Phase 1 study of CB-839, a first-in-class, glutaminase inhibitor in patients with multiple myeloma and lymphoma

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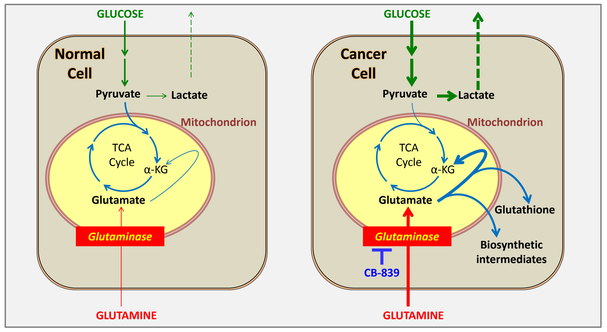
BACKGROUND AND RATIONALE

- Glutamine is required for the growth and survival of many tumor types[1,2]
- Glutaminase (GLS) controls the formation of glutamate , 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] preclinical studies demonstrate significant activity against multiple myeloma (MM) models as a monotherapy and in combination with pomalidomide
- CX-839-002 (ClinicalTrials.gov: NCT02071888) is a Phase 1 clinical trial of CB-839 in patients with multiple myeloma and other hematological tumors.

Altered Glucose and Glutamine Metabolism of Cancer Cells

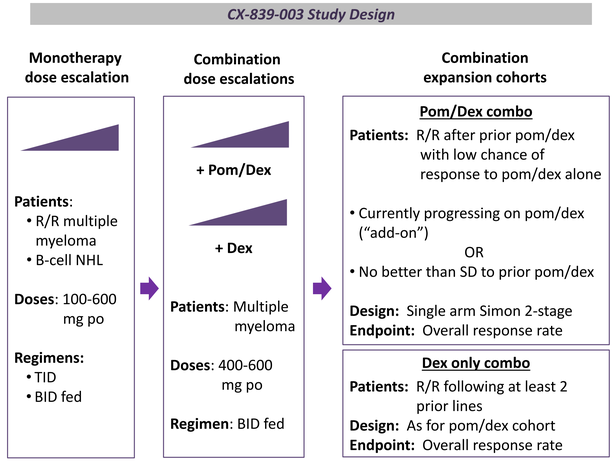


METHODS

Study Design

- Phase 1 dose escalation study of CB-839 in patients with multiple myeloma and other hematological tumors.
- Monotherapy: Accelerated titration dose escalation design with 3 week cycle length
- Combinations: standard 3+3 design with low-dose dexamethasone (see below) with or without standard pomalidomide regimen (4mg QD on 21 of 28 days)
- Expansion Cohorts planned in defined patient populations

CX-839-003 Study Design



METHODS (continued)

Key Inclusion Criteria

- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0-1
- Measurable disease

Key Exclusion Criteria

- Active GVHD, prior auto-SCT within 60 days or allo-SCT/DLI within 90 days
- Adequate renal function
  - NHL patients: CrCl ≥60 mL/min or serum creatinine <1.5x ULN
  - MM patients: CrCl ≥30 mL/min or serum creatinine <3x ULN
- Adequate hematological function
  - NHL patients: ANC ≥ 1000/mm^3, Hb ≥ 8g/dL, platelets ≥ 100,000/mm^3
  - MM patients: ANC ≥ 1000/mm^3, platelets ≥ 50,000/mm^3

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
- Combinations
  - Oral Dex dosed weekly (40mg for <75yo; 20mg for ≥75 yo) in 4 week cycle
  - Oral Pom (4mg) dosed daily for 3 weeks of each 4 week cycle

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

- PK: Serum CB-839 measured on Cycle 1/Day 1 (C1D1) and C1D15
- PDn: Blood draws for collection of platelets on C1D1 predose and at 4 hr
  - PDn data were analyzed together with PDn data from concurrent solid tumor Ph1 study (CX-839-001[7])
- Efficacy: Serum/urine M-protein and serum free light chain measured with each cycle. Bone marrow evaluated as clinically indicated

