A Phase 1 Dose-Escalation Study of the Oral CDK Inhibitor Voruciclib in Patients with Relapsed/Refractory B-Cell Malignancies or Acute Myeloid Leukemia (AML): Preliminary Results of the Completed Dose Escalation Stage in AML

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BACKGROUND

- Voruciclib is a potent oral cyclin-dependent kinase-9 (CDK9) inhibitor (Ki <10 nM) that indirectly suppresses the function of the pro-survival Mcl-1 protein[1,2]
- Dependence on Mcl-1 is associated with poor prognosis in various malignancies[3], and increased Mcl-1 levels is a common mechanism of resistance to venetoclax[4]
- Through transcriptional repression of Mcl-1, voruciclib elicits proapoptotic effects in chronic lymphocytic leukemia (CLL) and AML cells; combination of voruciclib with venetoclax has shown synergistic induction of apoptosis[2,5]
- In dose-escalation phase 1 studies of voruciclib in patients with solid tumors, the MTD was established at 350 mg when administered daily continuously and at 600 mg when administered on days 1-14 in a 21-day cycle[6,7]
- Based on concentrations needed for antitumoral activity in preclinical models and PK results in the prior phase 1 studies, we predict a dose of ~200 mg administered on 14 consecutive days in a 28-day cycle would be sufficient to achieve target inhibition[8]
- This phase 1 study was the first to evaluate voruciclib in hematologic malignancies

OBJECTIVES

The study will evaluate voruciclib

- Maximum tolerated dose (MTD)
- Recommended Phase 2 dose (RP2D)
- Dose-limiting toxicities (DLT)
- Safety
- Pharmacokinetics (PK)
- Preliminary efficacy

METHODS

- Patients with relapsed B-cell lymphoma, CLL, or AML were eligible if age ≥18 years, ECOG performance status ≤1, disease progression after failure of standard therapies, adequate organ function, and no prior CDK9 therapy
- Dose escalation started at 50 mg, followed a 3+3 design, and DLTs were assessed in Cycle 1 (28 days)
- Initially voruciclib was administered once daily continuously in a 28-day cycle (Group I)
- After 2 DLTs were observed at 100 mg daily, administration was changed to once daily on days 1 to 14 in a 28-day cycle (Group II). Patients with prior allogeneic transplant were excluded, and dose escalation (100, 150, 200 mg) proceeded in separate cohorts for AML and B-cell malignancies
- Disease response was assessed according to the criteria of Lugano for B-cell lymphoma, iwCLL for CLL, 2017 ELN for AML
- This trial is registered at clinicaltrials.gov (NCT03547115)
- Data cutoff date: October 1, 2021

RESULTS

Patients

- To date 29 patients have been enrolled: 15 AML, 7 diffuse large B-cell lymphoma (DLBCL), 3 follicular lymphoma (FL), 2 CLL and 2 mantle cell lymphoma
- Median age was 70 years (range 40-90) and 59% of patients were male (**Table 1**)
- Patients were generally heavily pretreated, with a median of 3 prior therapies (range 1-8)
- Of the 15 patients with AML, ELN Genetic Risk criteria were adverse in 9 (60%), intermediate in 4 (27%) and not reported in 2 (13%)
- Dose escalation in AML is complete

Table 1. Demographics and Patient Characteristics

	Group I		Group II				
	50 mg B-cell (n=8)	100 mg Mixed (n=8)	100 mg B-cell (n=2)	100 mg AML (n=3)	150 mg AML (n=4)	200 mg AML (n=4)	Total (N=29)
Median age, y (range)	77.0 (53-90)	70.0 (40-84)	70.5 (68-73)	71.0 (61-72)	77.5 (65-83)	60.5 (57-70)	70.0 (40-90)
Males, n (%)	4 (50)	2 (25)	2 (100)	3 (100)	3 (75)	3 (75)	17 (59)
ECOG PS, n (%)							
0	1 (13)	3 (38)	1 (50)	0	1 (25)	1 (25)	7 (24)
1	7 (88)	5 (63)	1 (50)	3 (100)	3 (75)	3 (75)	22 (76)
Prior anti-cancer therapies, n (%)							
1-2	1 (13)	2 (25)	1 (50)	0	1 (25)	2 (50)	7 (24)
≥3	7 (88)	6 (75)	1 (50)	3 (100)	3 (75)	2 (50)	22 (76)
Prior SCT, n (%)	1 (13)	3 (38)	0	1 (33)	0	0	5 (17)

Pharmacokinetics

- Dose proportional PK in the dose range studied of 50–200 mg
- Mean accumulation ratio of ~2.1 for C_{max} and ~2.4 for AUC, indicating doubling of plasma exposure at steady state; this is consistent with PK data from prior Phase 1 studies that showed a mean $t_{1/2}$ of ~24 hours
- Mean steady state C_{max} at 200 mg corresponds to a concentration of ~1.4 μM, the desired value for target inhibition based on non-clinical studies

Safety

- Median duration of exposure = 5.4 weeks (range, 0.9–27.0)

Dose-Limiting Toxicities

- Group I: 3 DLTs (differentiation syndrome, interstitial lung disease, pneumonitis) occurred in 2 AML patients at 100 mg daily. Both patients had been treated with allogeneic transplant complicated by GVHD in the preceding 12 months
- Group II: No DLTs reported

Safety (cont.)

