MYELOPROTECTION WITH TRILACICLIB PRIOR TO FIRST-LINE CHEMOTHERAPY IN EXTENSIVE-STAGE SMALL CELL LUNG CANCER: AN INTEGRATED ANALYSIS OF CLINICAL TRIALS

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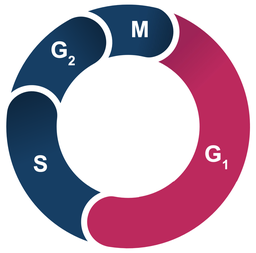
BACKGROUND

- The standard first-line treatment of extensive-stage small cell lung cancer (ES-SCLC) is chemotherapy with etoposide and carboplatin plus a programmed death-ligand 1 inhibitor (eg, atezolizumab)[1]
- Toxicity is dominated by chemotherapy-induced myelosuppression (CIM) and its downstream sequelae (such as fatigue)[2]
- Additional consequences of CIM include deviations from the chemotherapy plan, need for supportive care interventions and hospitalisation[3]
- Trilaciclib is an intravenous (IV) multilineage myeloprotection therapy approved for use in adults with ES-SCLC prior to a platinum/etoposide- or topotecan-containing regimen[4,5]
- Trilaciclib works by transiently inhibiting cyclin-dependent kinase (CDK) 4/6 in a highly potent, selective and reversible manner to induce transient G1 cell cycle arrest of haematopoietic stem and progenitor cells, thus protecting all lineages from CIM[5,6]

METHODS

- Post hoc pooled analysis of data from the randomised, double-blind, placebo-controlled, phase 2 and 3 portions of 3 multicentre studies: G1T28-02 (NCT02499770),[7] G1T28-05 (NCT03041311)[8] and TRACES (NCT04902885).[9] Trilaciclib was administered prior to standard first-line therapy[7-9]
- Administration of erythropoiesis-stimulating agents and primary prophylaxis with granulocyte colony-stimulating factors (G-CSFs) was prohibited in cycle 1
- Co-primary endpoints were duration of severe neutropenia in cycle 1 and percentage of patients with severe neutropenia during the treatment period
- The intent-to-treat population for the integrated myeloprotection analysis comprised all patients randomised to receive treatment, whereas the integrated safety cohort was the subset who also received ≥ 1 dose of study drug



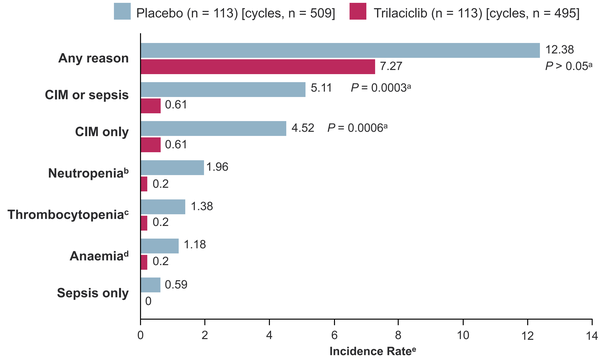
Trilaciclib (IV CDK 4/6 inhibitor)[10]
Transiently arrests normal cells in the G1 phase of the cell cycle during chemotherapy exposure to preserve bone marrow and immune system function from chemotherapy-induced damage

Baseline Demographics and Disease Characteristics

Parameter	Placebo (n = 114)	Trilaciclib (n = 116)
Age, years, median (min, max)	64 (39, 86)	64 (45, 82)
≥ 65 years, n (%)	55 (48.2)	57 (49.1)
Male, n (%)	82 (71.9)	87 (75.0)
White, n (%)	85 (74.6)	92 (79.3)
Country/region, n (%)		
United States	40 (35.1)	41 (35.3)
Europe	51 (44.7)	52 (44.8)
China	23 (20.2)	23 (19.8)
ECOG PS, n (%)		
0/1	103 (90.4)	103 (88.8)
2	11 (9.6)	13 (11.2)
Presence of brain metastases, n (%)	30 (26.3)	26 (22.4)
Missing	1 (0.9)	0
Smoking history, n (%)		
Never smoked	10 (8.8)	11 (9.5)
Former smoker	69 (60.5)	65 (56.0)
Current smoker	34 (29.8)	39 (33.6)
Missing	1 (0.9)	1 (0.9)
Baseline LDH > ULN, n (%)	54 (47.4)	58 (50.0)
Missing	3 (2.6)	5 (4.3)

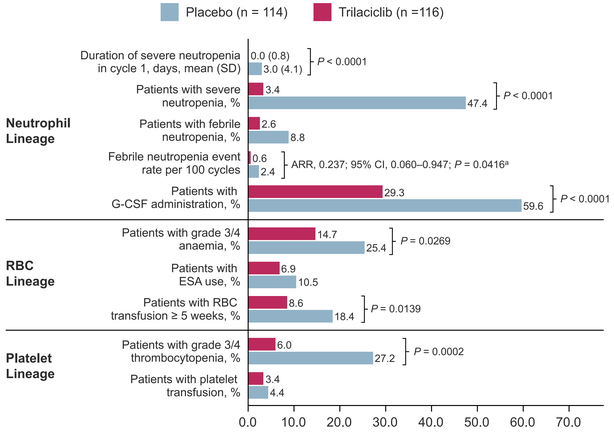
ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; max, maximum; min, minimum; ULN, upper limit of the normal range.

