#1666PD

TRILACICLIB DECREASES MULTI-LINEAGE MYELOSUPPRESSION IN EXTENSIVE-STAGE SMALL CELL LUNG CANCER (ES-SCLC) PATIENTS RECEIVING 1ST LINE CHEMOTHERAPY

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BACKGROUND

- Clinically significant, multi-lineage myelosuppression is the major acute toxicity of cytotoxic chemotherapy, leading to clinical complications including febrile neutropenia and symptomatic anemia, as well as dose reductions and dose delays, which decrease chemotherapy efficacy
- Current approaches to address chemotherapy-induced myelosuppression are reactive, lineage specific, and administered after chemotherapy damage has occurred
- No therapies exist to preserve the hematopoietic stem and progenitor cells (HSPCs) and multiple hematopoietic lineages from chemotherapy-induced damage
- Trilaciclib is a highly potent and selective, reversible, cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor in development to preserve HSPC and immune system function during chemotherapy (myelopreservation)
- Here we report the first clinical trial to provide randomized, double-blind, placebo-controlled efficacy and safety results for the addition of trilaciclib to standard SCLC cytotoxic chemotherapy

STUDY OBJECTIVES

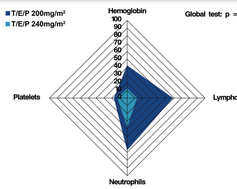
The primary objectives of this study were to assess the toxicities and define the Recommended Phase 2 dose (RP2D) of trilaciclib administered with etoposide and carboplatin (E/P; Part 1) and to assess the safety and tolerability of trilaciclib administered with E/P (i.e., effects on myelosuppression; Part 2).

STUDY DESIGN

- This was a randomized, double-blind, placebo-controlled, multicenter, Phase 1b/2 study of the safety, efficacy and PK of trilaciclib in combination with E/P for patients with newly diagnosed extensive-stage SCLC
- The study consisted of 2 parts: Part 1 was a limited Phase 1b, open-label, dose-finding portion and Part 2 was a Phase 2 randomized, double-blind placebo-controlled portion
- The study enrolled chemo-naïve extensive-stage SCLC patients with adequate organ function, ECOG 0-2, and no symptomatic brain metastases (NCT02499770)
- Patients received trilaciclib or placebo prior to E/P on days 1 to 3 of each cycle
- Supportive care was administered per ASCO guidelines for chemotherapy with a moderate risk of febrile neutropenia (no prophylactic growth factors in cycle 1)
- Endpoints for Part 2 were prespecified to assess the effect of trilaciclib on:
  - Multi-lineage myelosuppression: occurrence of febrile neutropenia (FN), duration of Grade 3/4 or severe (Grade 4) neutropenia, average ANC, ANC nadir, hemoglobin, platelet count, and lymphocyte count over time; occurrence of RBC transfusions, platelet transfusions, G-CSF use, ESA use, intravenous antibiotic use, infection serious adverse events (SAEs), and pulmonary infection SAEs
  - Antitumor efficacy: evaluated based on RECIST, Version 1.1 for best overall response (BOR), objective response rate (ORR), and progression-free survival (PFS)
  - Overall survival (OS), adverse events (AEs) and additional safety endpoints
- Statistical significance level was set at two-sided 0.2

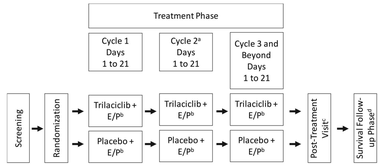
PART 1 RESULTS

- 19 enrolled
  - 10 in cohort 1 (EP + trilaciclib 200 mg/m^2); 9 in cohort 2 (EP + trilaciclib 240 mg/m^2)
  - Cohort 1: 2 of the first 6 experienced a DLT (Grade 4 thrombocytopenia and ANC of 1200 cells/µL on Cycle 2 Day 1)
  - Cohort 2: 1 of 6 experienced a DLT (ANC of 1200 cells/µL on Cycle 2 Day 1)
- 240 mg/m^2 picked as RP2D
  - Fewer ≥ Grade 3 hematologic AEs and ≥ Grade 3 laboratory abnormalities
- Tumor efficacy: cohorts 1 and 2, respectively
  - RR: 80%, 100%
  - Median PFS: 5.3 mos, 6.2 mos
  - Median OS: 10.6 mos, 12.8 mos
- PK consistent with healthy volunteers; no effect on etoposide/carboplatin



This radar chart displays grade 3/4 laboratory abnormalities for hemoglobin, lymphocytes, neutrophils, and platelets. Each axis of the chart represents the proportion (%) of patients with a grade 3/4 abnormality for a hematology laboratory parameter. The shaded area of the whole shape, reflecting the multi-lineage grade 3/4 abnormalities, was compared between treatment groups using a multivariate test to generate the p-value.

