Phase I study of single-agent CC-292, a highly selective Bruton's tyrosine kinase inhibitor, in relapsed/refractory chronic lymphocytic leukemia

B-cell receptor (BCR) signaling plays a key role in the pathogenesis of B-cell malignancies, mediating the survival and proliferation of malignant B cells.[1,2] Clinical studies have shown that Bruton's tyrosine kinase (BTK) inhibitors are well tolerated, with promising clinical activity. Ibrutinib has shown 30-month progression-free survival (PFS) of 69% in relapsed chronic lymphocytic leukemia (CLL) patients,[3-5] and has substantial activity in mantle cell lymphoma and activated B-cell-type diffuse large B-cell lymphoma.[6,7] CC-292 is a highly selective oral small-molecule inhibitor that binds covalently and irreversibly to the same cysteine 481 in BTK as ibrutinib, inhibiting its signaling.[8] We report here the results of a phase I study of CC-292 in patients with relapsed/refractory (R/R) CLL/small lymphocytic lymphoma (SLL), B-cell non-Hodgkin lymphoma (B-NHL), and Waldenström macroglobulinemia (WM). A total of 113 patients received continuous dosing with CC-292 in 28-day cycles at doses ranging from 125 mg to 1000 mg once daily, and 375 mg and 500 mg twice daily, continuing into dose-expansion cohorts of 750 mg once daily and a preliminary recommended phase II dose (RP2D)-expansion cohort of 500 mg twice daily. Four patients experienced dose-limiting toxicity (DLT) but only one in any treatment cohort. The most frequent grade 3-4 adverse events (AEs) were neutropenia (16%) and thrombocytopenia (8%). The most common non-hematologic treatment-emergent AEs (TEAEs) of any grade were diarrhea (68%) and fatigue (45%). Twice-daily administration of CC-292 was instituted to improve sustained BTK occupancy, and, in fact, did result in more than 90% BTK receptor occupancy at both the 4- and 24-h post-dose time points. Efficacy in the CLL/SLL population (n=84) showed that overall response rate (ORR) in patients receiving twice-daily dosing was 53%; an additional 10% had partial response with lymphocytosis (PR-L). CC-292 was, therefore, well tolerated and achieved high nodal and PR rates in relapsed CLL/SLL patients, but showed less durability than other BTK inhibitors.

The objectives of this phase I, multicenter, open-label, dose-escalation study (*clinicaltrials.gov identifier: 01351935*) in patients with R/R CLL, B-NHL, or WM were: a) to determine the recommended dose of CC-292 for phase II evaluation; b) to assess its pharmacokinetic (PK), pharmacodynamic (PD), and safety/tolerability profiles; and c) to assess its clinical activity. All patients received continuous dosing in 28-day cycles until progressive disease or intolerable toxicity. As maximum tolerated dose (MTD) was not established, 25 patients with CLL/SLL were enrolled in an early dose-expansion cohort of 750 mg once daily, and 27 patients in a preliminary RP2D-expansion cohort of 500 mg twice daily (*Online Supplementary Table S1*). We provide a detailed safety evaluation for all patients; however, due to the small heterogeneous cohort with B-NHL and WM (*Online Supplementary Table S2*), the PD and efficacy analyses are focused on CLL/SLL. Clinical response in CLL was investigator-assessed using International Workshop Group on CLL (IWCLL) criteria, with all nodal responses determined by computed tomography (CT) scan (1 patient magnetic resonance imaging).[9,10] Between August 1st 2011 and December 31st 2013, this study enrolled and treated 113 patients at 13 centers in the US; 84 were enrolled with a diagnosis of CLL/SLL, 23 with B-NHL, and 6 with WM (*Online Supplementary Table S3*). Median age of CLL patients was 66.5 years (range 34-89), and they had received a median of 3 prior regimens (range 1-12) (Table 1). Known risk factors for poor CLL prognosis included 21.4% with del(11q), 23.8% with del(17p), and 53.6% with unmutated immunoglobulin heavy chain variable region (IgVH).

