MYELOPRESERVATION WITH TRILACICLIB REGARDLESS OF RISK OF CHEMOTHERAPY-INDUCED FEBRILE NEUTROPENIA AND/OR ANEMIA/RED BLOOD CELL TRANSFUSIONS

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INTRODUCTION

- Chemotherapy-induced myelosuppression (CIM) is one of the most common dose-limiting complications of chemotherapy, and is associated with a range of debilitating complications, which can have a significant impact on patient care[1]
  - Febrile neutropenia (FN) and anemia are two clinically important manifestations of CIM that can negatively impact patient outcomes, and often incur significant costs[1–3]
- Trilaciclib is a transient intravenous CDK4/6 inhibitor administered prior to chemotherapy to reduce the occurrence of CIM[4–8]
  - 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)[4–8]
- The myelopreservation benefits of trilaciclib have been shown in three randomized, double-blind, placebo-controlled, phase 2 studies in adult patients with extensive stage small cell lung cancer[5–7]
- Consistent with findings from the individual studies, a pooled analysis of these data showed that administering trilaciclib prior to chemotherapy resulted in less hematologic toxicity, reduced the use of supportive care interventions, and improved quality of life[8,9]
- Using the pooled dataset, the aim of this analysis was to examine if patients at varying risk for FN or anemia/red blood cell (RBC) transfusions derived the same benefits from trilaciclib

METHODS

- Data were pooled from patients enrolled in the studies outlined in **Table 1** (intention-to-treat population)
- Primary prophylaxis with granulocyte colony-stimulating factor (G-CSF) and use of erythropoiesis-stimulating agents (ESAs) 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/m² 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/m² 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/m² IV QD or placebo IV QD prior to topotecan 1.5 mg/m² IV QD on days 1–5 of each 21-day cycle

[a] E/P therapy comprised standard-of-care etoposide (100 mg/m²) 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/m²) 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.

- Six baseline factors associated with an increased risk of FN and four baseline factors associated with an increased risk of anemia/RBC transfusions (**Table 2**) were identified based on published literature, and used to classify patients into four FN risk categories (0, 1–2, 3–4, and 5–6 risk factors) and three anemia risk categories (0, 1–2, and 3–4 risk factors)

TABLE 2. BASELINE FACTORS ASSOCIATED WITH AN INCREASED RISK OF FEBRILE NEUTROPENIA AND/OR ANEMIA/RED BLOOD CELL TRANSFUSIONS

CIM Manifestation	Baseline Risk Factors	
Febrile neutropenia[10–14]	• Age • Poor nutritional status • Renal dysfunction	• Cardiovascular disease • Multiple comorbid conditions • Prior cytotoxic chemotherapy
Anemia/RBC transfusions[15–19]	• Gender • ECOG PS	• Baseline hemoglobin • Prior cytotoxic chemotherapy

CIM, chemotherapy-induced myelosuppression; ECOG PS, Eastern Cooperative Oncology Group performance status; RBC, red blood cell.

- Subgroup analyses were conducted to evaluate the impact on:
  - Neutrophil-related endpoints: mean duration of severe (grade 4; absolute neutrophil count <0.5 × 10⁹ cells/L) neutropenia (DSN) in cycle 1 and the percentage of patients with severe neutropenia (SN)
  - RBC-related endpoints: percentage of patients with grade 3 or 4 decreased hemoglobin levels (anemia) and RBC transfusions on/after week 5

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 described previously, patient demographics and baseline disease characteristics were generally comparable between treatment groups[8]
- Patient distribution across the FN and anemia risk categories (**Table 3**) was comparable between the treatment groups