Figure 1. Study Schematic



E/P = etoposide 100 mg/m^2 + carboplatin AUC 5

[a] Trilaciclib + E/P continued until disease progression, unacceptable toxicity, or discontinuation by the patient or investigator (e.g., after completing 6 cycles). The tumor was assessed after every even cycle using Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1. Assessments were performed within 7 days of starting the subsequent cycle.

[b] Trilaciclib or placebo was administered prior to the administration of etoposide and carboplatin on Day 1 and administration of etoposide on Days 2 and 3 of 21-day cycles.

[c] Patients returned to the study center for a Post-Treatment Visit at 30 + 3 days after the last dose of study drug.

[d] The Survival Follow-up Phase will continue until at least 50% of the patients randomized to Part 2 of the study have died.

Table 1. Demographics and Baseline Disease Characteristics

	E/P + placebo (N=38)	E/P + trilaciclib 240 mg/m^2 (N=39)	Total (N=77)
Age (years)			
Mean (SD)	65 (9.5)	65 (8.4)	65 (8.9)
Median (Min, Max)	66 (39, 86)	64 (49, 82)	66 (39, 86)
Age < 65	17 (44.7%)	20 (51.3%)	37 (48.1%)
Age ≥ 65	21 (55.3%)	19 (48.7%)	40 (51.9%)
Sex, n (%)			
Male	27 (71.1%)	27 (69.2%)	54 (70.1%)
Female	11 (28.9%)	12 (30.8%)	23 (29.9%)
Body surface area (m^2)			
Mean (SD)	1.91 (0.210)	1.89 (0.223)	1.9 (0.216)
ECOG Score, n (%)			
0-1	35 (92.1%)	35 (89.7%)	70 (90.9%)
2	3 (7.9%)[a]	4 (10.3%)	7 (9.1%)
Weight loss in 6 months prior to randomization[b]			
Yes	14 (36.8%)	16 (41.0%)	30 (39.0%)
> 5%	7 (50.0%)	10 (62.5%)	17 (56.7%)
≤ 5%	7 (50.0%)	6 (37.5%)	13 (43.3%)
Brain metastases, n (%)[c]			
Present	8 (21.1%)	5 (12.8%)	13 (16.9%)
Baseline LDH, n (%)			
≤ ULN	18 (47.4%)	16 (41.0%)	34 (44.2%)
> ULN	17 (44.7%)	21 (53.8%)	38 (49.4%)
Any prior radiation therapy, n (%)			
Yes	4 (10.5%)	3 (7.7%)	7 (9.1%)
Smoking status, n (%)			
Former smokers	25 (65.8%)	25 (64.1%)	50 (64.9%)
Current smokers	12 (31.6%)	14 (35.9%)	26 (33.8%)

E/P = standard of care (etoposide + carboplatin); SD = standard deviation; Min = minimum; Max = maximum; ECOG = Eastern Cooperative Oncology Group; LDH = lactate dehydrogenase; ULN = upper limit of normal

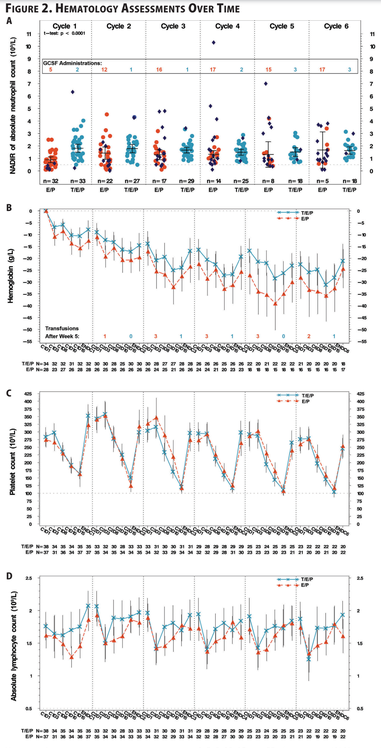
[a] Due to data discrepancies, one patient in the placebo group was labeled as ECOG 2 at randomization but had an ECOG performance score of 0 on Cycle 1 Day 1; therefore only 2 patients on placebo had ECOG 2

[b] Percentages are based on the number of patients with weight loss

[c] Patients with brain metastases at baseline could enroll if they were asymptomatic, did not require urgent treatment, and were off all steroids, i.e., did not require treatment prior to enrolment

