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Poster Session

Preliminary evidence of clinical activity in a phase 1 study of CAL-101, a potent selective inhibitor of the p110δ isoform of phosphatidylinositol 3-kinase, in patients with B-cell malignancies

Ian W Flinn[1], John C Byrd[2], Richard R Furman[3], Jennifer R Brown[4], Thomas S Lin[2], Celeste M Bello[5], Neill A Giese[6], Albert S Yu[6]

[1]Sarah Cannon Research Institute, Nashville, TN, [2]The Ohio State University, Columbus, OH, [3]Weill Cornell Medical College, New York, NY, [4]Dana Farber Cancer Institute, Boston, MA, [5]Moffitt Cancer Center, Tampa, FL, [6]Calistoga Pharmaceuticals Inc, Seattle, WA

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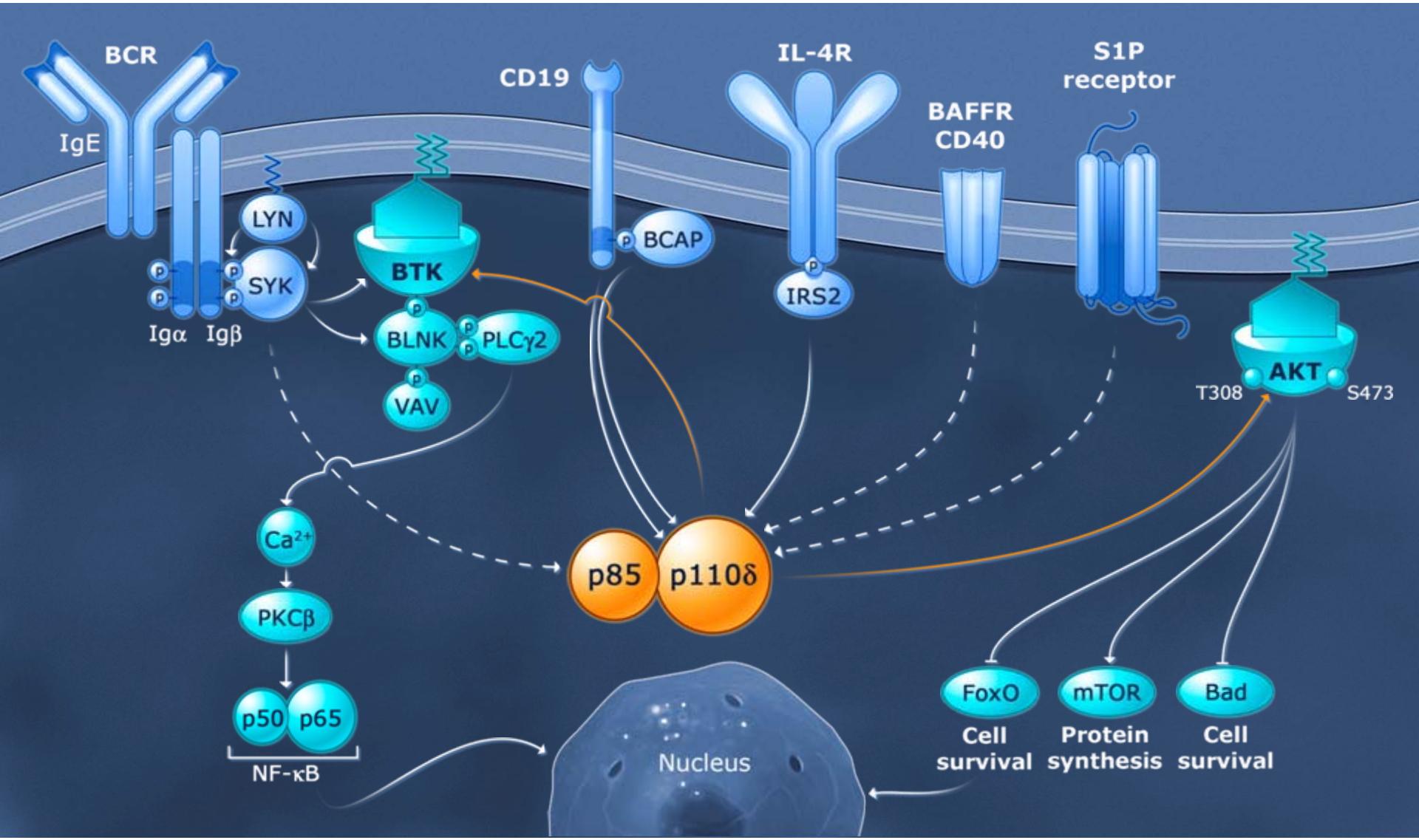
Background