STUDY STATUS

- 23 patients (14 monotherapy, 9 combinations) had data in the clinical database (as of Nov 9, 2015)
- Cohort Status
  - Monotherapy cohort – COMPLETE
  - Dex alone combo cohort – ONGOING
  - Pom/Dex combo cohort – ONGOING
- An MTD has not been established for monotherapy or combinations
  - Monotherapy dose levels up to 800mg QD have been demonstrated to be safe and well tolerated

Enrollment Summary

002 Single Agent Cohorts (N=14)	
TID: N=11 (6 MM, 4 FL, 1 DLBCL)	
Dose level	**#**
100 mg	1
200 mg	1
250 mg	3
400 mg	6
BID fed: N=3 (MM only)	
Dose Level	#
600 mg	3

002 MM Combination Cohorts (N=9)	
CB-839 + Pom/ Dex	
CB-839 Dose	**#**
400 mg BID	4
CB-839 + Dex	
CB-839 Dose	**#**
400 mg BID	5

Baseline Characteristics

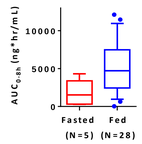
Characteristic		Monotherapy N=14	+Pom/Dex N=4	+Dex N=5
Age: median (range)		62 (45 — 84)	69 (32—72)	71 (64—74)
Female/Male: N (%)		6 (43%)/ 8 (57%)	2 (50%)/ 2 (50%)	3 (60%)/ 2 (40%)
Number of lines of prior systemic therapy	Median (range)	7 (2 — 16)	8 (2 — 15)	4 (3 — 8)
	4-10 regimens: N (%)	6 (43%)	1 (25%)	1 (20%)
	>10 regimens: N (%)	4 (29%)	2 (50%)	2 (40%)
ECOG ≥1: N (%)		8 (57%)	4 (100%)	4 (80%)

PHARMACOKINETICS

- CB-839 PK was evaluated most extensively in parallel Ph1 study (CX-839-001[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[8]
  - Similar C_{max} and C_{min} with BID fed vs. TID regimen
- Similar exposure was achieved in myeloma pts receiving 600mg BID fed (n=3)

Exposure with Food

First dose at 600 mg fed vs. fasted (from solid tumor study CX-839-001[7,8])



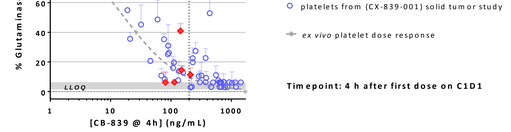
PK Parameters on Fed vs Fasted Schedules

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	600 mg TID (N=5)	1800	~8	495 (±390)	1565 (±922)	7344 (±4058)
	600 mg BID fed (N=23)	1200	~12	457 (±335)	1476 (±676)	7416 (±3757)
CX-839-002	600 mg BID fed (N=3)	1200	~12	725 (±590)	1559 (±960)	9970 (±6748)

PHARMACODYNAMICS

- Strong GLS inhibition was demonstrated in platelets in data from myeloma/lymphoma patients (CX-839-002) and solid tumor patents (CX-839-001[7,8])
  - GLS inhibition was measured in platelets 4 hr after dosing on C1D1
  - C_{min} concentrations with 600 mg BID fed regimen maintain exposures (≥ 200 ng/mL) that should provide ≥90% inhibition of GLS in most patients

Platelet and PBMC Pharmacodynamics



SAFETY AND TOLERABILITY

- Most AE's have been Gr1 events, including cytopenias, GI events, and fatigue.
- 21.4% (3/14) of pts experienced a total of 5 Gr3 AEs suspected to be related to CB-839
  - 4 of 5 Gr3/4 events were hematologic cytopenias (3 thrombocytopenia and 1 anemia), events that were not observed in the CX-839-001 solid tumor Ph1 study
- No patients discontinued due to an AE
- Development of Pom/Dex and Dex-only combinations are underway
  - One DLT of Gr4 neutropenia, which was considered possibly related to CB-839, has occurred in the Pom/Dex combination

