ABSTRACT #194528

TRILACICLIB (G1T28): A CYCLIN DEPENDENT KINASE 4/6 INHIBITOR, IN COMBINATION WITH ETOPOSIDE AND CARBOPLATIN (EP) FOR EXTENSIVE STAGE SMALL CELL LUNG CANCER (ES-SCLC): PHASE 1b RESULTS

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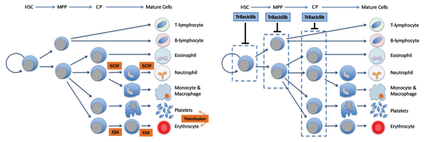
BACKGROUND

- Chemotherapy-induced toxicity to the bone marrow and immune system has significant acute and long-term consequences
- Hematopoietic stem and progenitor cells (HSPCs) proliferate through a CDK4/6-dependent mechanism to produce circulating blood cells
- Actively proliferating HSPCs are sensitive to the cytotoxic effects of chemotherapy, and myelosuppression is the most severe and dose-limiting toxicity of such agents
- While the depletion of committed hematopoietic progenitor cells (HPCs) is largely responsible for the acute toxicity of chemotherapy, damage and functional attrition (via forced proliferation) of hematopoietic stem cells (HSCs) contributes to late chemotherapy-induced myelotoxicity (i.e., bone marrow exhaustion)
- Trilaciclib (G1T28) is a highly potent and selective CDK4/6 inhibitor (CDK4/6i) in development to reduce chemotherapy-induced myelosuppression and preserve immune system function in patients with CDK4/6-independent cancers such as SCLC
- By inducing transient G_1 cell cycle arrest of HSPCs and immune cells in preclinical models, trilaciclib has demonstrated protection of the bone marrow from both the acute and long-term effects of cytotoxic chemotherapy thereby allowing faster hematopoietic recovery, preserving long-term bone marrow function, and enhancing anti-tumor activity[1,2]
- Trilaciclib 192 mg/m^2 (rounded to a starting dose of 200 mg/m^2 in this study) demonstrated robust G_1 cell cycle arrest of the HSPCs for up to 32 hours in a Phase 1a healthy normal volunteer study (NCT02243150), confirming biological activity of trilaciclib in the bone marrow[2]

FIGURE 1. TRILACICLIB PRESERVES ALL BLOOD LINEAGES BY PROTECTING HSPCS FROM DAMAGE BY CHEMOTHERAPY



CURRENT STANDARD OF CARE

- Multiple interventions needed for neutrophils, red blood cells (RBCs) and platelets, and no lymphocyte support
- Growth factors stimulate proliferation of a single lineage (granulocyte or RBC) after damage from cytotoxic chemotherapy
- G-CSF administration is associated with bone pain, fever, preferential myeloid differentiation and bone marrow exhaustion
- ESA use is associated with hypertension, thrombosis, tumor progression and increased mortality
- Transfusions are associated with infections, transfusion reactions, immunosuppression and antigen sensitization with repeated transfusions

TRILACICLIB

- IV administration prior to chemotherapy protects all lineages including lymphocytes
- Transient G_1 cell cycle arrest protects hematopoietic stem cells, multipotent progenitors (MPPs) and committed progenitors (CPs) from cytotoxic chemotherapy
- Potential decrease of preferential myeloid differentiation and bone marrow exhaustion
- Potential for reduced use of ESA and G-CSF
- Potential for reduced transfusions and attendant consequences

SCLC BACKGROUND

- Platinum (cisplatin or carboplatin) plus etoposide is the standard of care for extensive-stage SCLC
- Platinum/etoposide results in significant myelosuppression[3-8] (Grade 3/4 neutropenia 47-92%, leukopenia 8-66%, thrombocytopenia 10-46%, and anemia 7-34%), requiring growth factor support, transfusions, dose delays, dose reductions, and hospitalizations
- In one of the largest Phase III trials evaluating carboplatin and etoposide (n=455 in the carboplatin/etoposide arm), the objective response rate (ORR) was 52% (1 CR) and the clinical benefit rate (CBR) was 75%[3]

