Phase 1 study of CB-839, a first-in-class, orally administered small molecule inhibitor of glutaminase in patients with relapsed/refractory leukemia

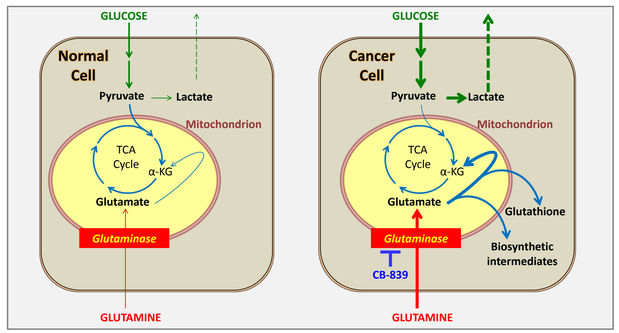
Wang ES[1], Frankfurt O[2], Orford KW[3], Bennett MK[3], Flinn IW[4], Maris MB[5], and Konopleva MY[6]

[1]Dept of Medicine, Roswell Park Cancer Institute, Buffalo, NY, [2]Dept of Medicine-Hematology/Oncology, Northwestern University Feinberg School of Medicine, Chicago, IL, [3]Calithera Biosciences, Inc., South San Francisco, CA,
[4]Hematologic Malignancies Research Program, Sarah Cannon Research Institute, Nashville, TN, [5]Colorado Blood Cancer Institute, Denver, CO, [6]Department of Leukemia, Division of Cancer Medicine, MD Anderson Cancer Center, Houston, TX

BACKGROUND AND RATIONALE

- Glutamine is required for the growth and survival of many tumor types[1,2]
- Glutaminase (GLS) controls the formation of glutamate (Figure 1), which is used to generate TCA cycle intermediates, synthesize glutathione, generate NADPH and maintain redox balance, and synthesize anabolic building blocks, including nucleotides and fatty acids
- CB-839 is a highly selective, reversible, allosteric inhibitor of glutaminase[3]
- CB-839 has broad preclinical *in vitro* and *in vivo* anti-tumor activity in solid and hematologic malignancies[3,4,5,6]
- Herein we describe the initial results from CX-839-003 (ClinicalTrials.gov Identifier: NCT02071927), a phase 1 study of CB-839 in relapsed/refractory leukemia patients

Figure 1: Altered Glucose and Glutamine Metabolism of Cancer Cells

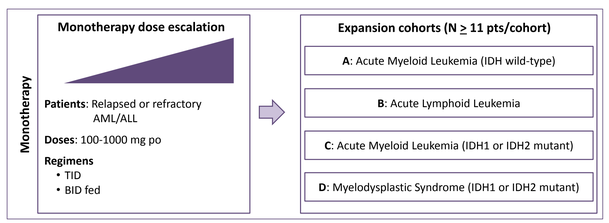


METHODS

Study Design

- Phase 1 multicenter, open-label, dose-escalation of CB-839 as a single-agent in AML/ALL
- Accelerated titration dose escalation design with three week cycle length
  - Pharmacodynamic assessments include assessment of GLS inhibition
  - Bone marrow evaluations after first and second cycle, then every three cycles
- Expansion Cohorts are planned in defined patient populations (see Figure 2)

Figure 2: CX-839-003 Study Design



Key Inclusion Criteria

- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0-2
- All patients must have bone marrow involvement of their tumor, with documented blast percentage of > 5%

Key Exclusion Criteria

- Patients with acute promyelocytic leukemia (APL)
- Newly diagnosed patients with favorable cytogenetic abnormalities
- Allogeneic hematopoietic stem cell transplant (HSCT) or Donor Lymphocyte Infusion (DLI) within 90 days prior to Day 1

Study Treatment

- Oral CB-839 administered in 21-day cycles using one of two regimens:
  - **TID**: Three times daily (upon waking, at ~3 pm and at bedtime)
  - **BID fed**: Two times daily with meals

METHODS – cont.

Pharmacokinetics (PK), Pharmacodynamics (PDn) and Efficacy Assessments

- PK: Serum CB-839 measured on Cycle 1/Day 1 (C1D1), C1D15 and D1 of each cycle
- PDn: Blood draws for collection of platelets/PBMCs on C1D1 predose and at 4 hr
  - PDn data were analyzed together with PDn data from parallel Phase 1 study in solid tumors (Study CX-839-001[7])
- Efficacy: Bone marrow evaluations were performed at baseline and on C2D1, C3D1, and after every third cycle thereafter

STUDY STATUS

- 26 patients have been treated and have data in the clinical database (as of Nov 9, 2015)
- An MTD has not been established (no DLTs on study)
- 600 mg po BID fed was selected for expansion cohorts based on results from this study and a concurrent larger Ph1 solid tumor study (CX-839-001[7,8]; N=59):
  - PK consistently above target threshold
  - Clear PK/PDn relationship in peripheral blood (platelets and PBMCs)
  - Evidence of pharmacodynamic activity in solid tumor biopsies
  - Reduced incidence of liver function abnormalities with BID dosing (see Table 4 below)

