Phase 1 study of selective BTK inhibitor zanubrutinib in B-cell malignancies and safety and efficacy evaluation in CLL

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Abstract:
Zanubrutinib is a potent and highly selective inhibitor of Bruton tyrosine kinase (BTK). In this first-in-human, open-label, multicenter, phase 1 study, patients in part 1 (3+3 dose escalation) had relapsed/refractory B-cell malignancies and received zanubrutinib 40, 80, 160, or 320 mg once daily or 160 mg twice daily. Part 2 (expansion) consisted of disease-specific cohorts, including treatment-naive or relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). The primary end points were safety and tolerability, and definition of the maximum tolerated dose (part 1). Additional end points included pharmacokinetics/pharmacodynamics and preliminary efficacy. Reported herein were results from 144 patients enrolled in the dose-finding and CLL/SLL cohorts. No dose-limiting toxicities occurred in dose escalation. Median BTK occupancy in peripheral blood mononuclear cells was >95% at all doses. Sustained complete (>95%) BTK occupancy in lymph node biopsy specimens was more frequent with 160 mg twice daily than 320 mg once daily (89% vs 50%; \( P = 0.0342 \)). Consequently, 160 mg twice daily was selected for further investigation. With median follow-up of 13.7 months (range, 0.4–30.5), 89 (94.7%) CLL/SLL patients remain on study. Most toxicities were grade 1/2; neutropenia was the only grade 3/4 toxicity observed in >2 patients. One patient experienced a grade 3 subcutaneous hemorrhage. Among 78 efficacy-evaluable CLL/SLL patients, overall response rate was 96.2% (95% CI, 89.2–99.2). Estimated progression-free survival at 12 months was 100%. Zanubrutinib demonstrated encouraging activity in CLL/SLL patients, with a low incidence of major toxicities. This study is registered with www.clinicaltrials.gov as #NCT02343120.

Conflict of interest:

COI notes: COI declared - see note

Preprint server: No;

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Phase 1 study of selective BTK inhibitor zanubrutinib in B-cell malignancies and safety and efficacy evaluation in CLL

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Key points

- Zanubrutinib is a potent and selective BTK inhibitor with greater selectivity and potentially fewer off-target effects than ibrutinib.
- In this study zanubrutinib was tolerable and demonstrated encouraging activity in patients with relapsed/refractory or treatment-naïve CLL.

Abstract

Zanubrutinib is a potent and highly selective inhibitor of Bruton tyrosine kinase (BTK). In this first-in-human, open-label, multicenter, phase 1 study, patients in part 1 (3+3 dose escalation) had relapsed/refractory B-cell malignancies and received zanubrutinib 40, 80, 160, or 320 mg once daily or 160 mg twice daily. Part 2 (expansion) consisted of disease-specific cohorts, including treatment-naïve or relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). The primary end points were safety and tolerability, and definition of the maximum tolerated dose (part 1). Additional end points included pharmacokinetics/pharmacodynamics and preliminary efficacy. Reported herein are results from 144 patients enrolled in the dose-finding and CLL/SLL cohorts. No dose-limiting toxicities occurred in dose escalation. Median BTK occupancy in peripheral blood mononuclear cells was >95% at all doses. Sustained complete (>95%) BTK occupancy in lymph node biopsy specimens was more frequent with 160 mg twice daily than 320 mg once daily (89% vs 50%; \( P = .0342 \)). Consequently, 160 mg twice daily was selected for further investigation. With median follow-up of 13.7 months (range, 0.4–30.5), 89 (94.7%) CLL/SLL patients remain on study.
Most toxicities were grade 1/2; neutropenia was the only grade 3/4 toxicity observed in >2 patients. One patient experienced a grade 3 subcutaneous hemorrhage. Among 78 efficacy-evaluable CLL/SLL patients, overall response rate was 96.2% (95% CI, 89.2–99.2). Estimated progression-free survival at 12 months was 100%. Zanubrutinib demonstrated encouraging activity in CLL/SLL patients, with a low incidence of major toxicities. This study is registered with www.clinicaltrials.gov as #NCT02343120.
Introduction

The B-cell receptor signaling pathway is essential for normal B-cell development but is also implicated in the survival and proliferation of malignant B cells.\textsuperscript{1-3} Inhibition of B-cell receptor signaling has recently been established as an effective approach for management of B-cell malignancies.\textsuperscript{4} Bruton tyrosine kinase (BTK) is a key component of the B-cell receptor signaling pathway, and the first-generation BTK inhibitor, ibrutinib, has become a standard of care in frontline and previously treated chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), previously treated mantle cell lymphoma (MCL), and Waldenström macroglobulinemia (WM).\textsuperscript{5-10}