TABLE 3. DISTRIBUTION OF FEBRILE NEUTROPENIA RISK AND ANEMIA RISK BY TREATMENT GROUP

	Trilaciclib Prior to Chemotherapy (n = 123)	Placebo Prior to Chemotherapy (n = 119)
Febrile neutropenia risk category, n (%)		
No risk factors	32 (26.0)	35 (29.4)
1 to 2 risk factors	85 (69.1)	77 (64.7)
3 to 4 risk factors	6 (4.9)	7 (5.9)
5 to 6 risk factors	0	0
Chi-square p-value[a]	0.7632	
Anemia risk category, n (%)		
No risk factors	48 (39.0)	47 (39.5)
1 to 2 risk factors	68 (55.3)	62 (52.1)
3 to 4 risk factors	7 (5.7)	10 (8.4)
Chi-square p-value[a]	0.6870	

[a] Calculated to test the treatment-by-risk category association. A non significant p-value indicates that patient distribution across risk categories was comparable between treatment groups.

Subgroup analysis for neutrophil-related endpoints by febrile neutropenia risk factors

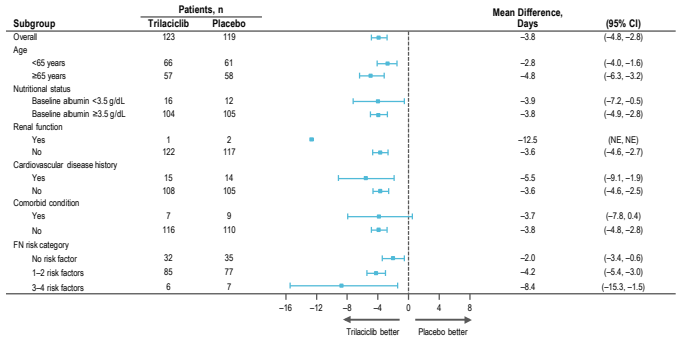
- Across the FN risk factors and categories, effects on neutrophil-related endpoints (mean DSN in cycle 1 and occurrence of SN) consistently favored trilaciclib versus placebo, including those patients with the highest risk of FN (**Table 4**; **Figures 1** and **2**)
  - This pattern indicates no difference in benefit between patients in different risk categories

TABLE 4. SUBGROUP ANALYSIS FOR NEUTROPHIL-RELATED ENDPOINTS BY FEBRILE NEUTROPENIA RISK FACTORS

		FN Risk Category		
Trilaciclib vs Placebo	**ITT Population**	**0**	**1–2**	**3–4**
Mean DSN in cycle 1, days (SD)	0 (1.8) vs 4 (5.1)	0 (1.2) vs 2 (3.8)	1 (2.1) vs 5 (5.1)	0 (0.8) vs 9 (7.5)
Patients with SN, n (%)	14 (11.4) vs 63 (52.9)	2 (6.3) vs 11 (31.4)	11 (12.9) vs 46 (59.7)	1 (16.7) vs 6 (85.7)

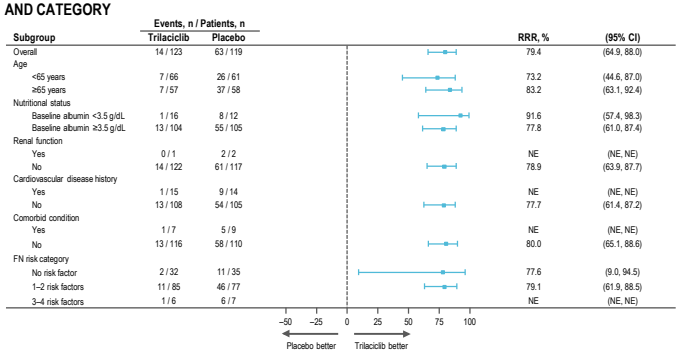
DSN, duration of severe neutropenia; ITT, intention-to-treat; SD, standard deviation; SN, severe neutropenia.

FIGURE 1. SUBGROUP ANALYSIS OF DSN IN CYCLE 1 BY RISK FACTOR AND CATEGORY



CI, confidence interval; FN, febrile neutropenia; NE, not estimable (statistical model did not converge).

FIGURE 2. SUBGROUP ANALYSIS OF PERCENTAGE OF PATIENTS WITH SN BY RISK FACTOR AND CATEGORY



CI, confidence interval; FN, febrile neutropenia; NE, not estimable (statistical model did not converge); RRR, relative risk reduction.