PART 2 RESULTS

Figure 2. Hematology Assessments Over Time



Hematological assessments were scheduled on days 1, 3, 8, 10, 15, and 22 of each cycle. **(A)** Mean nadir values (with 95% CI) for ANC over time for each cycle for patients who did not receive GCSF. Dark blue dots represent the nadir for patients receiving GCSF, but the data is not included in the mean ± 95% CI calculations. The dotted line represents the value required to start each new cycle, i.e. 1.5 x 10^9/L. **(B)** Mean (with 95% CI) change from baseline in hemoglobin in g/dL. Patients who received transfusions or ESAs were excluded. **(C)** and **(D)** Mean counts (with 95% CI) over time for platelet and lymphocyte counts, respectively. The dotted line on Panel C represents the value required to start each new cycle, i.e. 100 x 10^9/L. The dotted line on Panel D represents a CTCAE grade 3 lymphocyte count decreased value, i.e. 0.5 x 10^9/L. E/P + placebo (E/P) = orange; E/P + 240 mg/m^2 trilaciclib (T/E/P) = blue; C = cycle; D = day; ENDC = end of cycle which is defined as the last value measured prior to the first day of dosing in the subsequent cycle; CI = confidence interval.

- Exploratory peripheral blood immunophenotyping demonstrated that trilaciclib potentially enhances lymphocyte function as measured by: preserved or increased number of B and T cells; preserved number of activated CD8+ T and Th1 cells; increased CD8+ T/regulatory T cell ratio; and increased CD8+ T cell function

Table 2. Myelopreservation Observed Across Individual Lineage Endpoints

Endpoint, n (%)	E/P + placebo (N=37)	E/P + trilaciclib 240 mg/m^2 (N=38)	P-value[a]
Neutrophils			
Patients with Grade 4 ANC	16/37 (43.2%)	2/38 (5.3%)	0.0001
Median duration in days (95% CI)[b,c]	8 (7, 8)	3 (2, 3)	0.0097
Patients with Grade 4 ANC values in Cycle 1	13/37 (35.1%)	1/38 (2.6%)	0.0003
Mean Cycle 1 ANC nadir in all patients[b]	0.815 x 10^9/L	1.899 x 10^9/L	<0.0001
Mean Cycle 1 ANC nadir in patients who did not receive G-CSF in Cycle 1[d]	0.894 x 10^9/L	1.815 x 10^9/L	<0.0001
Patients with G-CSF administration[b]	24/37 (64.9%)	4/38 (10.5%)	<0.0001
Patients with febrile neutropenia TEAEs[b]	3/37 (8.1%)	1/38 (2.6%)	0.2773
Cycles with febrile neutropenia TEAEs[b]	5/190 (2.6%)	1/186 (0.5%)	0.1542
Red blood cells			
Patients with Grade 3/4 hemoglobin	7/37 (18.9%)	4/38 (10.5%)	ND
Patients with RBC transfusions	9/37 (24.3%)	4/38 (10.5%)	0.1109
Patients with transfusions on or after 5 weeks on study	8/37 (21.6%)	2/35 (5.7%)	0.0615
Number of units transfused/cycles of chemotherapy administered	0.11 (21/190)	0.05 (10/186)	0.0711
Patients with ESA administration[b]	2/37 (5.4%)	1/37 (2.6%)	0.5578
Platelets			
Patients with Grade 3/4 platelet count	6/37 (16.2%)	4/38 (10.5%)	ND
Patients with platelet transfusions[b,e]	0/37	2/38 (5.3%)	0.1542
Lymphocytes			
Mean ALC at end of Cycle 6	1.61 x 10^9/L (n=22)	1.94 x 10^9/L (n=20)	0.0499
Mean ALC at Post Treatment Visit	1.40 x 10^9/L (n= 8)	1.85 x 10^9/L (n=10)	ND
Drug Exposure, Relative Dose Intensity and Dose Modifications			
Duration of exposure in days (mean [SD])	116 (37.8)	107 (43.2)	ND
Number of cycles completed (mean [SD])	5 (1.7)	5 (2.0)	ND
Etoposide relative dose intensity (%, mean [SD])	89.3 (10.23)	91.8 (12.77)	ND
Carboplatin relative dose intensity (%, mean [SD])	90.4 (9.53)	95 (7.69)	ND
Patients with Chemotherapy Cycle Delays	25 (67.6%)	15 (39.5%)	0.0170
Patients with Chemotherapy Dose Reductions	13 (35.1%)	3 (7.9%)	0.0033

