TRILACICLIB DECREASES MYELOSUPPRESSION IN EXTENSIVE-STAGE SMALL CELL LUNG CANCER (ES-SCLC) PATIENTS RECEIVING FIRST-LINE CHEMOTHERAPY PLUS ATEZOLIZUMAB

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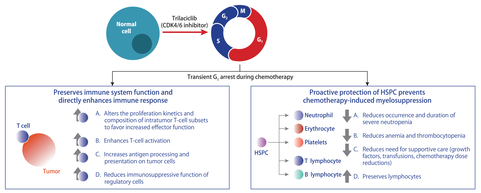
BACKGROUND

- Chemotherapy-induced damage of hematopoietic stem and progenitor cells (HSPCs) causes multilineage myelosuppression, which may antagonize the intended effects of chemotherapy/immune checkpoint inhibitor combinations[1,2]
- Current supportive therapies (eg, growth factors and transfusions) are lineage specific and are administered after chemotherapy damage has occurred[3]
- Trilaciclib is a highly potent, selective, reversible, transient cell cycle inhibitor that preserves HSPCs during chemotherapy (myelopreservation) and enhances antitumor immunity[3,4] **(Figure 1)**
- As previously reported, a randomized, double-blind, phase 1b/2 trial demonstrated the myelopreservation benefits of trilaciclib when combined with standard cytotoxic chemotherapy for patients with newly diagnosed extensive-stage small cell lung cancer (ES-SCLC)[5]
- Preclinical studies have shown that the immune-modulating effects of trilaciclib may enhance the efficacy of chemotherapy/immune checkpoint inhibitor combinations[6]
- This global, randomized, double-blind, placebo-controlled, multicenter, phase 2 study (NCT03041311) assessed the potential of trilaciclib to reduce the incidence and consequences of chemotherapy-induced myelosuppression in patients with newly diagnosed ES-SCLC treated with etoposide, carboplatin, and atezolizumab (a programmed death-ligand 1 inhibitor)

Figure 1 Trilaciclib: A First-in-Class Transient Cell Cycle Inhibitor



CDK, cyclin-dependent kinase; HSPC, hematopoietic stem and progenitor cell.

METHODS

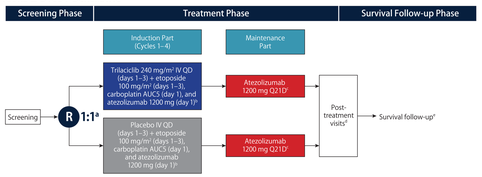
Patients

- Key eligibility criteria:
  - Aged ≥ 18 years
  - Chemotherapy and checkpoint inhibitor naïve
  - Histologically or cytologically confirmed ES-SCLC with measurable disease
  - Eastern Cooperative Oncology Group Performance Status 0 – 2
  - Adequate organ function
    - Hemoglobin ≥ 9.0 g/dL
    - Absolute neutrophil count ≥ 1.5 × 10^9 L
    - Platelet count ≥ 100 × 10^9 L
  - No symptomatic brain metastases
  - No active, known, or suspected autoimmune disease that required systemic treatment in the past 2 years

Study Design

- The study schematic is shown in **Figure 2**. The study objectives and endpoints are shown in **Table 1**
- Primary prophylactic hematopoietic growth factors were prohibited in cycle 1; otherwise, standard supportive care was allowed throughout the study

Figure 2 Study Schematic



[a] Randomization stratified by ECOG PS (0–1 vs 2) and presence of brain metastases (yes vs no).
[b] During the induction phase of the study, trilaciclib or placebo + E/P/A therapy continues for up to four 21-day cycles or until disease progression per RECIST v1.1, unacceptable toxicity, or discontinuation by the patient or investigator.
[c] Following the induction phase, patients proceed to the maintenance phase of the study and receive atezolizumab every 21 days until disease progression per RECIST v1.1, unacceptable toxicity, or discontinuation by the patient or investigator. Following disease progression per RECIST v1.1, if the patient appears to be deriving clinical benefit, if the investigator believes it is in the best interest of the patient, and if the patient has provided reconsent, study drug administration can be continued until loss of clinical benefit.
[d] All patients return to the study center for posttreatment visits at 30 ± 3 and 90 ± 7 days after the last dose of study drug.
[e] The survival follow-up phase continues until ≥ 70% of the patients randomized in the study have died.
AUC, area under the curve; ECOG PS, Eastern Cooperative Oncology Group Performance Status; E/P/A, etoposide, carboplatin, and atezolizumab; IV, intravenous; Q21D, every 21 days; QD, once daily; R, randomization; RECIST v1.1, Response Evaluation Criteria in Solid Tumors, Version 1.1.