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STUDY OBJECTIVES

PRIMARY OBJECTIVES

- Assess the toxicities and define the Recommended Phase 2 dose (RP2D) of trilaciclib administered with etoposide and carboplatin (EP)
- Assess the safety and tolerability of trilaciclib administered with EP

SECONDARY OBJECTIVES

- Assess the hematological profile and pharmacokinetics (PK) of trilaciclib administered with EP
- Assess the incidence of febrile neutropenia and infections
- Assess the utilization of transfusions (RBC and platelet), hematopoietic growth factors, and systemic antibiotics
- Assess tumor response based on RECIST v1.1, PFS, and OS

METHODS

STUDY DESIGN (NCT02499770)

- Multicenter Phase 1b/2a study
- Part 1 is open-label, dose-finding
- Part 2 is randomized (1:1), double-blind, in 70 patients (35 patients/arm)
- Trilaciclib (starting dose of 200 mg/m^2) is administered IV prior to EP on days 1-3 every 21 days
- Carboplatin dose is AUC of 5 and etoposide dose is 100 mg/m^2 every 21 days

SELECTED INCLUSION CRITERIA

1. Age ≥ 18 years
2. Histologically/cytologically confirmed SCLC
3. Extensive-stage disease
4. Measurable disease by RECIST, version 1.1
5. Organ Function: Hgb ≥ 9.0 g/dL, absolute neutrophil count (ANC) ≥ 1.5 × 10^9/L, platelet count ≥ 100 × 10^9/L, creatinine ≤ 1.5 mg/dL and GFR of ≥ 60 mL/min, bilirubin ≤ 1.5 × ULN, AST and ALT ≤ 2.5 × ULN or ≤ 5 × ULN in the presence of liver metastases, serum albumin ≥ 3 g/dL
6. ECOG performance status of 0 to 2

SELECTED EXCLUSION CRITERIA

1. Prior chemotherapy for limited or extensive-stage SCLC
2. Symptomatic brain metastases requiring immediate treatment
3. Concurrent radiotherapy to any site or radiotherapy within 2 weeks prior to enrollment
4. Significant cardiac or cerebrovascular disease
5. Receipt of any investigational medication within 4 weeks prior to enrollment

ASSESSMENTS

- Patients assessed for safety continuously
- Tumor response after every even cycle until disease progression
- Hematology assessments at screening, days 1, 3, 8, 10, 15 of each cycle, the Post-Treatment Visit, and 60 days after last dose

TRILACICLIB DOSE SELECTION CRITERIA FOR PART 2

- Selection of the RP2D was based on available pharmacokinetics (PK) and safety data
- Safety data included evaluation of cycle 1 toxicities as defined below:
  - ANC < 0.5 × 10^9/L for ≥ 7 days
  - ≥ Grade 3 febrile neutropenia/infection
  - Grade 4 thrombocytopenia or ≥ Grade 3 thrombocytopenia with bleeding
  - Unable to start next cycle of chemotherapy due to lack of recovery to an ANC ≥ 1.5 × 10^9/L and platelet count ≥ 100 × 10^9/L
  - ≥ Grade 3 nonhematologic toxicity

RESULTS

TABLE 1. SUMMARY OF STUDY DISPOSITION

	200 mg/m^2 (n=10)	240 mg/m^2 (n=9)
Patients screened, n	12	10
Patients enrolled, n	10	9
Safety population, n (%)[1]	10 (100)	9 (100)
Efficacy population, n (%)[2]	8 (80)	9 (100)
Patients discontinued study medication, n (%)		
Disease progression	1 (10)	2 (22)
Completed treatment (4-6 cycles)	6 (60)	6 (67)
Adverse event[3]	2 (20)	0
Other	1 (10)[4]	1 (11)[4]
Number of patients who died, n (%)	7 (70)	2 (22)
Reason for death, n (%)		
Lung cancer	7 (70)	2 (22)
Patients in survival follow-up, n (%)	3 (30)	7 (78)

[1] The safety population is defined as patients who received at least one dose of trilaciclib.

