Phase Ib dose-escalation study of the selective, non-covalent, reversible Bruton's tyrosine kinase inhibitor vecabrutinib in B-cell malignancies

John N. Allan,[1] Javier Pinilla-Ibarz,[2] Douglas E. Gladstone,[3] Krish Patel,[4] Jeff P. Sharman,[5] William G. Wierda,[6] Michael Y. Choi,[7] Susan M. O'Brien,[8] Mazyar Shadman,[9] Matthew S. Davids,[10] John M. Pagel,[4] Habte A. Yimer,[11] Renee Ward,[12] Gary Acton,[12] Pietro Taverna,[12] Daniel L. Combs,[13] Judith A. Fox,[12] Richard R. Furman[1] and Jennifer R. Brown[10]

[1]Weill Cornell Medicine, Department of Medicine, New York, NY; [2]Moffitt Cancer Center, Tampa, FL; [3]Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD; [4]Swedish Cancer Institute, Seattle, WA; [5]Willamette Valley Cancer Institute/US Oncology, Eugene, OR; [6]MD Anderson Cancer Center, Houston, TX; [7]Moores Cancer Center, University of California San Diego, La Jolla, CA; [8]Chao Family Comprehensive Cancer Center, University of California Irvine, Orange, CA; [9]Fred Hutchinson Cancer Research Center, Seattle, WA; [10]CLL Center, Medical Oncology, Dana-Farber Cancer Institute, Boston, MA; [11]Texas Oncology/US Oncology Research, Tyler, TX; [12]Sunesis Pharmaceuticals, South San Francisco, CA and [13]Combs Consulting Service, Mountain View, CA, USA

Correspondence: JENNIFER R. BROWN - jennifer_brown@dfci.harvard.edu

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SUPPLEMENTAL DATA

Supplemental Table 1. Patient Demographic and Disease Characteristics

	Patients with CLL (n=30)	All Patients (N=39)
Median age, years (range)	67.0 (47-86)	67.0 (47-86)
Male sex, n (%)	21 (70.0)	27 (69.2)
ECOG performance status, n (%)		
0	18 (60.0)	19 (48.7)
1	11 (36.7)	19 (48.7)
2	1 (3.3)	1 (2.6)
Disease type, n (%)		
CLL	30 (100)	30 (76.9)
MCL	N/A	4 (10.3)
LPL/WM	N/A	3 (7.7)
DLBCL	N/A	1 (2.6)
MZL	N/A	1 (2.6)
Median (range) time from initial diagnosis, years	8.03 (1.2-18.5)	8.43(0.9-30.7)
Median (range) number of prior therapies	4 (2-9)	4 (2-9)
Type of prior therapy, n (%)		
Covalent BTK inhibitor therapy, n (%)	30 (100)	39 (100)
Anti-Bcl2 therapy	13 (43.3)	16 (41.0)
CAR-T therapy	1 (3.3)	4 (10.3)
Known molecular characteristics at baseline, n (%)[a]		
BTK C481 mutation by NGS[b]	16/29 (55.2)	17/38 (44.7)
17p deletion and/or mutated *TP53*	22/30 (73.3)	28/38 (73.7)
17p deletion	14/30 (46.7)	14/33 (42.4)
TP53 mutation	20/30 (66.7)	26/39 (66.7)
13q deletion	14/29 (48.3)	15/32 (46.9)
Complex karyotype	12/25 (48.0)	13/28 (46.4)
11q deletion	10/26 (38.5)	10/28 (35.7)
Trisomy 12	9/28 (32.1)	9/31 (29.0)
Unmutated IGHV	24/27 (88.9)	24/36 (66.7)
ATM mutation	5/30 (16.7)	8/39 (20.5)
SF3B1 mutation	7/30 (23.3)	7/39 (17.9)
PLCγ2 mutation[c]	5/30 (16.7)	7/39 (17.9)
NOTCH1 mutation	4/30 (13.3)	5/39 (12.8)

BTK, Bruton's tyrosine kinase; CLL, chronic lymphocytic leukemia; ddPCR, digital droplet polymerase chain reaction; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; LPL/WM, lymphoplasmacytic lymphoma/Waldenström macroglobulinemia; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; NGS, next generation sequencing.

[a] Denominator indicates number of patients evaluated (excludes patients with unknown/missing data) and is used to calculate percentage given.

[b] As determined by NGS (detection limit 5%). In addition, ddPCR was performed on CLL patients; an additional 2 patients with CLL were identified with BTK C481 mutations by ddPCR.

[c] 1 activating mutation (S707F) was identified in a single CLL subject positive also for E1139del and M1141K on *PLCγ2* gene.

Supplemental Table 2. Most Common Grade ≥3 Adverse Events (Occurring in ≥5% of Patients)

Grade ≥ AE, n (%)	Cohort 1 20.5 mg (n=3)	Cohort 2 41 mg (n=10)	Cohort 3 82 mg (n=7)	Cohort 4 164 mg (n=4)	Cohort 5 246 mg (n=5)	Cohort 6 328 mg (n=4)	Cohort 7 410 mg (n=6)	All Patients (N=39)
Patients with Any Grade ≥3 AE	3 (100)	8 (80)	2 (29)	1 (25)	1 (20)	0	0	15 (39)
Blood and lymphatic system disorders								
Anemia	3 (100)	4 (40)	1 (14)	1 (25)	0	0	0	9 (23)
Neutropenia	2 (67)	3 (30)	0	0	0	0	0	5 (13)
Thrombocytopenia	2 (67)	2 (20)	0	0	0	0	0	4 (10)
Leukocytosis	0	2 (20)	0	0	0	0	0	2 (5)
Leukopenia	1 (33)	1 (10)	0	0	0	0	0	2 (5)
Lymphopenia	1 (33)	1 (10)	0	0	0	0	0	2 (5)
Investigations								
Blood bilirubin increased	0	1 (10)	0	1 (25)	1 (20)	0	0	3 (8)
Platelet count decreased	1 (33)	0	1 (14)	1 (25)	0	0	0	3 (8)
Metabolism and nutrition disorders								
Hyponatremia	0	1 (10)	1 (14)	1 (25)	0	0	0	3 (8)
Hypocalcemia	0	1 (10)	0	1 (25)	0	0	0	2 (5)
Hypophosphatasemia	0	1 (10)	1 (14)	0	0	0	0	2 (5)

Supplemental Figure 1. PK/PD Correlation: Vecabrutinib Exposure versus Cytokine Levels in Patients with CLL

Correlation analysis demonstrated trends for greater reductions in serum cytokine levels (CCL3, CCL4, and TNFα) in patients with CLL from baseline to Cycle 2 Day 1 with increasing C_{max}, AUC_{last}, and vecabrutinib dose. CCL3 and CCL4 showed r-squared correlation coefficient values greater than 0.2, or a modest correlation. This indicates that PK exposure accounts for at least 20% of the variability in biomarker levels. For TNFα there was a modest correlation for reduced serum levels with higher dose; there was also a trend for reduced TNFα levels with PK exposure (C_{max}, AUC_{last}), but the r-squared correlation was less than 0.2.