CC-292 was well tolerated in these heavily pre-treated patients; 4 patients had a DLT, with only 1 DLT in any treatment cohort. Correspondingly, the MTD was not defined. The DLTs comprised 2 patients experiencing grade 4 thrombocytopenia (1 each at 400 mg once daily and 500 mg twice daily); one patient with grade 3 drug-related pneumonitis at 1000 mg once daily; and one patient with a grade 3 reversible mental-status change at 500 mg twice daily. Of four DLTs, only one (grade 4 thrombocytopenia at 500 mg twice daily) occurred in a CLL patient. For the overall patient population, grade 3-4 thrombocytopenia was observed in 8% of patients, and grade 3-4 neutropenia in 16%, with only 2% incidence of febrile neutropenia (*Online Supplementary Table S4*). The most common non-hematologic grade ≥3 TEAEs were pneumonia (4%) and hyperglycemia (3%) (*Online Supplementary Table S4*). Common non-hematologic TEAEs of any grade were diarrhea (68%), fatigue (45%), nausea (35%), cough (27%), pyrexia (27%), and headache (25%) (*Online Supplementary Table S5*). Only 5.3% of patients experienced ecchymosis and 2.7% had hematoma. Atrial fibrillation was observed in 4 of 113 patients, 3 of whom had a prior history. The proportion of patients who discontinued treatment due to AEs was low (6.2%). As of December 31st 2013, 69 of 113 (61.1%) patients enrolled in the study had discontinued treatment; 45 of 84 (53.6%) were CLL/SLL patients. Reasons for treatment discontinuation included disease progression (n=51), patient request (n=7), AEs (n=7), death (n=3),

Table 1. Baseline chronic lymphocytic leukemia/small lymphocytic lymphoma patients' characteristics.

Characteristic	n=84
Age, median (range), years	66.5 (34-89)
Male sex, %	58.3
Rai stage 3-4, %	54.7
Time from diagnosis, median (range), months	92.4 (3.8-317.7)
Prior therapies, median (range)	3 (1-12)
Time from last prior therapy, median (range), months	0.73 (0.07-117.2)
Refractory to last prior regimen, %	34.5
Fludarabine-refractory, %	27.4
Risk factors with poor prognosis, n (%) del(11q) del(17p) Unmutated IgVH	56 (66.7) 18 (21.4) 20 (23.8) 45 (53.6)
Absolute lymphocyte count, median × 10^9/L	5.56
Absolute neutrophil count, median × 10^9/L	3.00
Hemoglobin level, median	12.00
Platelet count, median	115
Serum β2-microglobulin level, median	3.50
Lactate dehydrogenase level, median	193.00

IgVH: immunoglobulin heavy chain variable.

and lack of response (n=1). Overall, patients received a median of 9.1 cycles of treatment (range 0.6-28.5) (*Online Supplementary Figure S1*), and median follow up over all doses was 13.4 months. A total of 6 patients died on study: 3 experienced disease progression (including 1 patient with Richter transformation), 2 had respiratory failure, and 1 had a *Klebsiella pneumoniae* infection. Some rapid disease progression events were observed on discontinuation of CC-292, similar to what has been reported for ibrutinib.[11,12]

Pharmacokinetic sampling was performed on all patients (*Online Supplementary Table S6*). CC-292 was readily absorbed and reached maximum concentration (C_{max}) within 1-2 h post dose. Plasma concentrations declined in an apparent mono-phasic manner and were below the limit of quantitation (0.50 ng/mL) by 12 h. Based on graphical evaluation, AUC_{0-24} and C_{max} exposures of CC-292 were approximately dose proportional within the 125-1000 mg once daily dose range. CC-292 concentrations appeared to be at steady state by day 2 at all dose levels. As assessed from the geometric percent coefficient of variation, relatively high intersubject variability was noted for both the AUC_{0-24} and C_{max} parameters.