Table 1 Study Objectives and Endpoints

Primary Objective	Primary Endpoints[a]
Evaluate the potential of trilaciclib to reduce chemotherapy-induced myelosuppression	• Duration of severe (Grade 4) neutropenia in cycle 1 • Occurrence of severe (Grade 4) neutropenia
Key Secondary Objectives	**Key Secondary Endpoints[a]**
Evaluate the potential of trilaciclib to reduce chemotherapy-induced myelosuppression and its consequences	• Occurrence of RBC transfusions on/after week 5 • Occurrence of G-CSF use • All-cause dose reductions (event rate) • OS[b]
Supportive Secondary Objectives	**Supportive Secondary Endpoints**
Evaluate the antitumor activity of trilaciclib in combination with E/P/A	• ORR (INV assessed) • Duration of OR (INV assessed) • PFS (INV assessed)
Determine the safety and tolerability of trilaciclib in combination with E/P/A	• Occurrence and severity of AEs • Relative dose intensity • Dose modifications
Assess effect of trilaciclib on multiple lineages and current standard of care interventions to treat myelosuppression	• Occurrence of G-CSF use, ESA use, platelet transfusions, and RBC transfusions • ANC, hemoglobin, platelet counts, and lymphocyte counts over time
Exploratory Objectives	**Exploratory Endpoints**
Evaluate the effects of trilaciclib on PROs	• Assess change from baseline in FACT instrument scores
Explore changes in peripheral blood immune subsets by immunophenotyping	• Change from baseline of immune cell subsets • Relationship between immune cell subsets and biological/clinical endpoints

[a] To adjust for the multiple comparisons from the primary and key secondary endpoints, a Hochberg-based gatekeeping procedure was utilized to control the overall type I error rate at a 1-sided 0.025 level.
[b] Though OS was listed as a key secondary endpoint it was not built into the multiplicity control; the intention of the OS analysis was to show 'no harm'.
AE, adverse event; ANC, absolute neutrophil count; E/P/A, etoposide, carboplatin, and atezolizumab; ESA, erythropoiesis-stimulating agent; FACT, Functional Assessment of Cancer Therapy; G-CSF, granulocyte colony-stimulating factor; INV, investigator; OR, objective response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PRO, patient-reported outcome; RBC, red blood cell.

- Data presented are from the following data cuts: May 17, 2018 for final myelosuppression endpoints (ie, after all patients had the opportunity to receive 4 cycles of induction therapy) and Aug 05, 2019 for all other endpoints

Assessments

- Complete blood counts were obtained on days 1, 3, 8, and 15 of each cycle of trilaciclib/placebo plus etoposide, carboplatin, and atezolizumab (induction) or atezolizumab (maintenance)
- Adverse events (AEs) were graded according to the National Cancer Institute's Common Terminology Criteria for AEs version 4.03
- Patient-reported outcomes were assessed using Functional Assessment of Cancer Therapy-Lung (FACT-L) and Functional Assessment of Cancer Therapy-Anemia (FACT-An) instruments, administered to patients on day 1 of each cycle and at posttreatment visits
- Tumor response was assessed per Response Evaluation Criteria in Solid Tumors version 1.1

RESULTS

Patient Disposition and Baseline Characteristics

- As of Aug 05, 2019, 125 patients were screened and 107 eligible patients (intention-to-treat analysis set) were randomized to receive trilaciclib (n = 53) or placebo (n = 54) in combination with etoposide, carboplatin, and atezolizumab
- 105 patients received ≥ 1 dose of study drug (safety analysis set), and 24 patients are ongoing in the study, with 11 patients ongoing with atezolizumab treatment in the maintenance phase
- Primary reasons for study discontinuation were similar between treatment arms; across both arms, these were death (n = 65, 60.7%) and withdrawal of patient consent (n = 9, 8.4%)
- Baseline demographic and disease characteristics were generally comparable across the treatment groups **(Table 2)**