Hospitalisation Incidence Rate



[a] Calculated using stratified exact Cochran-Mantel-Haenszel method to account for stratification factors of ECOG PS (0–1 vs 2), presence of brain metastases (yes vs no) and study (G1T28-02, G1T28-05, TRACES). Between-arm statistical significance in favour of trilaciclib was also attained using negative binomial method (adjusting for number of cycles and stratification factors as fixed effects). [b] AEs coded with the PTs neutropenia and febrile neutropenia were consolidated. [c] AEs coded with the PTs thrombocytopenia and platelet count decreased were consolidated. [d] AEs coded with PTs anaemia, anaemia macrocytic and pancytopenia were consolidated. [e] Incidence rate per 100 cycles equals number of events divided by total number of cycles × 100. AE, adverse event; PT, Preferred Term.

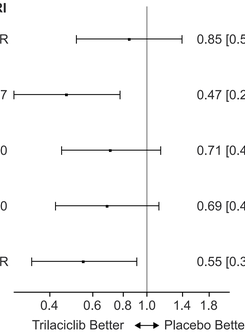
Summary of Myelosuppression Endpoints



[a] Event rate was calculated as total number of cycles with an event divided by total number of cycles × 100. ARR (trilaciclib vs placebo), 95% CI and *P*-value were calculated using negative binomial method adjusting for number of cycles, with study baseline absolute neutrophil count value as covariate, stratification factors of ECOG PS (0–1 vs 2), presence of brain metastases (yes vs no) and study (G1T28-02, G1T28-05, TRACES) as fixed effects. ARR, adjusted rate ratio; ESA, erythropoiesis-stimulating agent; RBC, red blood cell; SD, standard deviation.

Patient-Reported Outcomes: Risk for a Clinically Meaningful Deterioration of Patient Well-Being

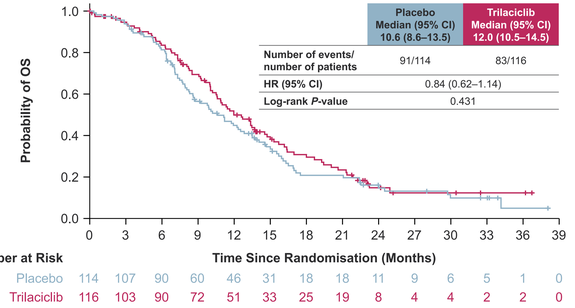
Domain	Treatment	No. of Events	TTD (Months)	HR [95% CI]
	PLA/TRI	PLA/TRI	PLA/TRI	
PWB	91/93	36/28	6.90/NYR	0.85 [0.51–1.39]
FWB	91/93	44/24	3.91/8.57	0.47 [0.29–0.78]
Fatigue	91/93	44/31	3.48/7.20	0.71 [0.45–1.14]
Anemia TOI	91/93	41/28	6.51/7.20	0.69 [0.42–1.12]
FACT-An Total	91/93	44/25	3.84/NYR	0.55 [0.34–0.91]



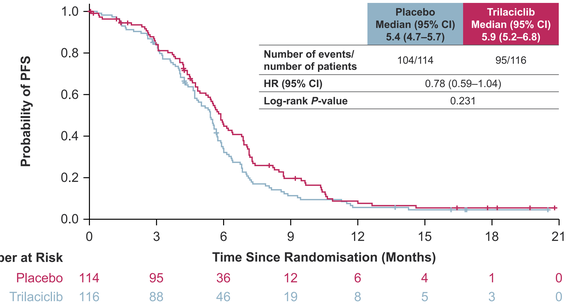
Deterioration was defined based on the established clinically meaningful thresholds: 3 for PWB, FWB and Fatigue; 7 for FACT-An Total; 6 for FACT-An TOI. HR (trilaciclib/placebo) and 95% CI were calculated using Cox proportional hazard regression model with treatment and stratification factors of ECOG PS (0–1 vs 2), presence of brain metastases (yes vs no) and study (G1T28-02, G1T28-05). Treatment-by-study interaction was tested in a separated model by adding a treatment-by-study interaction to the Cox model as described above. FACT-An Total, Functional Assessment of Cancer Therapy-Anaemia total score; Fatigue, fatigue subscale score; FWB, functional well-being; HR, hazard ratio; NYR, not yet reached; PLA, placebo; PWB, physical well-being; TOI, Trial Outcome Index; TRI, trilaciclib; TTD, time to deterioration.

Efficacy Endpoints: (A) OS and (B) PFS

(A) OS



(B) Radiographic PFS



HR and 95% CI were calculated using the Cox regression model with treatment and stratification factors of ECOG PS (0–1 vs 2) and presence of brain metastases (yes vs no) and study (G1T28-02, G1T28-05, TRACES). *P*-value was calculated using the stratified log-rank test to account for stratification factors of ECOG PS (0–1 vs 2), presence of brain metastases (yes vs no) and study (G1T28-02, G1T28-05, TRACES). OS, overall survival; PFS, progression-free survival.

CONCLUSIONS

- Trilaciclib significantly reduced the burden of CIM in patients receiving first-line treatment for ES-SCLC
- This reduction coincided with fewer clinically meaningful complications, including lower rates of hospitalisation related to CIM and sepsis
- Trilaciclib delayed the time to clinically meaningful deterioration in patient-reported outcomes
- Favourable trends in PFS and OS were observed
- Collectively, these findings highlight the importance of proactive myeloprotection in maintaining treatment continuity while alleviating patient burden and optimising healthcare resource use

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JMW: consultancy/advisory role support for and research funding from Pharmacosmos; **LA:** no conflicts or declarations related to this work; **MD:** honoraria for speaking and advisory roles for G1 Therapeutics and Pharmacosmos; **RVB:** institution funding for trilaciclib trials, consultant, and has moderated advisory boards for Pharmacosmos