The level of receptor occupancy of BTK was also assessed. Over 90% occupancy was observed in a majority of patients at 4 h post-dose during cycle 1 (Figure 1).[8] However, BTK receptor occupancy was reduced at the 24-h time point with once-daily dosing, leading to testing of twice-daily dosing. Patients receiving twice-daily CC-

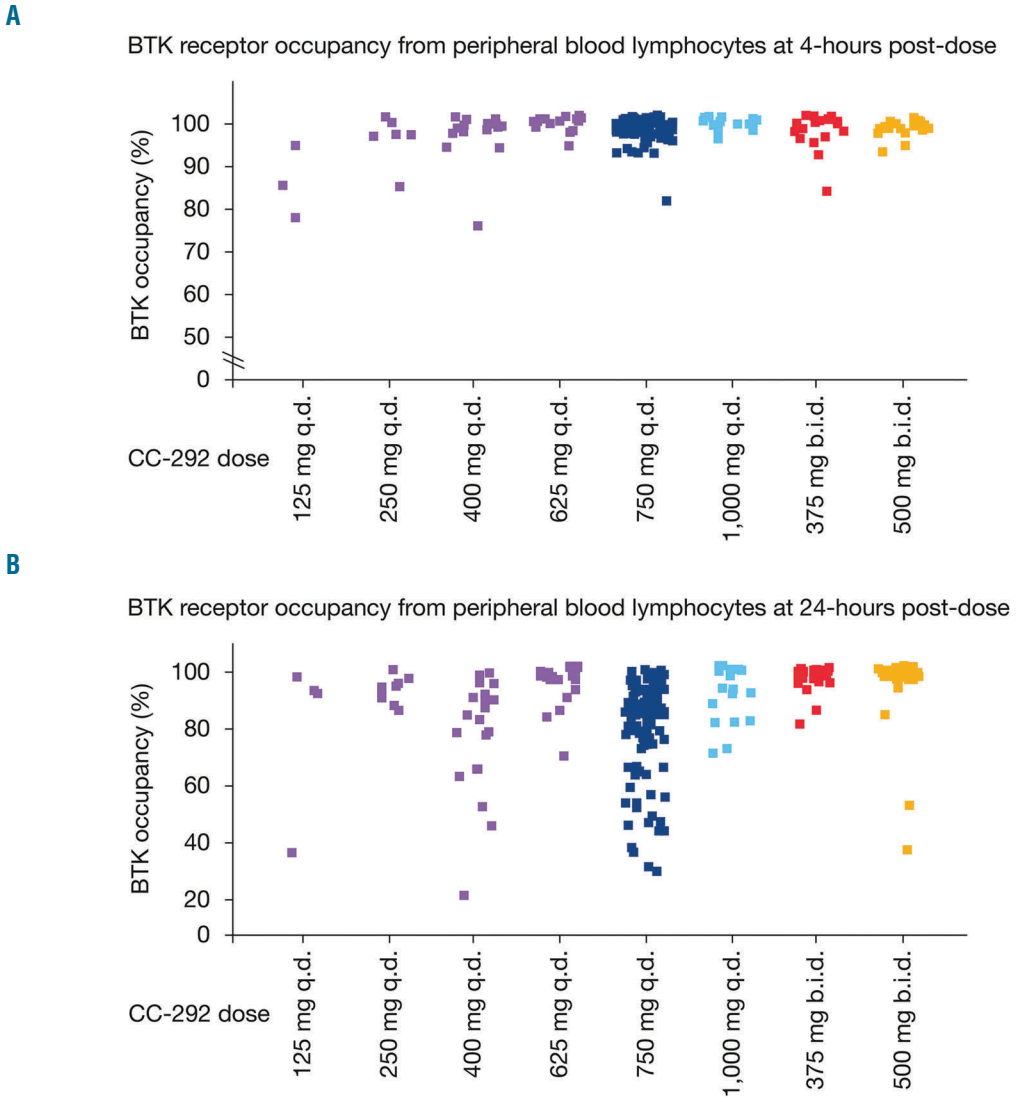

Figure 1. Twice daily dosing of CC-292 extends Bruton's tyrosine kinase (BTK) inhibitor receptor occupancy. Percentage BTK receptor occupancy at 4 h (A) and 24 h (B) post dose for each dose level and dosing schedule. Peripheral blood lymphocytes were obtained from patients treated with CC-292 administered on either a once- or twice-daily schedule. Level of free BTK (without CC-292 in the active site) was quantitatively determined using an ELISA assay, and occupancy determined by reference to the pre-treatment level of free BTK normalized to lysate protein concentration for each patient. Time points sampled were: cycle 1 day 1 pre-dose and 4 h post-dose; day 2 pre-dose, day 15 pre-dose and 4 h post-dose, day 16 pre-dose, and cycle 2 day 1 pre-dose and 4 h post-dose. Here, the data have been pooled across days but separated by pre- *versus* post-dose time point. b.i.d.: twice daily; ELISA: enzyme-linked immunosorbent assay; q.d.: once daily.

292 showed more than 90% BTK receptor occupancy at both the 4- and 24-h time points (Figure 1).[8] On-treatment levels of free BTK in lymph node tissue were determined in 11 patients who participated in optional biopsies taken 4 h post-dose, of which 10 were evaluable (*Online Supplementary Figure S2*). In 9 patients, no free BTK was detectable in lymph node lysates (<12.5 pg/μL detection limit), although BTK was present by immunoblot. The remaining patient had a free BTK level of 34 pg/μL, compared with a total BTK level of 867 pg/μL, which indicates 96% receptor occupancy. Control experiments on 5 untreated lymph node samples obtained from breast reduction surgery tissue showed that free BTK levels more than 400 pg/μL were present if