Zanubrutinib (BGB-3111) is a highly specific next-generation BTK inhibitor with favorable oral bioavailability, as shown in preclinical studies.\textsuperscript{11-13} Compared with ibrutinib, zanubrutinib has shown greater selectivity for BTK and fewer off-target effects in multiple in vitro enzymatic and cell-based assays (Supplemental Table S1).\textsuperscript{13} Zanubrutinib, ibrutinib, and other active BTK inhibitors covalently bind cysteine 481 in the adenosine triphosphate (ATP)-binding pocket of BTK, and display varying affinities (depending on specificity of the individual drug) for related and unrelated ATP-binding kinases that contain a sterically available cysteine at this position, including epidermal growth factor receptor (EGFR), human EGFR-2 (HER2), human EGFR-4 (HER4), interleukin-2–inducible T-cell kinase (ITK), bone marrow tyrosine kinase gene in chromosome X (BMX), Janus-associated kinase 2 (JAK2), TEC, and B-lymphocyte kinase (BLK).\textsuperscript{3,12,14,15} Off-target inhibition likely contributes to the toxicities reported in patients treated with ibrutinib, such as
diarrhea and rash (toxicities associated with EGFR inhibition), bleeding or bruising, and atrial fibrillation, and that are not seen in patients with congenital X-linked agammaglobulinemia due to germline mutations in the BTK gene; a more specific BTK inhibitor may have fewer toxicities.

Based on promising preclinical data, we conducted a phase 1 study of zanubrutinib to evaluate its safety, pharmacokinetic, and pharmacodynamic properties. Herein, we report results in patients with various relapsed or refractory B-cell malignancies and preliminary safety and efficacy results in patients with treatment-naïve or relapsed/refractory CLL/SLL.

**Patients and methods**

**Study design and participants**

This multicenter, phase 1, first-in-human study of zanubrutinib in patients with B-cell malignancies comprises 2 parts: dose escalation (part 1) and cohort expansion (part 2). Part 1 evaluated the safety, pharmacokinetics, and pharmacodynamics (BTK occupancy in peripheral blood mononuclear cells [PBMCs]) in patients with relapsed/refractory B-cell malignancies who had received at least 1 prior therapy, with no therapy of higher priority available in the assessment of the investigator. Part 2 characterized the safety and preliminary efficacy of zanubrutinib in multiple cohorts of patients with B-cell malignancies. One cohort (cohort 2a) enrolled patients with mixed histologies of relapsed/refractory B-cell malignancies (see Supplemental Figure S1). These patients underwent pharmacodynamic evaluations consisting of evaluation of pre- and on-treatment lymph node biopsy
specimens and PBMC assessments for quantitation of BTK occupancy. Other
cohorts were disease-specific, for example CLL/SLL, MCL, and WM. Protocol
amendment version 5 provided for the inclusion of patients with CLL/SLL who had
not received prior treatment for their disease. This provision was based on the
acceptable safety profile of zanubrutinib observed in part 1 (dose escalation) and
early part 2 (dose expansion) of this study, as well as emerging data with ibrutinib
and acalabrutinib demonstrating that BTK inhibition is safe and active, including in
previously untreated patients.\textsuperscript{5}

Eligible patients were at least 18 years old, had an Eastern Cooperative Oncology
Group performance status of 0 to 2, and adequate organ function and peripheral
blood counts (absolute neutrophil count $\geq 1.0 \times 10^9$/L, platelet count $\geq 50 \times 10^9$/L).
Key exclusion criteria included central nervous system disease, previous exposure
to a BTK inhibitor, or a requirement for concurrent strong cytochrome P450 3A
(CYP3A) inhibitors or inducers. Additional eligibility criteria are included in the
Supplemental Material. All patients provided written informed consent before
enrollment and Institutional Review Boards and an Independent Ethics Committees
reviewed and approved the study protocol. This study is registered with
ClinicalTrials.gov (NCT02343120).

\textit{Procedures}

\textbf{Part 1}
In Part 1, patients received daily zanubrutinib until disease progression or intolerable toxicity, with dose escalation according to a modified “3 + 3” design. The dose-limiting toxicity (DLT) assessment window was 21 days after first dose. A safety monitoring committee was established to determine dose levels and schedules for dose escalation, using data from previous dose cohorts. Dose-limiting toxicities were defined as: treatment-related grade 4 neutropenia lasting >7 days; grade ≥3 febrile neutropenia of any duration; grade 4 thrombocytopenia or grade ≥3 thrombocytopenia associated with bleeding; any nonhematologic grade ≥3 event; any grade ≥2 toxicity requiring dose modification or ≥1 week treatment delay; or any toxicity that required study drug discontinuation. Patients tolerating their assigned dose were permitted to escalate to a higher dose if it was deemed safe in a subsequent cohort and after sponsor review. If no maximum tolerated dose was identified, decisions as to the dose and schedule(s) to be evaluated in part 2 were to be based on pharmacokinetic data, assessments of BTK inhibition in PBMCs, safety, and preliminary efficacy.