The class I PI3Ks regulate a variety of cellular functions relevant to oncogenesis, including metabolism, proliferation and survival. Class Ia PI3Ks consists of p110α, p110β and p110δ isoforms and mediate cell signaling downstream of receptor tyrosine kinase activation. The p110α and p110β isoforms are broadly expressed whereas the p110δ isoform is primarily expressed in cells of hematopoietic origin. The phenotype of mice with an inactive PI3K p110δ gene is characterized by defects in B cell maturation and survival, providing one rationale for p110δ inhibition in B-cell malignancies. Moreover, p110δ mediates signaling from a variety of extracellular triggers that may be important in the pathogenesis of B-cell malignancies with respect to proliferation and protection from apoptosis, e.g., B-cell receptor, pro-survival cytokines and CD40.

Background (continued)

CAL-101 is a potent inhibitor of PI3K p110δ (IC_{50}=2.5 nM against purified enzyme and EC_{50}=65 nM in a cellular assay) with 40 to 300-fold selectivity compared to other PI3K isoforms. The lack of inhibitory activity against the PI3K p110α isoform should minimize the potential to alter insulin signaling and may provide a better therapeutic index relative to pan-PI3K inhibitors. In vitro studies of 0.1 to 10 μM CAL-101 showed inhibition of AKT phosphorylation and/or apoptotic effects against primary chronic lymphocytic leukemia (CLL) and acute myeloid leukemia (AML) cells and against a range of leukemia and lymphoma cell lines. Data on the effects of CAL-101 on non-Hodgkin's lymphoma (NHL) cell lines are presented at this meeting (Abstract 558, NHL Biology).

p110δ Signaling in B-cell Malignancies



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CAL-101 is Highly Selective for PI3K p110δ

Purified enzyme assay

IC_{50} (nM)	Class I PI3Ks Fold-Selectivity		
p110δ	p110γ	p110β	p110α
2.5	>40X	>200X	>300X

- >400X selective against non-Class I PI3Ks, mTOR and DNA-PK
- No off-target activity seen in >300 protein kinases (Ambit KINOME*scan*™)

Cellular assay

PI3Kδ EC_{50} (nM)	PI3Kγ EC_{50} (nM)	PI3Kα EC_{50} (nM)
Anti-FCεR1-induced CD63+ in basophils (whole blood)	fMLP-induced CD63+ in basophils (whole blood)	PDGF induced pAKT expression in fibroblast cell line
65	3,190	>20,000

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Methods

This ongoing phase 1 study is enrolling patients with relapsed or refractory CLL, select B-cell NHL and AML. Part 1 of the study was dose escalation, in which sequential cohorts of 3 patients (CLL or NHL) were enrolled to determine dose limiting toxicity (DLT). Part 2 is cohort expansion during which 12 patients are to be enrolled for each indication: CLL, indolent NHL, aggressive NHL and AML. Preliminary results from the first 32 patients enrolled in the study (12 patients from Part 1 and 20 patients from Part 2) are reported here. CAL-101 was administered orally twice daily for 28 days per cycle without breaks between cycles. Clinical response was evaluated according to IWG criteria (NHL and AML) or revised IWCLL criteria (CLL) at the end of Cycles 1 and 2 and every 2 cycles thereafter. Toxicity was reported using CTCAE v3.0 and DLT was defined as any adverse event related to study drug during Cycle 1 that was ≥ grade 3 non-hematological toxicity or grade 4 hematological toxicity persisting for > 7 days. Dose escalation decision was based on the standard 3+3 algorithm for DLT. The study was approved by the Institutional Review Boards and written informed consent was obtained from all patients. Clinicaltrials.gov ID NCT00710528.