Table 1: Enrollment Summary

TID: N=16 (14 AML , 1 B-ALL , 1 Mixed)	
Dose level	**#**
100 mg	1
200 mg	1
400 mg	1
600 mg	8
800 mg	3
1000 mg	2
BID fed: N=10 (AML only)	
Dose Level	**#**
600 mg	10

Table 2: Baseline Characteristics

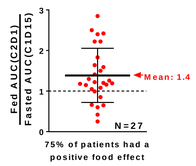
Characteristic		N=26
Age: median (range)		75 (35 — 86)
Female/Male: N (%)		14 (54%)/12 (46%)
Number of lines of prior systemic therapy	Median (range)	2.5 (0 — 7)
	2-3 regimens: N (%)	10 (38%)
	≥4 regimens: N (%)	6 (23%)
Prior transplant: N (%)	Allogeneic	6 (23%)
	Autologous	0
ECOG Score: N (%)	1	17 (65%)
	2	6 (23%)

PHARMACOKINETICS

- CB-839 PK was evaluated most extensively in parallel Ph1 solid tumor study[7,8]
- CB-839 has good PK properties in cancer patients
  - Half-life ~4 hr
  - Exposure generally increases with dose
- Dosing with food enabled switch to BID dosing regimen
  - Increased exposure with fed regimen (Figures 3)[8]
  - Similar C_{max} and C_{min} with BID fed vs. TID regimen (Table 3)
  - AML patients receiving 600mg BID fed also had a similar or higher exposure than AML patients receiving 600mg TID (Table 3)

Figure 3: Increase in Exposure with Food (from CX-839-001 solid tumor study[8])

Steady State Fed vs Fasted AUC on TID Schedule



First Dose Fed vs Fasted at 600 mg

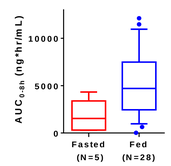


Table 3: PK Parameters on Fed vs Fasted Schedules

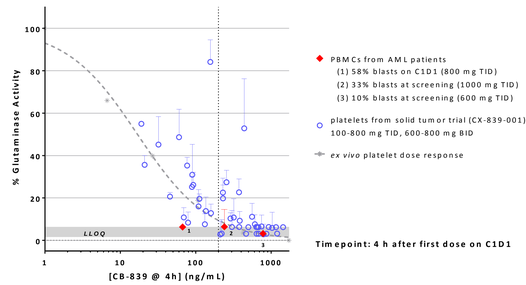
Study	Dosing Regimen	Daily dose (mg)	Dosing interval (hr)	C1D15 PK Parameter: Mean (±SD) C_{min} (ng/mL)	C_{max} (ng/mL)	AUC_{0-8h} (ng*hr/mL)*
CX-839-001 (solid tumor)	600 mg BID fed (N=23)	1200	~12	457 (±335)	1476 (±676)	7416 (±3757)
	600 mg TID (N=5)	1800	~8	495 (±390)	1565 (±922)	7344 (±4058)
CX-839-003	600 mg BID fed (N=5)	1200	~12	1142 (±548)	2900 (±1331)	15322 (±5462)
	600 mg TID (N=7)	1800	~8	428 (±222)	1567 (±503)	7316 (±3093)

*Note: AUC_{0-8h} does not fully cover dosing interval on BID schedule

PHARMACODYNAMICS

- Strong inhibition of GLS was demonstrated in PBMCs and platelets in data from Phase 1 studies (CX-839-003 and CX-839-001[7])(Figure 4)
  - A clear exposure-response relationship is evident in platelets
  - C_{min} concentrations with 600 mg BID fed regimen maintain exposures that should provide ≥90% inhibition of GLS (≥ 200 ng/mL)

Figure 4: Platelet and PBMC Pharmacodynamics



SAFETY AND TOLERABILITY

- The most frequent adverse events (AEs) were Gr1/2 events and included transaminitis, thrombocytopenia, gastrointestinal events, and fatigue (Table 4).
- 34.6% (9/26) of patients experienced a Gr3 AE suspected to be at least possibly related to CB-839 (Table 5)
  - The most frequent G3/4 events were hematologic cytopenias, events that were not frequently observed in solid tumor patients (CX-839-001)[8].
- No DLTs occurred and no patients discontinued due to an AE
- The frequency and severity of ALT elevations is reduced when CB-839 is dosed BID with food

Table 4: All Adverse Events in ≥ 6 Patients (comparison with CX-839-001 study)