Mouse pharmacokinetic/pharmacodynamic models and human pharmacokinetic data predicted that zanubrutinib dosed at 80 mg/d would achieve complete BTK inhibition in PBMCs. In an attempt to achieve the anticipated therapeutic dose with ≤4 dose levels, 40 mg/d was selected as the starting dose for dose escalation with a planned maximum of 320 mg/d as either a single or split daily dose (160 mg twice daily).

Part 2
Patients enrolled in part 2 were to receive zanubrutinib at the maximum tolerated dose or maximally administered dose until disease progression, loss of clinical benefit, or intolerable toxicity. Continuous safety evaluation was performed by the sponsor and study investigators. Patients enrolled to cohort 2a provided consent to undergo paired lymph node biopsies for quantitation of BTK occupancy; biopsies were optional for patients enrolled to other part 2 cohorts. Safety and efficacy results from CLL/SLL patient cohorts (either treatment-naïve or relapsed/refractory disease) in part 2 are also presented.

Pharmacokinetic and pharmacodynamic assessments (part 1 and cohort 2a patients)

Blood samples for pharmacokinetic analyses were collected predose on days 1, 2, and 3 of week 1; day 1 of weeks 2, 5, and 9; and up to 8 hours postdose on day 1 of weeks 1 and 2. Zanubrutinib plasma concentrations were measured using a validated high-performance liquid chromatography tandem mass spectrometry assay with a lower limit of quantitation for zanubrutinib of 1.00 ng/mL. Pharmacokinetic parameters, including maximal plasma concentration ($C_{\text{max}}$) and area under the concentration-time curve (AUC), were estimated using noncompartmental methods and were computed using Phoenix WinNonlin®, Version 7.0 (Certara, Princeton, NJ, USA).

Blood samples for quantitation of BTK occupancy were collected predose on days 1, 2, and 3 of week 1, on day 1 of week 2, and 4 hours postdose on day 1 of week 1. For quantitation of BTK occupancy in nodal tissues, patients enrolled on cohort
2a with accessible tissue underwent lymph node biopsies (core needle biopsy in most cases) at screening and predose (ie, at trough plasma concentrations) on day 3 of week 1. BTK occupancy was measured using an enzyme-linked immunosorbent assay. Free BTK proteins in the cell lysates were captured by a biotinylated-zanubrutinib probe coupled to plates coated with NeutrAvidin. Total BTK protein levels were measured in a parallel assay using plates coated with anti-BTK antibody (BD Biosciences Cat # 611116, RRID: AB_398427) and detected by another anti-BTK antibody (Abcam Cat # AB137503). As this was a phase 1 (first-in-human) study of zanubrutinib, and given that quantitation of BTK occupancy was exploratory, no specific acceptance criteria were prespecified in the study protocol.

Clinical outcomes

End points for part 1 included a preliminary assessment of safety (including determination of the maximum tolerated dose), pharmacokinetics, and BTK occupancy in PBMCs. Part 2 end points included additional pharmacokinetic assessments, BTK occupancy in PBMCs and safety (all cohorts), an assessment of BTK occupancy in nodal tissues (cohort 2a and optionally for other part 2 patients), and a preliminary evaluation of efficacy in specific B-cell malignancies (including cohort 2a). Treatment-emergent adverse events (AEs) were collected until 28 days after the last dose of study treatment or until resolution of drug-related events and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03, and coded using the Medical Dictionary for Regulatory Activities, version 19.0. Efficacy end points included overall response rate (ORR) and complete response (CR) and partial...
response (PR) rates, including PR with lymphocytosis (PR-L), using published criteria, including computed tomography imaging,\textsuperscript{20,21,22} as well as progression-free survival and overall survival. Bone marrow examination was required at screening and to confirm CR. Progression-free survival was defined as the duration from treatment initiation until disease progression or death; overall survival was defined as the time from treatment initiation until death. For the CLL/SLL cohorts, patients were considered evaluable for response if they were enrolled at least 3 months before the data cutoff date or if they had progressed before that date. All results are presented as of September 15, 2017, for dose-finding analysis and November 3, 2017, for CLL/SLL safety and efficacy analyses.

