blood®

642. CLL: THERAPY, EXCLUDING TRANSPLANTATION: POSTER I | NOVEMBER 15, 2013

Phase 1 Study Of Single Agent CC-292, a Highly Selective Bruton's Tyrosine Kinase (BTK) Inhibitor, In Relapsed/ Refractory Chronic Lymphocytic Leukemia (CLL)

Jennifer R. Brown, MD, PhD,[1] Wael A. Harb, MD,[2] Brian T. Hill, MD, PhD,[3] Janice Gabrilove, MD,[4] Jeff P. Sharman, MD,[5] Marshall T. Schreeder, MD, MPH,[*,6] Paul M. Barr, MD,[7] James M. Foran, MD,[8] Thomas P. Miller, MD,[9] Jan A. Burger, MD, PhD,[10] Kevin R. Kelly, MD, PhD,[11] Daruka Mahadevan, MD, PhD,[12] Shuo Ma, MD, PhD,[13] Evelyn Barnett,[*,14] Jeffrey Marine,[*,14] Pilar Nava-Parada,[*,14] Ada Azaryan,[*,15] Jay Mei, MD,[14] Thomas J. Kipps, MD, PhD[16]

[1]Dana-Farber Cancer Institute, Boston, MA, USA,

[2]Horizon Oncology Center, Lafayette, IN, USA,

[3]Department of Hematologic Oncology and Blood Disorders, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH, USA,

[4]Mount Sinai School of Medicine, New York, NY, USA,

[5]Willamette Valley Cancer Institute and Research Center/US Oncology Research, Eugene, OR, USA,

[6]Clearview Cancer Institute, Huntsville, AL, USA,

[7]Hematology/Oncology, University of Rochester Medical Center, Rochester, NY, USA,

[8]Hematology and Oncology, Mayo Clinic, Jacksonville, FL, USA,

[9]University of Arizona Cancer Center, Tucson, AZ, USA,

[10]Department of Leukemia, MD Anderson Cancer Center, Houston, TX, USA,

[11]University of Texas Health Science Center at San Antonio, CTRC Institute for Drug Development, San Antonio, TX, USA,

[12]The West Clinic, University of Tennessee Health Sciences Center, ACORN Research, LLC, Memphis, TN, USA,

[13]Robert H. Lurie Comprehensive Cancer Center, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA,

[14]Celgene Corporation, Summit, NJ, USA,

[15]Celgene Corporation, Berkeley Heights, NJ, USA,

[16]University of California, San Diego, Moores Cancer Center, La Jolla, CA, USA

Blood **(2013) 122 (21) : 1630.**

http://doi.org/10.1182/blood.V122.21.1630.1630

Abstract

Introduction

CC-292, an oral, highly selective, small-molecule irreversible-inhibitor of Btk is under investigation for the treatment of CLL and other B-cell malignancies. This phase 1 trial investigated the safety, dose limiting toxicities (DLT), and clinical activity of CC-292 monotherapy in subjects with relapsed or refractory (R/R) CLL or non-Hodgkin's lymphoma. This interim analysis focused on the safety and clinical activity in subjects with CLL and small cell lymphocytic leukemia (SLL).

Methods

Eligible subjects with R/R (≥ 1 prior therapy) CLL/SLL were treated with monotherapy CC-292 in a dose-escalation study with doses ranging from 125 mg to 1000 mg QD and BID dose levels of 375 mg and 500 mg. As a maximum tolerated dose was not established, CLL patients have been enrolled in an early dose expansion cohort of 750 mg QD and preliminary recommended phase 2 dose expansion cohort at 500 mg BID. All subjects received continuous dosing in 28-day cycles until progressive disease or intolerable toxicity. Clinical activity was investigator assessed per the 2008 iwCLL criteria.