Subgroup analysis for red blood cell-related endpoints by anemia risk factors

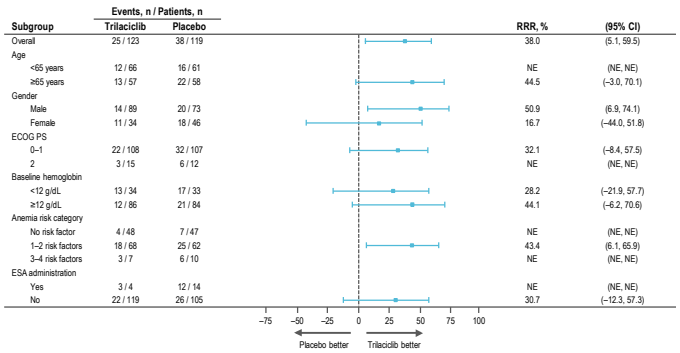
- Effects on RBC-related endpoints (occurrence of grade 3/4 decreased hemoglobin levels and RBC transfusions on/after week 5) consistently favored trilaciclib versus placebo across the anemia risk factors and categories, including those at the highest risk of anemia/RBC transfusions (**Table 5**; **Figures 3** and **4**)

TABLE 5. SUBGROUP ANALYSIS FOR RED BLOOD CELL-RELATED ENDPOINTS BY ANEMIA RISK FACTORS

		Anemia Risk Category		
Trilaciclib vs Placebo	**ITT Population**	**0**	**1–2**	**3–4**
Patients with grade 3/4 decreased hemoglobin levels, n (%)	25 (20.3) vs 38 (31.9)	4 (8.3) vs 7 (14.9)	18 (26.5) vs 25 (40.3)	3 (42.9) vs 6 (60.0)
Patients with RBC transfusion on/after week 5, n (%)	18 (14.6) vs 31 (26.1)	1 (2.1) vs 6 (12.8)	14 (20.6) vs 19 (30.6)	3 (42.9) vs 6 (60.0)

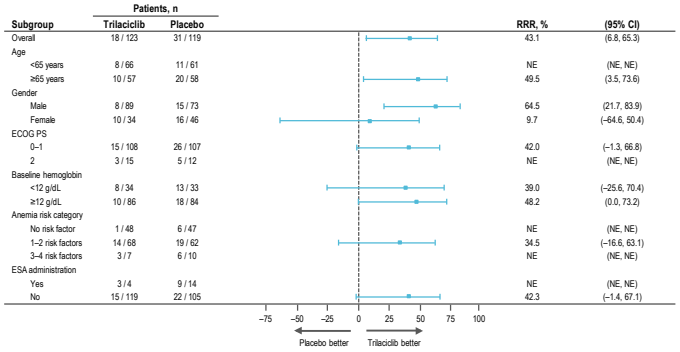
ITT, intention-to-treat; RBC, red blood cell.

FIGURE 3. SUBGROUP ANALYSIS OF PERCENTAGE OF PATIENTS WITH GRADE 3 OR 4 ANEMIA BY RISK FACTOR AND CATEGORY



CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; ESA, erythropoiesis-stimulating agent; NE, not estimable (statistical model did not converge); RRR, relative risk reduction.

FIGURE 4. SUBGROUP ANALYSIS OF PERCENTAGE OF PATIENTS WITH RBC TRANSFUSIONS ON/AFTER WEEK 5 BY RISK FACTOR AND CATEGORY



CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; ESA, erythropoiesis-stimulating agent; NE, not estimable (statistical model did not converge); RRR, relative risk reduction.

CONCLUSIONS

- Compared with placebo, the myelopreservation benefits of trilaciclib were observed regardless of the underlying risk for FN or anemia/RBC transfusions, indicating that trilaciclib is effective at reducing CIM regardless of risk category, including in patients with the highest risk

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