse events (AEs) was consistently lower in the trilaciclib group than in the placebo group across all subgroups, including patients aged ≥65 years (**Table 3**)
- The addition of trilaciclib prior to chemotherapy consistently decreased the percentage of patients with high-grade hematologic AEs compared with the placebo group across all subgroups, including patients aged ≥65 years, consistent with the effects of trilaciclib in reducing the occurrence of CIM

TABLE 3. GRADE 3 OR 4 ADVERSE EVENTS OCCURING IN ≥5 PATIENTS

	Age <65 years		Age ≥65 years	
Patients, n (%)	Trilaciclib (n = 66)	Placebo (n = 61)	Trilaciclib (n = 56)	Placebo (n = 57)
Any grade 3/4 AE	40 (60.6)	48 (78.7)	33 (58.9)	50 (87.7)
Neutropenia	20 (30.3)	33 (54.1)	15 (26.8)	37 (64.9)
Thrombocytopenia	13 (19.7)	11 (18.0)	7 (12.5)	22 (38.6)
Anemia	10 (15.2)	18 (29.5)	10 (17.9)	21 (36.8)
Pneumonia	5 (7.6)	5 (8.2)	3 (5.4)	3 (5.3)
Leukopenia	2 (3.0)	4 (6.6)	1 (1.8)	10 (17.5)
Neutrophil count decreased	2 (3.0)	10 (16.4)	2 (3.6)	6 (10.5)
Febrile neutropenia	2 (3.0)	4 (6.6)	2 (3.6)	7 (12.3)
Platelet count decreased	2 (3.0)	3 (4.9)	1 (1.8)	5 (8.8)

Occurring in ≥5 patients in any subgroup. AE, adverse event.

CONCLUSIONS

- Data from this analysis indicate that the myelopreservation benefits of trilaciclib are observed regardless of a patient's age, with greater effects among older patients who are more susceptible to CIM
- Administering trilaciclib prior to chemotherapy in patients aged ≥65 years reduces CIM to levels equivalent to those seen in younger patients receiving trilaciclib, suggesting that trilaciclib negates the negative impact of aging on susceptibility to CIM
- By both reducing CIM and improving symptoms and functional limitations associated with cancer and CIM, trilaciclib has the potential to allow older patients to receive chemotherapy on schedule and at standard-of-care doses, as well as improve the experience for older patients receiving chemotherapy to treat SCLC

IASLC North America Conference on Lung Cancer | October 16–17, 2020 | Virtual Meeting

ACKNOWLEDGMENTS:
- We thank all of the investigators and site staff, with special thanks to the patients and their families, for their participation in the studies
- Medical writing assistance was provided by Alligent Europe (Envision Pharma Group), funded by G1 Therapeutics, Inc.

REFERENCES:
1. Ries LAG, et al. SEER Cancer Statistics Review 1975–2000. Bethesda, MD: National Cancer Institute. http://seer.cancer.gov/csr/1975_2000. Accessed 10 August 2020.
2. Epstein RS, et al. *Adv Ther*. 2020;37:3606–18.
3. Roe H, Lennan E. *Nurs Res Rev*. 2014;4:103–15.
4. Lai AY, et al. *J Immunother Cancer*. 2020:In press (doi:10.1136/jitc-2020-000847).
5. Daniel D, et al. *Ann Oncol*. 2019;30:v713.
6. Hart LL, et al. *J Clin Oncol*. 2019;37:8505.
7. Weiss JM, et al. *Ann Oncol*. 2019;30:1613–21.
8. Weiss J, et al. *J Clin Oncol*. 2020;38:12096.
9. Weiss J, et al. *Support Care Cancer*. 2019;27:S274.