Table 2 Patient Demographic and Baseline Disease Characteristics (ITT Analysis Set)

	E/P/A + Placebo (n = 53)	E/P/A + Trilaciclib 240 mg/m² (n = 54)	Total (N = 107)
Median (range) age, years	64 (46–83)	65 (45–81)	64 (45–83)
Age group, years, n (%) 18 to < 65 ≥ 65	27 (50.9) 26 (49.1)	27 (50.0) 27 (50.0)	54 (50.5) 53 (49.5)
Male, n (%)	34 (64.2)	41 (75.9)	75 (70.1)
Country, n (%) USA Non-USA	22 (41.5) 31 (58.5)	20 (37.0) 34 (63.0)	42 (39.3) 65 (60.7)
ECOG PS, n (%) 0–1 2	46 (86.8) 7 (13.2)	45 (85.2) 8 (14.8)	92 (86.0) 15 (14.0)
Baseline LDH ≤ ULN > ULN Missing	29 (54.7) 24 (45.3) 0	26 (48.1) 25 (46.3) 3 (5.6)	55 (51.4) 49 (45.8) 3 (2.8)
Presence of brain metastases, n (%)	15 (28.3)	15 (27.8)	30 (28.0)
Smoking history, n (%) Never smoked Former or current smoker Missing	6 (11.3) 47 (88.7) 0	4 (7.4) 49 (90.7) 1 (1.9)	10 (9.3) 96 (89.7) 1 (0.9)

ECOG PS, Eastern Cooperative Oncology Group Performance Status; E/P/A, etoposide, carboplatin, and atezolizumab; ITT, intention-to-treat; LDH, lactate dehydrogenase; ULN, upper limit of normal.

Dose Exposure and Dose Modifications

- Patients receiving trilaciclib received a higher relative dose intensity of chemotherapy compared with those receiving placebo
- The difference in relative dose intensity was due to fewer patients having etoposide or carboplatin dose reductions and/or cycle delays with trilaciclib compared with placebo **(Table 3)**
- The frequency of dose reductions for etoposide or carboplatin over time (event rate) was also lower for patients who received trilaciclib compared with placebo

Table 3 Summary of Dose Exposure and Dose Modifications (Safety Analysis Set)

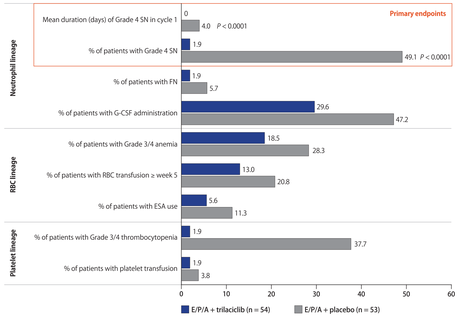
	E/P/A + Placebo (n = 53)	E/P/A + Trilaciclib 240 mg/m² (n = 52)
Duration of exposure (induction + maintenance) Median (range) days Median (range) cycles	182 (21–705) 8 (1–28)	205 (42–660) 8 (2–31)
Median relative dose intensity, % Etoposide Carboplatin Atezolizumab (induction + maintenance)	92.3 93.3 95.0	98.1 98.8 96.3
Dose reductions, n (%)[a] Etoposide Carboplatin	14 (26.4) 13 (24.5)	3 (5.8) 1 (1.9)
Cycle delays, n (%)	31 (58.5)	18 (34.6)
All-cause dose reductions[b] Event rate (per 100 cycles)	8.5	2.1

[a] No dose reductions were allowed for atezolizumab or trilaciclib during the study.
[b] Based on intention-to-treat analysis data set (E/P/A + placebo, n = 53; E/P/A + trilaciclib, n = 54); data reported for induction period only, unless otherwise stated.
E/P/A, etoposide, carboplatin, and atezolizumab.