Treatment-Related Adverse Events (AEs)

- The incidence of treatment-related AEs was low (Table 2)

Table 2. Treatment-Related AEs of Any Grade in >5% of All Patients

n (%)	Group I (n=16)	Group II (n=13)	Total (N=29)
Any related adverse event	9 (56.3)	4 (30.8)	13 (44.8)
Fatigue	0	3 (23.1)	3 (10.3)
Nausea	1 (6.3)	2 (15.4)	3 (10.3)
Diarrhea	2 (12.5)	0	2 (6.9)
Vomiting	1 (6.3)	1 (7.7)	2 (6.9)

- Grade 3-4 treatment-related AEs in Group I were primarily pulmonary and affected 3 patients (Table 3)
- No non-hematologic Grade 3-4 toxicities reported in Group II
- The 4-week mortality was 17% (4 in Group I and 1 in Group II), all associated with disease progression
- No evidence of drug-related neutropenia in patients with B-cell malignancies (Group I and II)
- No tumor lysis syndrome reported

Table 3. Grade 3-4 Treatment-Related Adverse Events*

	Group I (n=16)		Group II (n=13)		Total (N=29)	
n (%)	Gr 3	Gr 4	Gr 3	Gr 4	Gr 3	Gr 4
Acute respiratory failure	0	1 (6.3)	0	0	0	1 (3.4)
Dyspnea exertional	0	1 (6.3)	0	0	0	1 (3.4)
Respiratory failure	0	1 (6.3)	0	0	0	1 (3.4)
Hypoxia	1 (6.3)	0	0	0	1 (3.4)	0
Interstitial lung disease	1 (6.3)	0	0	0	1 (3.4)	0
Pneumonitis	1 (6.3)	0	0	0	1 (3.4)	0
AML differentiation syndrome	1 (6.3)	0	0	0	1 (3.4)	0
Lymphocyte count decreased	1 (6.3)	0	0	0	1 (3.4)	0
Malignant pleural effusion	1 (6.3)	0	0	0	1 (3.4)	0
Neutropenia	0	0	0	1 (7.7)	0	1 (3.4)
Thrombocytopenia	0	0	0	1 (7.7)	0	1 (3.4)
Anemia	0	0	1 (7.7)	0	1 (3.4)	0

* A patient may have ≥1 AE reported

Efficacy

- Among AML patients:
  - 1 (100 mg Group I) achieved a morphologic leukemia-free state
  - 2 (100 mg and 150 mg Group II) achieved stable disease (SD)
- 3 patients with B-cell lymphoma (2 FL, 1 DLBCL) had a best response of SD, including 1 FL patient who achieved a 42% reduction in the sum of the product of longest perpendicular diameters (SPD) lasting 18 weeks
- 1 CLL patient with relapsed disease after chemoimmuno-therapy, venetoclax, and ibrutinib, achieved SD on voruciclib lasting 27 weeks

CONCLUSIONS

- Voruciclib at doses up to 200 mg administered on 14 consecutive days in a 28-day cycle (Group II) was well tolerated, with no DLTs reported
- Consistent with the phase 1 studies in solid tumors, no significant myelosuppression was seen in patients with B-cell malignancies
- The safety profile does not indicate overlapping toxicities with venetoclax
- Disease stabilization was observed in heavily pretreated patients and differentiation syndrome was observed in AML indicating biologic activity
- Enrollment at 200 mg in Group II is ongoing in an expansion cohort in AML
- Dose escalation is ongoing in the B-cell malignancy cohort
- A forthcoming protocol amendment will evaluate voruciclib in combination with venetoclax in patients with relapsed AML to exploit the dual inhibition of Bcl-2 and Mcl-1

Acknowledgments: We extend our thanks to the patients, their families, and the investigators and their staff members who are making this trial possible. Editorial support was provided by Ingrid Koo, PhD. This study is supported by MEI Pharma, Inc.

References
1. Paiva et al. PLoS One. 2015;10:1-16
2. Luedtke et al. Signal Transduct Ther. 2020;5(1):17
3. Li et al. Onco Targets Ther. 2019;12:3295-3304
4. Bhatt et al. Cancer Cell. 2020;38(6):872-890.e6
5. Lesnick et al. J Clin Oncol. 2020;38(15_suppl):e20009
6. Hao et al. J Clin Oncol. 2012;30:3013
7. Gupta et al. J Clin Oncol. 2012;30:3011
8. MEI Pharma, data on file.