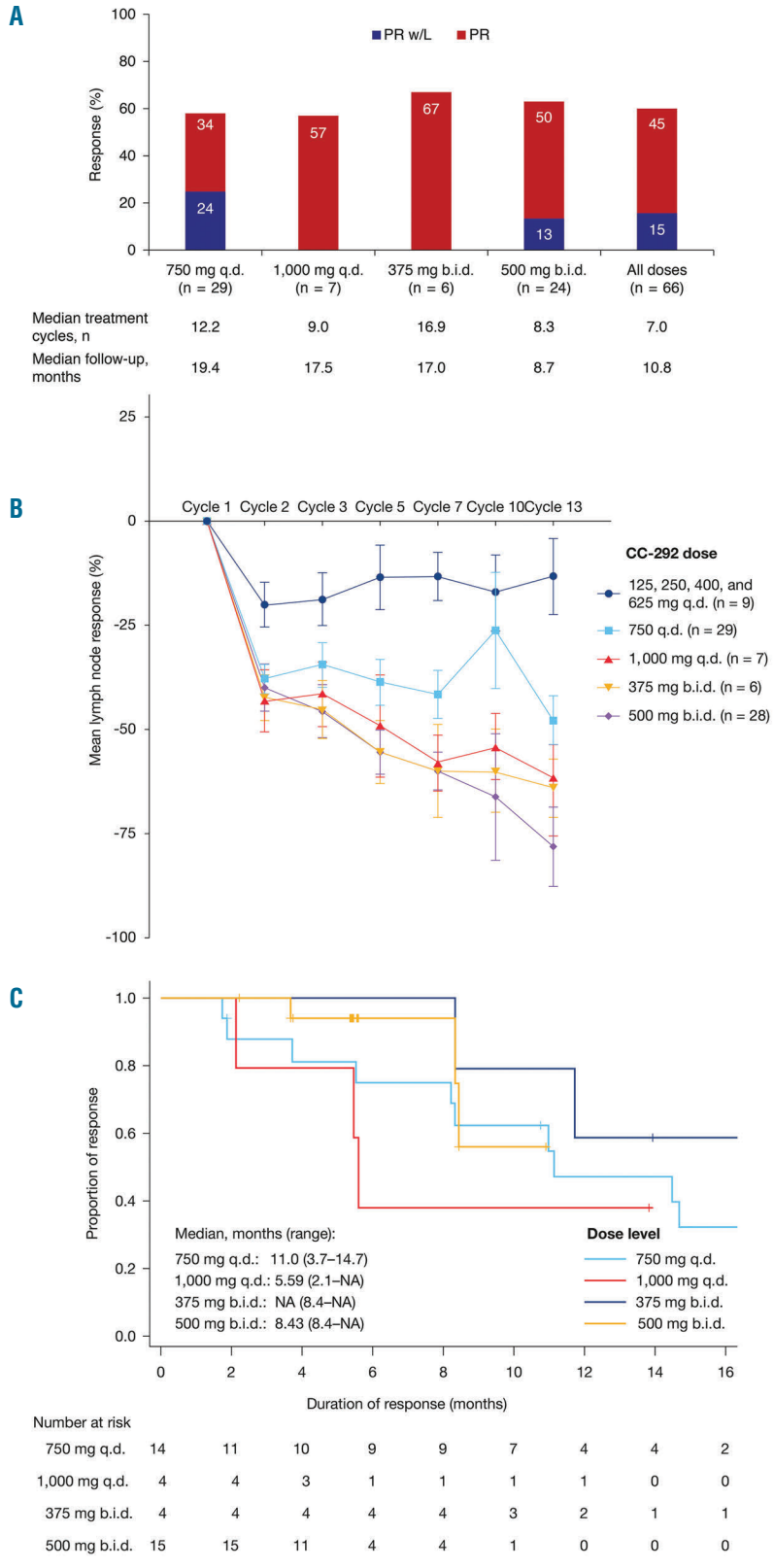

Figure 2. Responses to CC-292 in relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma (R/R CLL/SLL) patients are dose-dependent. (A) Efficacy assessment in the efficacy evaluable population. Overall response rates (PR and PR-L defined according to International Workshop Group on CLL criteria) by dose level for the efficacy evaluable population of chronic lymphocytic leukemia/small lymphocytic lymphoma (n=66). (B) Lymph node response by time and dose. Mean lymph node responses (± standard error of mean) over time with each dose and schedule of CC-292. (C) Median response duration for CLL patients treated on the four highest CC-292 dose levels. b.i.d.: twice daily; PR: partial response; NA: not yet achieved; PR-L: PR with lymphocytosis; q.d.: once daily.

BTK was detectable by Western blot (*Online Supplementary Figure S2*). Taken together, these data demonstrate a qualitatively high level of BTK receptor occupancy in peripheral blood and lymph nodes at a post-dose peak time point, although some variability is still present at pre-dose trough points.

Limited efficacy was observed in the early dose-finding phase among 23 patients with B-NHL, with just one PR in a splenic marginal zone lymphoma patient, while among 6 patients with WM, one PR and 3 minor responses were observed, suggesting some activity. Among CLL patients treated at the four highest dose levels, 71% of patients had a more than 50% absolute lymphocyte count increase, with median time to resolution of 6 cycles. At least 50% reduction in lymph node diameter was seen in 60% of patients on the four highest dose