#4286

A Phase 1 Study of the Oral CDK9 Inhibitor Voruciclib in Relapsed/Refractory (R/R) B-cell Lymphoma (NHL) or Acute Myeloid Leukemia (AML)

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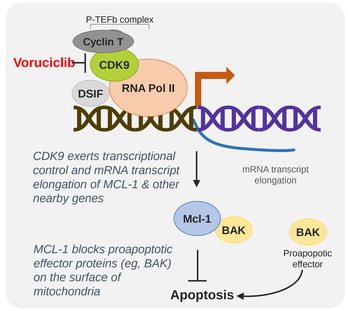
BACKGROUND

BCL-2

- BCL-2 inhibitor venetoclax is approved in CLL and unfit/elderly patients with AML
- Resistance to therapy occurs, including from MCL-1 overexpression

MCL-1

- Dependence on MCL-1 is associated with poor prognosis in AML and CLL, and with resistance to venetoclax
- Direct inhibition of MCL-1 has been associated with cardiotoxicity



CDK9

- MCL-1 expression is regulated by CDK9, and CDK9 inhibition can be an alternative approach to MCL-1 suppression
- CDK9 facilitates transcriptional activation and mRNA transcript elongation of MCL-1 and other genes through phosphorylation of RNA polymerase and proteins mediating promotor proximal pausing (Figure)

VORUCICLIB

- Oral CDK inhibitor with higher affinity (Ki <2 nM) and longer residence time on CDK9 compared to other CDKs
- Indirectly suppresses MCL-1[1]
- Elicits proapoptotic effects in AML, CLL and DLBCL cells[1-4]
- Combination of voruciclib and venetoclax shows synergy for cell apoptosis and improves survival in AML and DLBCL murine models[3,4]
- Phase 1 dose-escalation studies in patients with solid tumors have identified MTD at 350 mg on continuous daily dosing and 600 mg when administered on days 1-14 in a 21-day cycle[5,6]

STUDY OBJECTIVE

To evaluate the safety, dose-limiting toxicities (DLT), preliminary efficacy, pharmacokinetics, and pharmacodynamics of voruciclib in R/R AML and B-cell malignancies

METHODS

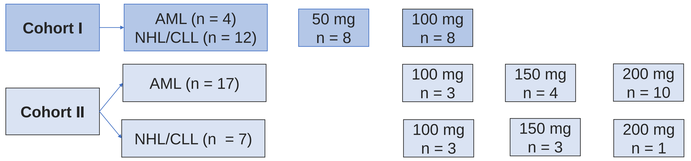
- **Eligibility**: Age ≥18 years, relapsed B-cell NHL, CLL, or AML, ECOG performance status ≤1, disease progression after failure of standard therapies, adequate organ function, and no prior CDK9 inhibitors
- **Design:** 3+3 dose escalation with DLTs assessed in Cycle 1 (28 days)
- **Schedule**
  - Cohort I: Once daily continuously in a 28-day cycle
  - Cohort II: Intermittent schedule (IS) on days 1-14 in a 28-day cycle implemented when 2 DLTs were observed at 100 mg daily continuously
- **Doses**
  - Cohort I: 50 and 100 mg; patients with AML and B-NHL enrolled in the same group at each dose level
  - Cohort II: 100, 150, and 200 mg; patients with AML and B-NHL enrolled in separate groups at each dose level
- **Disease response assessment:** Lugano criteria for NHL, iwCLL for CLL, and 2017 ELN for AML
- Study registered at clinicaltrials.gov (NCT03547115)
- Analysis based on data cutoff of 1 May 2023

RESULTS

Patients and Disease Characteristics

- 40 patients enrolled
- Diagnosis: 21 AML, 9 DLBCL, 3 FL, 3 CLL, 3 MCL, 1 MZL
- Median age = 75 years (range 63-80)
- ECOG performance status of 1 in 78% of patients
- Median prior therapies = 3 (range 1-9)
  - 75% of patients had ≥3 prior lines of therapy
  - Prior hematopoietic stem cell transplant in 5 patients

Voruciclib Dose Levels



- Dose escalation in Cohort II stopped at 200 mg to focus on evaluation of venetoclax combination
- Median duration of exposure = 5 weeks (range 1-22)

Safety

Dose-Limiting Toxicities (DLT) and Maximum Tolerated Dose (MTD)

- Cohort I: 2 patients with AML at 100 mg had grade 3 hypoxia/interstitial pneumonitis; both had prior allogeneic HSCT and active GVHD, 1 of whom also had a grade 3 differentiation syndrome concurrent to the interstitial pneumonitis
- Cohort II: No DLTs, and MTD not identified

Adverse Events (AEs)

- Most common AEs, independent of relationship to study drug, shown in Table
- 1 patient with AML had grade 3 hyperbilirubinemia
- 1 of 19 patients (5%) with NHL/CLL had grade 3 thrombocytopenia; no grade 3 neutropenia
- No drug-related cardiovascular events