E/P = etoposide + carboplatin; TEAE = treatment emergent adverse event; ANC = absolute neutrophil count; ESA = erythropoiesis-stimulating agents; G-CSF = granulocyte-colony stimulating factor; ND = not done; RBC = red blood cell; ALC = absolute lymphocyte count; [a] Significance was set at two-sided 0.2 alpha; [b] Prospectively defined endpoints; [c] duration of Grade 4 ANC calculated for patients who experienced the event; [d] Four patients in the placebo arm got G-CSF in Cycle 1 and 2 patients in the trilaciclib arm got G-CSF in Cycle 1; [e] 1 patient hospitalized on C1D2 for pneumonia respiratory failure and was transfused prior to their death 11 days after C1D1. 2nd patient had large decline in platelets between screening and C1D1 resulting in a platelet count < lower limit of normal prior to receiving the first dose of therapy; bone metastasis and enoxaparin use may have been possible contributing factors to the decrease in platelet count prior to dosing.

- Despite an increased risk of febrile neutropenia and complications from neutropenia for patients ≥65 years of age, trilaciclib had a more pronounced clinically significant reduction in neutropenia related endpoints in this patient subgroup:
  - 11/20 (55.0%) patients on placebo and 1/19 (5.3%) on trilaciclib had Grade 4 ANC (p=0.0009)
  - 6/20 (30.0%) patients on placebo and 0/19 (0%) on trilaciclib required dose reductions (not estimable)
  - 11/20 (55.0%) patients on placebo and 1/19 (5.3%) on trilaciclib required dose delays (p=0.0011)
- There were notably fewer ≥ Grade 3 TEAEs with trilaciclib compared to placebo, mostly due to a significantly lower number of ≥ Grade 3 hematologic TEAEs for trilaciclib compared to placebo (9/38 patients, 23.7% vs 27/37 patients, 73.0%, respectively), which is consistent with the MOA of trilaciclib
- Almost all patients reported TEAEs related to etoposide or carboplatin, while approximately half the patients reported TEAEs related to trilaciclib, none of which were ≥ Grade 3
- Few patients had infection SAEs (2/37 patients, 5.4% in the placebo arm and 4/38 patients, 10.5% in the trilaciclib arm), and most were pulmonary in nature
  - Only one event (trilaciclib arm) may have been influenced by hematologic toxicity
- An equal number of patients in each arm received intravenous antibiotics (8/37 patients, 21.6% in the placebo arm and 8/38 patients, 21.1% in the trilaciclib arm)

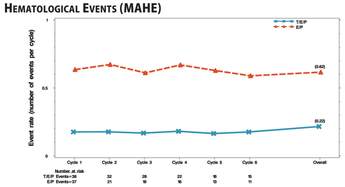
Table 3. TEAE Reported in ≥5 Patients in Either Treatment Group

	E/P + placebo (N=37)		E/P + trilaciclib 240 mg/m^2 (N=38)	
Preferred Term, n (%)	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
Any TEAE	35 (94.6%)	28 (75.7%)	34 (89.5%)	11 (28.9%)
Hematologic[a]				
Neutropenia	23 (62.2%)	21 (56.8%)	9 (23.7%)	3 (7.9%)
Anemia	15 (40.5%)	6 (16.2%)	10 (26.3%)	2 (5.3%)
Thrombocytopenia	10 (27.0%)	3 (8.1%)	10 (26.3%)	3 (7.9%)
Neutrophil decreased	9 (24.3%)	7 (18.9%)	3 (7.9%)	1 (2.6%)
Leukopenia	5 (13.5%)	1 (2.7%)	2 (5.3%)	0
Nonhematologic[a]				
Alopecia	11 (29.7%)	0	6 (15.8%)	0
Nausea	8 (21.6%)	1 (2.7%)	13 (34.2%)	2 (5.3%)
Constipation	8 (21.6%)	0	9 (23.7%)	0
Diarrhea	7 (18.9%)	1 (2.7%)	6 (15.8%)	0
Fatigue	6 (16.2%)	0	16 (42.1%)	1 (2.6%)
Dyspnea	5 (13.5%)	1 (2.7%)	8 (21.1%)	0
Dizziness	5 (13.5%)	0	4 (10.5%)	0
Pyrexia	5 (13.5%)	0	1 (2.6%)	0
Cough	4 (10.8%)	0	5 (13.2%)	0
Decreased appetite	3 (8.1%)	0	7 (18.4%)	1 (2.6%)
Arthralgia	3 (8.1%)	0	5 (13.2%)	0
Headache	2 (5.4%)	0	7 (18.4%)	0
Abdominal pain upper	1 (2.7%)	0	7 (18.4%)	0

TEAE = treatment emergent adverse event; E/P = standard of care (etoposide + carboplatin)