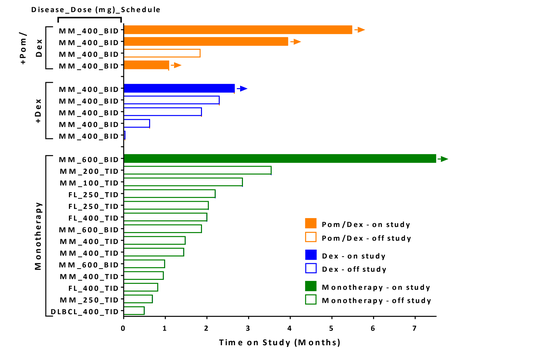
All Adverse Events in ≥ 3 Patients on Monotherapy

	All AEs (N=14)		≥Gr3 AEs (N=14)	
MedDRA Preferred Term	Total	Drug Related	Total	Drug Related
Patients with any AE	14 (100)	10 (71)	6 (43)	3 (21)
Anemia	5 (36)	2 (14)	3 (21)	1 (7.1)
Fatigue	5 (36)	4 (29)	1 (7.1)	0
Nausea	5 (36)	4 (29)	0	0
Thrombocytopenia	5 (36)	3 (21)	5 (36)	3 (21)
Vomiting	4 (29)	2 (14)	0	0
Constipation	3 (21)	1 (7.1)	0	0
Epistaxis	3 (21)	0	0	0
Headache	3 (21)	1 (7.1)	0	0
Myalgia	3 (21)	1 (7.1)	0	0

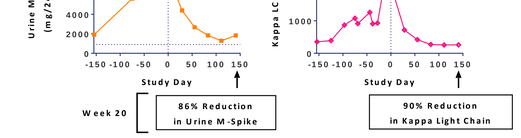
CLINICAL OUTCOMES

- In the monotherapy cohorts (n=14), best response was SD for 7 patients and PD for 6 patients.
- 3 of 14 monotherapy patients remained on study >3 months.
  - One patient on the 600mg BID fed regimen has remained on study for >7 months with stable disease.
- First patient to receive the Pom/Dex combination had a clinically significant reduction in myeloma markers, including serum free light chain and urine M-protein

Treatment Duration



Serum and Urine Markers Decrease in Patient Receiving Pom/Dex Combo



Myeloma labs in heavily pretreated patient with receiving CB-839 combined with Pom/Dex. 67 year-old male with long-standing IgG kappa light chain myeloma. Since diagnosis in 2008, the patient received 10 prior lines of therapy, including 3 proteasome inhibitor-containing lines and 2 "IMID"-containing lines. The disease became refractory to both lines of Imid-containing therapy. The patient had not received a prior pomalidomide-containing regimen.

SUMMARY AND CONCLUSIONS

- **Single agent CB-839 is well tolerated in advanced multiple myeloma and lymphoma patients**
  - Evaluation of safety and clinical efficacy in combination with pomalidomide/dexamethasone is ongoing
- **Robust inhibition of GLS is demonstrated in platelets**
- **BID dosing with meals provides optimal PK and safety profile**
- **Preliminary evidence of clinical activity was demonstrated in combination with pomalidomide/dexamethasone in a heavily pre-treated myeloma patient.**

REFERENCES

1. Wise and Thompson (2010) *Trends Biochem Sci* **35**:427
2. DeBerardinis and Cheng (2010) *Oncogene* **29**:313
3. Gross et al. (2014) *Mol Cancer Ther* **13**:890
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)**:abstr 2512
8. Meric-Bernstam et al. (2015) *AACR-NCI-EORTC Conference*; abstr: C49