Results

83 subjects with R/R CLL/SLL have been enrolled as of June 30, 2013. Baseline characteristics include median age of 67 years (34-89), 52% Rai stage 3/4 disease, median 3 prior therapies (1-12), and 34% refractory to last treatment. Poor-risk factors were present in 67% of subjects, including del11q (22%), del17p (24%), and unmutated IgVH (54%). 67% of subjects remain on study. Subjects have received a median of 6 treatment cycles (0.2-21.6). The most frequent grade 3/4 adverse events (AEs) included neutropenia (21%), thrombocytopenia (15%), pneumonia (10%), and anemia (8%). Rates of febrile neutropenia were low (4%). The most common treatment-emergent AEs (≥ 10% of subjects) were diarrhea (59.7%), fatigue (37.5%), neutropenia (26.4%), thrombocytopenia (26.4%), nausea (26.4%), pyrexia (22.2%), headache (19.4%), cough (19.4%), upper respiratory infection (16.7%), peripheral edema (15.3%), abdominal pain (15.3%), dizziness (13.9%), muscle spasms (13.9%), contusion (13.9%), anemia (12.5%), pneumonia (12.5%), sinusitis (12.5%), and urinary tract infection (11.1%). One CLL patient at the 500 mg BID dose level has experienced a drug-related adverse event of grade 4 thrombocytopenia during Cycle 1 that was assessed as a DLT. The number of patients discontinuing study treatment due to AEs was low (2.4%). Results are summarized for efficacy-evaluable patients treated at the 4 dose levels where at least a partial response (PR) was achieved (750 mg, 1000 mg, 375 mg bid and 500 mg bid) (n = 55). During cycle 1, 89% experienced a ≥ 25% increase in absolute

lymphocyte count (ALC), which usually resolved with continued treatment. The table below details the best responses achieved to date. In subjects with del11q, del17p, unmutated IgVH, and no high-risk genomic factors, the PR rate was 42% (5/12), 25% (3/12), 44% (7/16), and 47% (7/15), respectively. Importantly, nodal responses were induced in the majority of subjects receiving BID dosing (375 mg: 67%; 500 mg: 62%) with an overall PR rate of 40%. When achieved, nodal responses were typically observed by cycle 2 and were sustained with continued treatment. Although the sample size is small, subjects treated at 375 mg or 500 mg BID showed continued lymph node size reduction over time from cycle 2 (mean reduction of 42% and 45%, respectively) to cycle 7 (mean reduction of 60% and 71%, respectively).

Conclusion

CC-292 is well tolerated as an oral daily therapy. Single-agent therapy with CC-292 is sufficient to achieve high nodal and partial response rates in relapsed/refractory CLL subjects, including those with high-risk genomic features. These results support continued development of CC-292 for the treatment of patients with CLL/SLL.

Dose Level (mg)	Evaluable (n)	Total Responders	PR	Nodal Response w/ increased ALC	Median Time on Study (cycles)	Median Follow-up (Months)
750 mg QD	29	16 (55%)	9 (31%)	7 (24%)	11.2	12.7
1000 mg QD	7	4 (57%)	4 (57%)	0	9.9	10.4
375 mg BID	6	4 (67%)	4 (67%)	0	10.6	10.6
500 mg BID	13	8 (62%)	5 (38%)	3 (23%)	2.9	2.9

*Per investigator assessment via imaging.

Disclosures:

Brown: *Pharmacyclics:* Consultancy; *Genentech:* Consultancy; *Celgene:* Consultancy, Research Funding; *Emergent:* Consultancy; *Onyx:* Consultancy; *Sanofi Aventis:* Consultancy; *Vertex:* Consultancy; *Novartis:* Consultancy; *Genzyme:* Research Funding. **Off Label Use:** The abstract shows scientific information on CC292 which is an investigational product developed by Celgene. This investigational product is not approved by any health authority for any indication. **Harb:** *Celgene:* Research Funding. **Hill:** *Celgene:* Honoraria, Research Funding. **Sharman:** *Celgene:* Consultancy, Research Funding; *Genentech:* Consultancy, Research Funding; *Gilead:* Consultancy, Research Funding; *Pharmacyclics:* Consultancy, Research Funding; *Seattle Genetics:* Consultancy, Research Funding; *Cylene*

Pharmaceuticals: Consultancy, Research Funding; *Avila Pharmaceuticals:* Consultancy, Research Funding. **Barr:** *Celgene:* Consultancy. **Foran:** *Celgene:* Research Funding. **Burger:** *Pharmalytics:* Research Funding; *Gilead:* Research Funding. **Mahadevan:** *Novartis:* Speakers Bureau; *Millennium:* Speakers Bureau. **Ma:** *Genentech:* Consultancy; *Abbvie:* Consultancy. **Barnett:** *Celgene:* Employment, Equity Ownership. **Marine:** *Celgene:* Employment, Equity Ownership. **Nava-Parada:** *Celgene:* Employment, Equity Ownership. **Azaryan:** *Celgene:* Employment, Equity Ownership. **Mei:** *Celgene:* Employment, Equity Ownership. **Kipps:** *Celgene:* Membership on an entity's Board of Directors or advisory committees, Research Funding.

Author notes

* Asterisk with author names denotes non-ASH members.