Monotherapy All AEs	CX-839-003 study all grades (N=26)		CX-839-001 study all grades (N=98)	
MedDRA Preferred Term	Total	Drug Related	Total	Drug Related
Patients with any AE	26 (100)	17 (65)	93 (95)	67 (68)
Alanine aminotransferase increased	8 (31)	7 (27)	16 (16)	14 (14)
Aspartate aminotransferase increased	7 (27)	7 (27)	14 (14)	13 (13)
Fatigue	7 (27)	2 (7.7)	34 (35)	24 (24)
Nausea	7 (27)	2 (7.7)	24 (24)	14 (14)
Thrombocytopenia	7 (27)	4 (15)	4 (4.1)	2 (2.0)
Gamma-glutamyltransferase increased	6 (23)	5 (19)	9 (9.2)	7 (7.1)
Hypokalemia	6 (23)	1 (3.8)	4 (4.1)	0
Vomiting	6 (23)	2 (7.7)	18 (18)	7 (7.1)

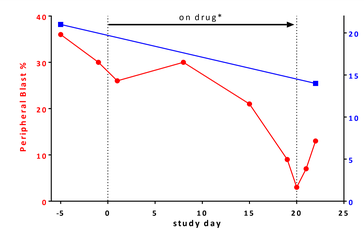
Table 5: All ≥Gr3 Adverse Events in ≥ 3 Patients (comparison with CX-839-001 study)

Monotherapy ≥Gr3 AEs	CX-839-003 study ≥Gr3 (N=26)		CX-839-001 study ≥Gr3 (N=98)	
MedDRA Preferred Term	Total	Drug Related	Total	Drug Related
Patients with any AE	22 (85)	9 (35)	33 (34)	10 (10)
Thrombocytopenia	7 (27)	4 (15)	0	0
Febrile neutropenia	5 (19)	0	0	0
Pneumonia	4 (15)	0	3 (3.1)	0
Anemia	3 (12)	3 (12)	3 (3.1)	0

CLINICAL OUTCOMES

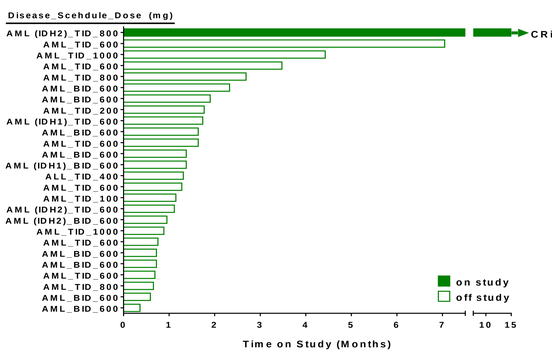
- Two patients with evidence of blast reductions
  - An IDH2-mutant AML patient achieved a Complete Response with incomplete recovery of peripheral counts (CRi) and remains on study (14+ months)
  - An IDH-wild type patient achieved a rapid reduction in peripheral blasts from 30% at baseline to 3% on Day 20 (Figure 5)
- 5 of 26 patients remained on study for at least 4 cycles (Figure 6)

Figure 5: Peripheral Blast Response



**subject discontinued due to CNS involvment*

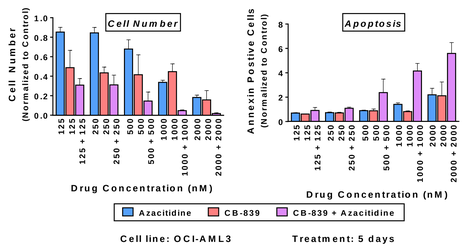
Figure 6: Treatment Duration



SUMMARY AND CONCLUSIONS

- **CB-839 is well tolerated in advanced leukemia patients**
- **Robust inhibition of GLS demonstrated in platelets and PBMCs**
- **Two patients achieved significant reductions in blast counts**
  - Includes one patient with a CRi that has been on study for >14 months
  - 4 additional patients remained on study for at least 4 cycles
- **Optimal PK and safety profile achieved with BID dosing with meals**
- **Future development of CB-839 in AML will include the combination with azacitidine**
  - Supported by preclinical combination activity in AML cell line (Figure 7)

Figure 7: Enhanced Anti-tumor Activity In Vitro With CB-839 + Azacitidine Combination



References

1. Wise and Thompson (2010) *Trends Biochem Sci* 35:427-433
2. DeBerardinis and Cheng (2010) *Oncogene* 29:313-324
3. Gross et al. (2014) *Mol Cancer Ther* 13:890-901
4. Parlati et al. (2014) *Blood* 124:4720
5. MacKinnon et al. (2014) *Blood* **124**:3429
6. Matre et al. (2014) *Blood* **124**:3763
7. Harding et al. (2015) *JCO* **33 (suppl):** abstract 2512
8. Meric-Bernstam et al. (2015) *AACR-NCI-EORTC Conference:* abstract C49

57th American Society of Hematology Annual Meeting & Exposition, December 5-8, 2015, Orlando, Florida