[a] Ordered by descending frequency in the all grades placebo arm

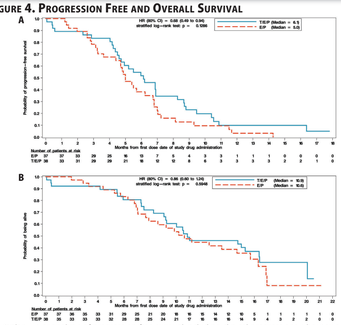
Figure 3 and Table 4. Exploratory Composite Endpoint: Major Adverse Hematological Events (MAHE)



Component	E/P + placebo (N=37)	E/P + trilaciclib 240 mg/m^2 (N=38)	P-value
Composite of all events per cycle	81/190	27/186	<0.0001
All-cause mortality	4/190	7/186	0.2826
All hospitalizations regardless of cause	16/190	12/186	0.5227
All-cause dose reductions	16/190	4/186	0.0176
Febrile neutropenia	5/190	1/186	0.1542
Duration of Grade 4 ANC > 5 days	27/190	0/186	NE
RBC transfusions occurring on/after 5 weeks on study	13/190	3/183	0.0358

To assess the totality of the potential multi-lineage benefit of trilaciclib, a composite endpoint of six individual components referred to as "major adverse hematologic event" (MAHE) was assessed. Both the event rate per cycle (Figure 3) and the cumulative incidence (Table 4) are shown. The p-value for testing the ratio between the overall incidence rate (trilaciclib versus placebo) was calculated using Poisson method accounting for the ECOG status (0-1 versus 2) as the stratification factor. Events occurring between the first dose and 60 days after the last dose of study drug were included in the event rate over time analysis. RBC = red blood cell; E/P + placebo (E/P) = orange; E/P + 240 mg/m^2 trilaciclib (T/E/P) = blue.

Figure 4. Progression Free and Overall Survival



(A) Kaplan Meier analysis of progression free survival including clinical progressions. The X axis depicts months from first dose of study drug administration and number of patients at risk. The Y axis depicts the probability of being progression free. **(B)** Kaplan Meier analysis of overall survival. The X axis depicts months from first dose of study drug administration and number of patients at risk. The Y axis depicts the probability of being alive. E/P + placebo (E/P) = orange; E/P + 240 mg/m^2 trilaciclib (T/E/P) = blue

- ORR (CR + PR) for the response evaluable population, as assessed by the investigators, was higher for trilaciclib (66.7%) than for placebo (56.8%), although not statistically significant (similar to previously reported BICR)
- Median DOR (duration of response) was comparable for trilaciclib compared with placebo (5.7 versus 5.4 months, respectively)
- Median PFS, including clinical progression, was longer for trilaciclib (6.1 [4.6, 8.3] months) than placebo (5.0 [4.4, 6.7] months; HR 0.68; p=0.1286)
- Median OS was comparable for trilaciclib and placebo (10.9 [9.1, 16.4] months and 10.6 [7.7, 15.7] months; HR 0.86; p=0.5948), although OS results are still immature (~68% of events)
- Subsequent anticancer therapies, of which topotecan was most common, were reported in 44.7% of patients (17/38) in the E/P + trilaciclib group and 40.5% of patients (15/37) in the E/P + placebo group
  - In the trilaciclib arm, 14, 2, and 1 patients received 1, 2, and 3 subsequent lines of therapy, respectively, compared to 10, 5 and 0 for the placebo arm
  - Data are immature as survival follow-up is ongoing

CONCLUSIONS

- Trilaciclib is the first therapeutic approach in clinical development with the potential to preserve HSPC and immune system function during chemotherapy (myelopreservation)
- This Phase 2 trial in SCLC demonstrated proof-of-concept for the potential myelopreservation benefits of trilaciclib:
  - Reduced multi-lineage myelosuppression (neutrophils, RBCs, lymphocytes)
  - Reduced supportive care requirements and dose reductions
  - Changes in peripheral blood immunophenotyping suggesting enhanced immune system function compared to patients who received placebo (data shown on poster 1671P)
- Measures of antitumor efficacy (ORR, PFS and OS) trended in favor of trilaciclib, although not statistically different from placebo, indicating that trilaciclib does not interfere with the intended effects of the chemotherapy
- Trilaciclib is being evaluated in three additional randomized Phase 2 studies: 1st line SCLC (+atezolizumab/etoposide/carboplatin; NCT03041311), 2nd/3rd line SCLC (+topotecan; NCT02514447), and triple negative breast cancer (+gemcitabine/carboplatin; NCT02978716)

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