Myelopreservation

- Trilaciclib reduced both the duration of severe neutropenia in cycle 1 ($P < 0.0001$), a surrogate for febrile neutropenia and infections, and the occurrence of severe neutropenia ($P < 0.0001$), compared with placebo **(Figure 3)**
- Although not statistically significant, trilaciclib also reduced the need for red blood cell (RBC) and platelet transfusions and the use of granulocyte colony-stimulating factor and erythropoiesis-stimulating agents, compared with placebo **(Figure 3)**

Figure 3 Summary of Myelosuppression Endpoints (ITT Analysis Set)



E/P/A, etoposide, carboplatin, and atezolizumab; ESA, erythropoiesis-stimulating agent; FN, febrile neutropenia; G-CSF, granulocyte colony-stimulating factor; ITT, intention-to-treat; RBC, red blood cell; SN, severe neutropenia.

Safety

- The most common all-grade and Grade ≥ 3 treatment-emergent AEs (TEAEs) occurring during the induction and maintenance phases are shown in **Table 4**
- There were fewer Grade ≥ 3 TEAEs with trilaciclib compared with placebo, mostly due to a lower number of Grade ≥ 3 hematologic AEs
  - Overall Grade ≥ 3 TEAEs: 63.5% with trilaciclib versus 86.8% with placebo
  - Drug-related Grade ≥ 3 TEAEs: 51.9% with trilaciclib versus 75.5% with placebo
- 16 patients had TEAEs considered related to trilaciclib
  - The most common TEAEs considered related to trilaciclib were fatigue (9.6%), nausea (7.7%), and anemia and infusion-related reaction (5.8% each); most of these were low grade, with the exception of Grade 3 fatigue (1.9%)
- 12 (23.1%) patients in the trilaciclib arm and 11 (20.8%) in the placebo arm had atezolizumab AEs of special interest, which were mostly immune-related
- Serious TEAEs were reported in 32.7% of patients treated with trilaciclib and 47.2% of patients treated with placebo; 1 (1.9%) serious TEAE (deep vein thrombosis) was considered possibly related to trilaciclib
- In the trilaciclib treatment group, there were 2 deaths due to TEAEs: hemoptysis (n = 1) and pneumonia (n = 1), both considered unrelated to trilaciclib

Table 4 Summary of TEAEs Occurring in ≥ 15% of Patients in Either Arm (Safety Analysis Set)

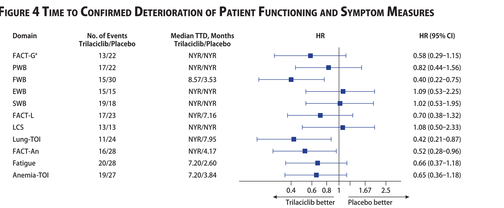
	E/P/A + Placebo (n = 53)		E/P/A + Trilaciclib 240 mg/m² (n = 52)	
	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
Any TEAE	52 (98.1)	46 (86.8)	49 (94.2)	33 (63.5)
Hematologic[a]				
Anemia	33 (62.3)	16 (30.2)	19 (36.5)	9 (17.3)
Neutropenia	40 (75.5)	32 (60.4)	22 (42.3)	11 (21.2)
Thrombocytopenia	35 (66.0)	21 (39.6)	12 (23.1)	1 (1.9)
Leukopenia	20 (37.7)	11 (20.8)	10 (19.2)	3 (5.8)
Nonhematologic[a]				
Nausea	18 (34.0)	1 (1.9)	20 (38.5)	0
Fatigue	20 (37.7)	2 (3.8)	16 (30.8)	1 (1.9)
Dyspnea	12 (22.6)	3 (5.7)	8 (15.4)	3 (5.8)
Dizziness	8 (15.1)	1 (1.9)	9 (17.3)	0
Constipation	12 (22.6)	1 (1.9)	5 (9.6)	0
Dehydration	11 (20.8)	3 (5.7)	5 (9.6)	0
Asthenia	8 (15.1)	2 (3.8)	8 (15.4)	4 (7.7)
Diarrhea	6 (11.3)	0	9 (17.3)	1 (1.9)
Cough	8 (15.1)	0	7 (13.5)	1 (1.9)
Pneumonia	8 (15.1)	8 (15.1)	7 (13.5)	4 (7.7)
Pyrexia	5 (9.4)	0	8 (15.4)	0
Decreased appetite	9 (17.0)	0	4 (7.7)	0

[a] TEAEs are presented by Preferred Term.
E/P/A, etoposide, carboplatin, and atezolizumab; TEAE, treatment-emergent adverse event.