Results – Enrollment and Disposition

- 32 patients enrolled to date
  - 12 patients enrolled to each of 4 cohorts during dose escalation
    - Cohort 1: 50 mg BID n=3; Cohort 2: 100 mg BID n=3;
      Cohort 3: 200 mg BID n=3; Cohort 4: 350 mg BID n=3
  - 20 patients enrolled in cohort expansion
    - 200 mg BID n=6, 350 mg BID n=14
- Duration of treatment ranged from 1 to 9 cycles (1 cycle = 28 days)
- Patient disposition
  - On study n=20
  - Discontinued for disease progression n=8
  - Died n=2 (AML patient during Cycle 1 due to respiratory arrest and NHL patient during Cycle 4 due to pneumonia)
  - Discontinued due to adverse event n=1 (NHL patient during Cycle 1 due to acute on chronic renal failure)
  - Withdrew for personal reason n=1

Demographic and Baseline Characteristics

Age Mean (range)	**66 (37-81)**
Gender	**Male n=23** **Female n=9**
Diagnosis	**CLL n=16** **B-cell NHL n=14** **Indolent NHL n=6** **Aggressive NHL n=8** **AML n=2**
Disease Status	**Relapsed n=15** **Refractory n=17**
No. prior therapies Median (range)	**5 (1-15)**

Objective Response Rate

Population	No. of Evaluable Patients	No. with Partial Response	Objective Response Rate
Treated for ≥ 1 cycle	24	12	50%
Treated for ≥ 1 cycle at 200 mg or 350 mg	18	10	56%

Characteristics of Responding Patients

Dose Level	Diagnosis	Time to Response (No. cycles)	Duration of Response
50 mg	MCL[1]	2	4 cycles
100 mg	FL[2]	1	>5 cycles, continuing
200 mg	MCL[1]	4	<1 cycle, died 2° pneumonia
200 mg	CLL	1	>3 cycles, continuing
350 mg	CLL	1	>1 cycle, continuing
350 mg	MZL[3]	1	>1 cycle, continuing
350 mg	SLL[4]	1	Currently in Cycle 2
350 mg	SLL[4]	1	Currently in Cycle 2
350 mg	MZL[3]	1	Currently in Cycle 2
350 mg	MCL[1]	1	Currently in Cycle 2
350 mg	CLL	1	Currently in Cycle 2
350 mg	CLL	1	Currently in Cycle 2

[1]mantle cell lymphoma, [2]follicular lymphoma, [3]marginal zone lymphoma, [4]small lymphocytic lymphoma

Safety Overview

- One dose limiting toxicity reported out of 32 patients enrolled – Grade 3 serious adverse event of acute renal failure in a patient with chronic renal insufficiency
- One other treatment-related serious adverse event – Grade 2 fluid retention that was worsening of pre-existing condition
- Hematological parameter effects
  - Grade 3 neutropenia in 2 patients
  - Lymphocytosis in some CLL patients, temporally associated with decreased lymphadenopathy
  - No thrombocytopenia
- Transient Grade 2 transaminase elevation in 2 patients, resolved without interruption of CAL-101 dosing