[2] The efficacy population is defined as patients who had at least one post-baseline tumor assessment, or had clinical progression before the first post-baseline scan.

[3] Adverse events were unrelated to trilaciclib.

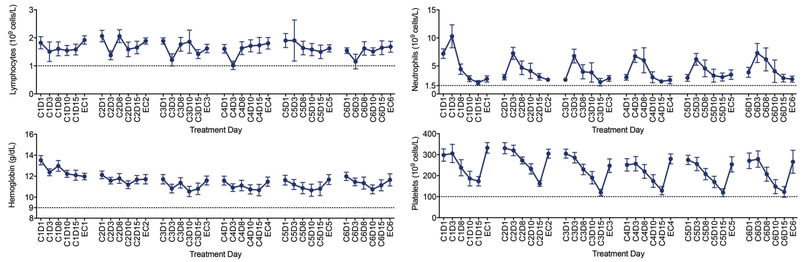
[4] One patient decided to go to hospice and the second patient completed 6 cycles of chemotherapy with the reason for discontinuation selected as "other", which is being queried.

TABLE 2. BASELINE PATIENT AND DISEASE CHARACTERISTICS FOR ENROLLED PATIENTS

	200 mg/m^2 (n=10)	240 mg/m^2 (n=9)
Age, years median (range)	73.5 (45-80)	61 (51-76)
Gender, n (%)		
Male	4 (40)	7 (78)
Female	6 (60)	2 (22)
Race, n (%)		
White	8 (80)	8 (89)
African-American	2 (20)	1 (11)
Ethnicity, n (%)		
Not Hispanic or Latino	9 (90)	9 (100)
Hispanic or Latino	1 (10)	0
ECOG Performance Status, n (%)		
0	2 (20)	5 (56)
1	7 (70)	4 (44)
2	1 (10)	0
History of Brain Metastasis, n (%)		
No	8 (80)	8 (89)
Yes	2 (20)	1 (11)

Abbreviations: ECOG, Eastern Cooperative Oncology Group.

FIGURE 2. HEMATOLOGY ASSESSMENTS



Data shown are from patients enrolled in the 240 mg/m^2 cohort (n=9). Mean blood counts with standard error of the mean are shown.
Abbreviations: C, cycle; D, day; EC, end of cycle.
Dotted horizontal lines represent clinically relevant thresholds of hematological toxicity.

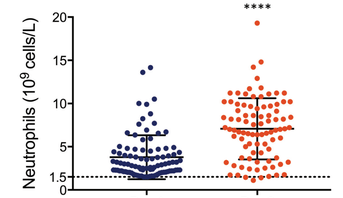
TABLE 3. GRADE 3/4 TREATMENT-EMERGENT ADVERSE EVENTS BY DOSE LEVEL*

Event	200 mg/m^2 (n=10)		240 mg/m^2 (n=9)	
	Grade 3	Grade 4	Grade 3	Grade 4
Blood and Lymphatic System Disorders				
Anemia	4 (40)	0	1 (11)	0
Neutropenia	1 (10)	4 (40)	1 (11)	0
Thrombocytopenia	0	1 (10)	0	1 (11)
Investigations				
Lymphocyte decrease	2 (20)	1 (10)	0	0
White blood cell decrease	3 (30)	1 (10)	0	0
Infections and Infestations				
Pneumonia	1 (10)	0	1 (11)	0
Metabolism and Nutrition Disorders				
Dehydration	1 (10)	0	1 (11)	0
Hyponatremia	1 (10)	0	1 (11)	0

*Toxicities were graded using NCI CTCAE (Common Terminology Criteria for Adverse Events), Version 4.03. Treatment-emergent Adverse Events Reported in ≥ 10% of Patients in the Total Group by Preferred Term are shown.