Health-Related Quality of Life

- Enrolled patients had a moderate level of functioning and were moderately symptomatic at baseline as measured by the validated FACT-L and FACT-An instruments
- Trilaciclib improved the patient experience by delaying deterioration of patient functioning and symptom measures over time, compared with placebo. Overall, the benefit of trilaciclib was seen with functional well-being, quality of life measures specific for patients with lung cancer, and symptoms and impact of fatigue, as well as with symptoms and effects on physical and functional well-being due to anemia **(Figure 4)**
- Statistically significant differences between the trilaciclib and placebo treatment groups were observed for Functional Well-being, Lung-Trial Outcome Index, and FACT-An total score **(Figure 4)**

Figure 4 Time to Confirmed Deterioration of Patient Functioning and Symptom Measures



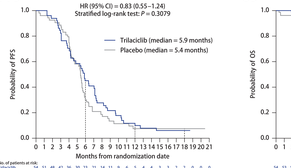
*FACT-G constitutes the core of FACT-L and FACT-An (not repeated at each assessment).
EWB, Emotional Well-being; FACT-An, Functional Assessment of Cancer Therapy-Anemia; FACT-G, Functional Assessment of Cancer Therapy-General; FACT-L, Functional Assessment of Cancer Therapy-Lung; FWB, Functional Well-being; HR, hazard ratio; LCS, Lung Cancer Subscale; NYR, not yet reached; PWB, Physical Well-being; SWB, Social Well-being; TOI, Trial Outcome Index; TTD, time to deterioration.

Antitumor Efficacy

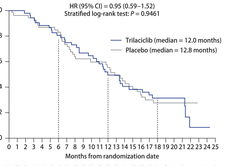
- Investigator-assessed objective response rate (ORR) was comparable between trilaciclib (56.0%) and placebo (63.5%) treatment groups
- The clinical benefit rate, including patients with confirmed complete response, confirmed partial response, or stable disease for at least 5 weeks from cycle 1, day 1, was 96.0% with trilaciclib compared with 90.4% with placebo
- Median progression-free survival (PFS) was 5.9 (95% CI, 4.2–7.1) months for trilaciclib compared with 5.4 (95% CI, 4.3–5.7) months for placebo (hazard ratio [HR], 0.83; $P = 0.3079$; **Figure 5**)
- With a median follow-up of 10.9 months (range, 0.0–24.3 months), median overall survival (OS) was 12.0 (95% CI, 9.6–16.2) months for trilaciclib compared with 12.8 (95% CI, 7.9–15.5) months for placebo (HR, 0.95; $P = 0.9461$; **Figure 5**)

Figure 5 PFS and OS

PFS



OS[a]



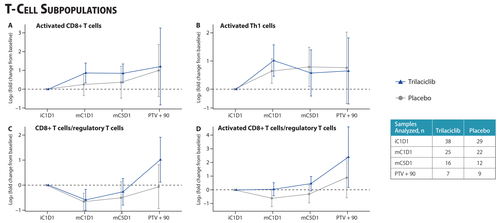
[a] OS data are not yet mature.
HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

Flow Cytometry

- The addition of trilaciclib to etoposide, carboplatin, and atezolizumab treatment increased the number of circulating activated CD8+ T and Th1 cells during chemotherapy, and increased the ratio of total and activated CD8+ T cells to regulatory T cells in both the induction and maintenance phases of treatment in peripheral blood **(Figure 6A–D)**
- Patients treated with trilaciclib had significantly higher numbers of expanded T-cell clones than patients treated with placebo ($P = 0.01$; **Figure 6E**)
- Regardless of treatment, patients with high levels of T-cell clones had longer PFS **(Figure 6F)**