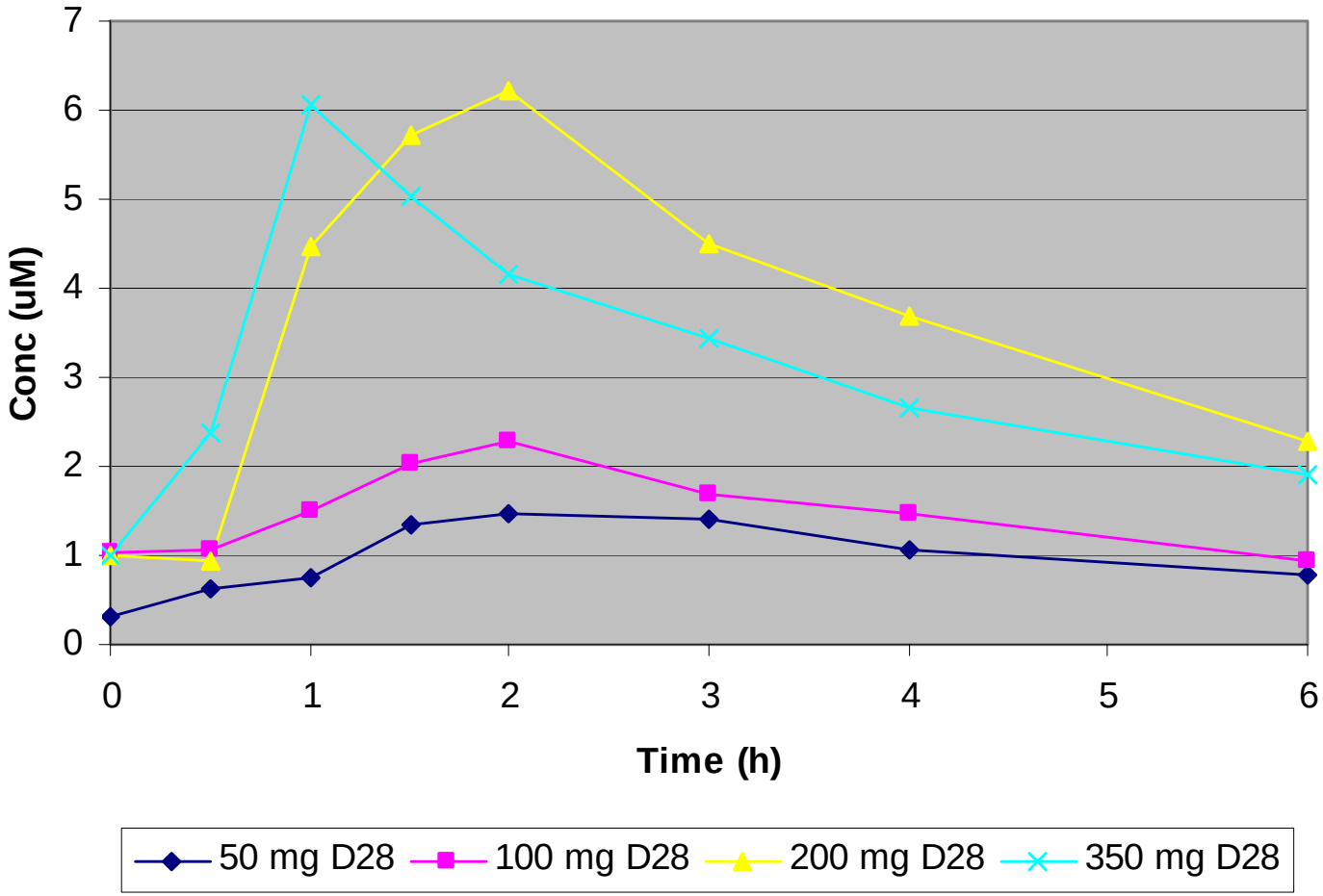
Treatment-Related Adverse Events

	Number of Patients (Toxicity Grade)			
Event Term	**50 mg**	**100 mg**	**200 mg**	**350 mg**
Anemia		**1 (G1)**		
Vision blurred		**1 (G1)**		
Diarrhea				**1 (G1)**
Vomiting		**1 (G1)**	**1 (G1)**	
Fatigue		**1 (G2)**		
Mucositis	**1 (G1)**	**2 (G1)**		
Peripheral edema			**1 (G1)**	**1 (G1)**

ALT increased		1 (G2)	1 (G2)	
AST increased			1 (G1)	
Periph. neuropathy	1 (G2)			
Pleural effusion				1 (G1)
Renal failure				1 (G3)
Orthopnea				1 (G1)

Data cutoff 27 May, 2009

Day 28 Mean Plasma Concentration (N=3/group)



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Conclusions

- **Preliminary results from this ongoing study shows that CAL-101 treatment is well tolerated without a clear DLT**
- **CAL-101 is active in patients with relapsed/refractory B-cell malignancies, with partial responses in 12/24 patients with CLL and several sub-types of NHL**
- **Trough concentrations in all dose groups were in the range where in vitro apoptotic effects for primary CLL patient cells and NHL cell lines were observed**
- **CAL-101 drug exposure increased from 50 mg to 200 mg without apparent further increase at 350 mg, both dose levels are being explored in ongoing cohort expansion**

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