AEs in ≥15% of Patients in Overall Population

	Cohort I (n=16)			Cohort II (n=24)			Total (N=40)
Event, n (%)	Grade 1-2	Grade 3-4	All Grades	Grade 1-2	Grade 3-4	All Grades	All Grades
Diarrhea	3 (19)	0	3 (19)	8 (33)	1 (4)	9 (38)	12 (30)
Nausea	3 (19)	0	3 (19)	7 (29)	0	7 (29)	10 (25)
Anemia	0	2 (13)	2 (13)	2 (8)	5 (21)	7 (29)	9 (23)
Fatigue	2 (13)	0	2 (13)	7 (29)	0	7 (29)	9 (23)
Constipation	2 (13)	0	2 (13)	5 (21)	0	5 (21)	7 (18)
Decreased appetite	0	0	0	7 (29)	0	7 (29)	7 (18)
Dizziness	2 (13)	0	2 (13)	4 (17)	0	4 (17)	6 (15)
Dyspnea	1 (6)	1 (6)	2 (13)	4 (17)	0	4 (17)	6 (15)

Safety (cont.)

- 9 patients (22.5%) discontinued voruciclib due to an AE
  - 3 had AEs related to voruciclib (1 acute respiratory failure, 1 interstitial lung disease, and 1 pneumonitis), all in Cohort I
  - 6 had AEs related to underlying disease
- 7 patients (17.5%) had AEs resulting in death
  - 6 related to underlying disease
  - 1 due to a new malignancy

Efficacy

AML (n = 21)

- 1 patient (5%) at 100 mg achieved a morphologic leukemia-free state
  - 81 yo female with adverse risk AML, TP53 and NPM1 mutation, enrolled in the study after failure of 4 prior lines of therapy
- 9 patients had disease stabilization, which lasted ≥3 months in 2 and qualified as stable disease by ELN 2017

B-cell malignancies (n = 19)

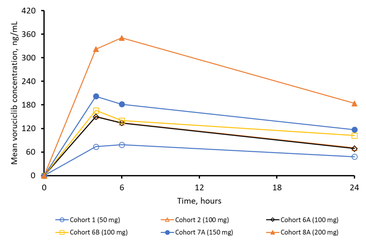
- No objective responses observed
- 4 patients had stable disease (SD) with reduction in SPD (Table)

Change in SPD in Patients with B-cell Malignancies with SD

Diagnosis	No. of Prior Therapies	Therapy Duration (weeks)	Baseline SPD (cm^2)	Change SPD (%)
FL	2	18	49.8	-49%
DLBCL	3	16	14.5	-28%
CLL	5	22	74.5	-7%
MZL	4	22	28.4	-4%

Pharmacokinetics

- Dose proportional PK across range studied (Figure)
- Mean half-life ~24 hours supports once daily dosing



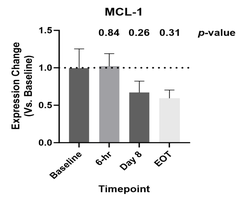
Voruciclib + Venetoclax Combination

- Enrolling in a study arm evaluating voruciclib in combination with venetoclax in patients with R/R AML
- Voruciclib doses from 50 mg to 200 mg evaluated as of November 2023 and dose escalation continuing
- No DLTs reported to date
- No evidence of overlapping toxicity
- Anti-tumor activity demonstrated by objective responses, reduction in transfusions, and some patients with therapy for 4+ months

Correlative Studies

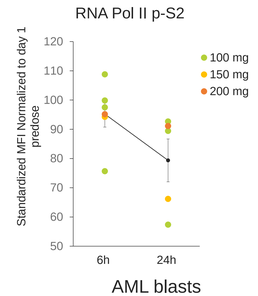
- Correlative assays to assess voruciclib effect on pharmacodynamic biomarkers are in development and being optimized
- Initial results in a limited number of patients indicate on-target effects
- Longitudinal transcriptomic analysis by RNA-Seq of sequential blood samples from 3 CLL patients shows a trend towards reduced Mcl-1 mRNA after voruciclib treatment (panel A)
- Analysis of RNA Pol II phosphorylation on Ser2 of the CTD repeat in AML blasts by flow cytometry showed a significant ($p = 0.043$) decrease in phosphorylation in on-treatment samples compared to pre-treatment (panel B). Data is normalized to pre-dose values

A



CLL (PBMCs)
N = 3

B



AML blasts
N = 5

CONCLUSIONS

- Voruciclib at doses up to 200 mg administered on 14 consecutive days in a 28-day cycle (Cohort II) was well tolerated, with no DLTs reported
- No significant myelosuppression seen in patients with B-cell malignancies, consistent with 3 prior phase 1 studies in solid tumors
- Disease stabilization was observed in heavily pretreated patients and differentiation syndrome was observed in AML indicating biologic activity
- As the safety profile suggested non-overlapping toxicities with venetoclax, the study is now evaluating voruciclib in combination with venetoclax in patients with R/R AML to exploit dual inhibition of Bcl-2 and Mcl-1

Acknowledgments

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