- Grade 3/4 hematologic toxicities were the most common toxicities observed, and may be overrepresented due to observation bias as a result of frequent hematologic monitoring
- There were no occurrences of febrile neutropenia, Grade 4 neutropenia lasting ≥ 7 days, or thrombocytopenia related bleeding
- Fewer Grade 3/4 hematological toxicities were reported in the trilaciclib 240 mg/m^2 cohort

FIGURE 3. TIMING OF NEUTROPHIL COUNT RECOVERY



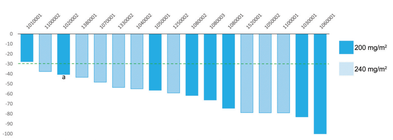
Individual neutrophil counts from Days 1 and 3 for all patients/all cycles are shown. Mean neutrophils counts were significantly higher on Day 3 compared to Day 1 (7.07 ± 3.54, n=89 versus 3.78 ± 2.54; n=94; **** p<0.0001). Statistics evaluated using two-sided t-test.

- Assessment of neutrophil count recovery revealed:
  - ANC values do not peak on Day 1 of each cycle, but continue to recover into the next cycle
  - Based on the kinetics of ANC recovery observed in Part 1, it may be reasonable to consider an ANC threshold of 1.0 X 10^9 cells/L to start the next cycle for future studies

SELECTION OF TRILACICLIB RP2D

- Three patients experienced protocol defined cycle 1 toxicities and were asymptomatic
  - Cohort 1 (trilaciclib 200 mg/m^2)
    - ANC of 1.2 X 10^9/L on planned Cycle 2, Day 1; Cycle 2 delayed 1 day
    - Grade 4 thrombocytopenia (platelets 24 X 10^9/L and extensive bone disease that may have compromised bone marrow function); Cycle 2 started on time
  - Cohort 2 (trilaciclib 240 mg/m^2)
    - ANC of 1.2 X 10^9/L on planned Cycle 2, Day 1; Cycle 2 delayed 1 day
- Based on the dose-dependent reduction in Grade 3/4 hematologic toxicities, improved blood cell counts, and PK,[9,10] trilaciclib 240 mg/m^2 was chosen as the RP2D

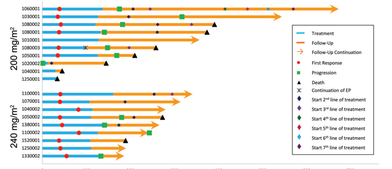
FIGURE 4. BEST CHANGE IN TUMOR SIZE FROM BASELINE



[a] Target lesion change consistent with PR at cycle 2; best response was PD due to occurrence of new lesions at cycle 2

- Of the 17 patients in the efficacy population, 1 patient had a confirmed CR and 14 patients had a confirmed partial response (PR)
- Objective response rate (ORR; CR+PR) was 88% across the two cohorts

FIGURE 5. TIME TO AND DURATION OF RESPONSE



Swimmer plots show time to first response and duration of response (in accordance with Response Evaluation Criteria in Solid Tumors version 1.1)

CONCLUSIONS

- In the Phase 1b part of the study, the combination of trilaciclib with EP was well tolerated, with no episodes of febrile neutropenia or treatment-related SAEs
- Neutrophil count recovery appears to continue up to day 3 of the subsequent cycle, likely due to the G_1 cell cycle arrest of HSPCs during the 3 days of trilaciclib administration
- Fewer Grade 3/4 hematologic TEAEs were reported at the trilaciclib 240 mg/m^2 dose, suggesting a dose response effect in decreasing hematologic toxicities
- Anti-tumor activity in the Phase 1b portion of this study are promising with 15 of 17 evaluable patients responding to therapy (CR or PR; 88% ORR)
- These results support the hypothesis that trilaciclib will ameliorate the significant acute and long-term consequences of chemotherapy-induced myelosuppression by preserving hematopoietic and immune system function
- Based on these results, the randomized part of the study is ongoing with the RP2D of 240 mg/m^2 (NCT02499770)

OTHER ONGOING TRILACICLIB TRIALS

1. SCLC: second/third line with topotecan (NCT02514447)
2. mTNBC: first/second line with gemcitabine/carboplatin (NCT02978716)
3. SCLC: first line with carboplatin/etoposide/atezolizumab (NCT03041311)

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