Figure 6 T-Cell Subpopulations and Clonal Expansion

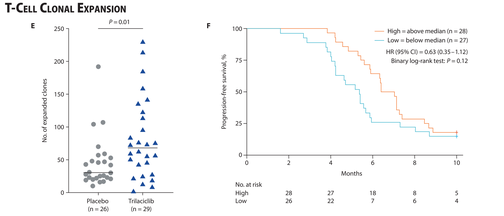
T-Cell Subpopulations



Samples Analyzed, n	Trilaciclib	Placebo
iC1D1	38	29
mC1D1	25	22
mC5D1	16	12
PTV + 90	7	9

Normalized mean cell counts for (A) activated CD8+ T cells (CD38+HLADR+CD3+CD8+) and (B) activated Th1 cells (CXCR3+CXCR6-CD38+HLADR+CD3+CD4+). Normalized mean ratios of absolute (C) CD8+/regulatory T cells and (D) activated CD8+/regulatory T cells. Regulatory T-cell population is defined as CD45+CD25+CD127lowCD3+CD4+. Cell populations in whole blood were analyzed by flow cytometry at the indicated time points (C, cycle; D, day; i, induction; m, maintenance; PVT, post-treatment visit + 90 days). Error bars represent 95% CI.

T-Cell Clonal Expansion



(E) The number of expanded T-cell clones was determined by the differential abundance analysis of T-cell receptor β sequences in whole blood from patients at cycle 1, day 1 (C1D1) of maintenance versus C1D1 of induction. Horizontal bars indicate median number of expanded clones in each group. (F) Patients were stratified into low (below median) and high (above median) number of expanded T-cell clones (median 48 clones for all patients) for Kaplan-Meier analysis of progression-free survival.
HR, hazard ratio.

CONCLUSIONS

- Compared with placebo, trilaciclib makes etoposide, carboplatin, and atezolizumab treatment safer and more tolerable by protecting patients from chemotherapy-induced myelosuppression as evidenced by:
  - Effects on neutrophils (statistically significant improvement in primary endpoints of duration of severe neutropenia, and occurrence of severe neutropenia), RBCs (lower rates of Grade 3/4 anemia and transfusions), and platelets (lower rates of Grade 3/4 thrombocytopenia and transfusions)
  - Fewer supportive care requirements
  - Fewer chemotherapy dose reductions
  - Numerically increased relative dose intensities of etoposide, carboplatin, and atezolizumab
  - Improved overall safety profile, primarily due to a reduction in high-grade hematologic AEs attributable to cytotoxic chemotherapy
- Validated patient-reported outcome instruments suggest that the addition of trilaciclib improves the patient experience on chemotherapy
- ORR, PFS, and OS data demonstrate that trilaciclib does not impair chemotherapy/atezolizumab antitumor efficacy
- Flow cytometry data suggest that during treatment with etoposide, carboplatin, and atezolizumab, coadministration of trilaciclib can enhance the T-cell immune response
- These data confirm the myelopreservation benefits of trilaciclib observed in another first-line trial of trilaciclib in combination with etoposide and carboplatin in ES-SCLC (NCT02499770)[5] as well as in combination with topotecan in patients treated for ES-SCLC (NCT02514447)[7]

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CONFLICT OF INTERESTS

DD: research funding from AstraZeneca, Boehringer Ingelheim, Celgene, Eli Lilly, ER Squibb & Sons, G1 Therapeutics, Genentech, Novartis, Pfizer, and Roche; **DS:** research funding from Genentech/Roche and G1 Therapeutics; advisory board for Genentech/Roche; **JJ:** research grant from AstraZeneca; advisory board for AstraZeneca, Boehringer Ingelheim, and MSD; **LH:** research funding, 1 time consulting fee, and travel expenses from G1 Therapeutics; **KK:** honoraria from Amgen, Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Intellect Pharma, Merck, MSD, Novartis, Pfizer, Roche, and Servier; travel/accommodation/expenses from Amgen, Astellas, AstraZeneca, Eli Lilly, MSD, Pfizer, and Roche; advisory board for AstraZeneca, Astellas, Roche, and Servier; **ZY, SW, RM, SRM, JMA:** employees of G1 Therapeutics; **VK, IB, OI, AD, ST, TM, IK, AM, JG:** no conflicts of interest