levels, as was progressive dose-dependent improvement in nodal response between cycles 2 and 7 (Figure 2). In patients with del(11q), del(17p), or unmutated IgVH treated at the four highest doses, the rates of IWCLL-defined PR and PR-L were 71% (10 of 14 patients), 69% (11 of 16), and 63% (10 of 16), respectively (*Online Supplementary Table S7*). The median response duration was 11.0, 5.6, not yet reached, and 8.4 months for the 750 mg and 1000 mg once daily, and 375 mg and 500 mg twice daily groups, respectively (Figure 2), although occasionally patients had more durable benefit (*Online Supplementary Table S8*).

In conclusion, this study confirms that CC-292 is well tolerated as a daily oral monotherapy at doses up to 1000 mg once daily or 500 mg twice daily. Administration of single-agent CC-292 achieved high BTK receptor occupancy, particularly with twice-daily dosing, and resulted in dose-dependent responses in R/R CLL/SLL patients, including those with high-risk cytogenetic features. However, its clinical activity (in particular, durability of response) was inferior to that of ibrutinib or acalabrutinib.[3,13] Although the reasons are not completely clear, given reasonably high BTK occupancy in most patients on BID dosing, it seems likely that highly variable PK and PD limited the ability of CC-292 to consistently reach its target *in vivo*. As the importance of BCR signaling is now well established in the treatment of CLL, the suboptimal efficacy of CC-292 represents a valuable cautionary clinical experience in the development of next generation BTK inhibitors.

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