Statistical analysis

The Kaplan-Meier method was used for time-to-event analyses with censoring. For response rates, 95% exact (Clopper-Pearson) confidence intervals (CIs) were provided. Toxicity data for all patients who received ≥1 dose of zanubrutinib were summarized using standard descriptive statistics for part 1/cohort 2a, and CLL/SLL patients separately.

Data sharing statement

All authors had access to original data for the analyses described here. For original data, please contact: constantine.tam@petermac.org

Results
This first-in-human study of zanubrutinib in B-cell malignancies includes results from 144 patients, including 17 enrolled to part 1, 39 enrolled to cohort 2a, and 94 with CLL/SLL in part 2 (including 6 CLL/SLL patients from cohort 2a who were also included in dose-finding analyses; Supplemental Figure S1). Independent audits for one of the trial sites revealed violations of good clinical practice involving 12 patients, including 8 enrolled to part 1. Consequently, all data from these 12 patients were excluded from the primary analyses reported here, and are summarized separately in Supplemental Tables S2–S5.

**Dose finding**

Patients enrolled to dose escalation (part 1) and cohort 2a comprised the dose-finding set (n=56). Patient characteristics are shown in Table 1. In part 1, sequential patient cohorts received oral zanubrutinib at 40 mg once daily (n=3), 80 mg once daily (n=4), 160 mg once daily (n=5), 320 mg once daily (n=1) or 160 mg twice daily (n=4). No dose-limiting toxicities were observed. Based on part 1 safety as well as pharmacokinetic and pharmacodynamic data, the maximally administered dose (either 320 mg once daily or 160 mg twice daily) was chosen for further study in part 2.

Additional information regarding dose and schedule was derived from 39 patients enrolled in cohort 2a, a cohort designed specifically to assess BTK occupancy by zanubrutinib in lymph node tissue. In this cohort, patients were assigned to receive either 320 mg once daily or 160 mg twice daily. Patients were evaluated for safety
and pharmacokinetic and pharmacodynamic properties in combination with those from part 1 to further define the optimal dosing schedule.

The most common AEs in the dose-finding set were upper respiratory tract infection (n=22; 39.3%), contusion (n=20; 35.7%), and cough and diarrhea (n=15; 26.8% each). Grade ≥3 AEs reported in more than 2 patients were anemia (n=7); pneumonia and pyrexia (n=4 each); acute kidney injury and neutropenia (n=3 each; Supplemental Table S6). At the cutoff date, 32 patients (57.1%) in the dose-finding set had discontinued study treatment, including 20 because of disease progression and 8 because of AEs (Supplemental Table S7). Although numbers were small, no significant differences in AE profiles were observed between the 320 mg daily and 160 mg twice daily treatment schedules (Supplemental Table S8).

Pharmacokinetics

Zanubrutinib is rapidly absorbed after oral administration with $C_{\text{max}}$ observed ~2 hours after dosing (Figure 1). The $C_{\text{max}}$ and AUC increased in a nearly dose-proportional manner from 40 to 320 mg after initial dose (Supplemental Table S9). Mean $C_{\text{max}}$ was 346 and 658 ng/mL after a single dose of 160 and 320 mg, respectively. The mean half-life of zanubrutinib administered either as 160 mg twice daily or 320 mg once daily was ~4 hours with minimal accumulation observed after repeated dosing.

Pharmacodynamics
BTK occupancy was assessed in PBMCs from 45 patients across all cohorts and in lymph nodes from 30 patients with available and adequate paired biopsy specimens. In PBMCs, complete or near complete (>95%) BTK occupancy was achieved starting at doses of 40 mg/d; BTK occupancy >95% was observed 4 hours postdose in almost all patients across all doses (Figure 2A). No significant differences were observed across dose groups. These results indicate that BTK remains fully occupied by zanubrutinib well after achieving peak plasma levels.

Median (range) BTK occupancy on day 3 of week 1 (predose) in the 30 pairs of nodal tissue was 94% (82.4%-100%) in the 320-mg once-daily group (n=12) and 100% (86.3%-100%) in the 160-mg twice-daily group (n=18; \( P=0.0189 \) via Mann-Whitney exact test). Nodal BTK occupancy was >95% in 50% of patients receiving 320 mg once daily and in 89% of patients receiving 160 mg twice daily \( (P=0.0342 \) via Fisher’s exact test; Figure 2B). Based on the higher proportion of patients who achieved >95% sustained BTK occupancy in lymph nodes at trough concentrations of zanubrutinib, the 160-mg twice-daily regimen was determined to be the recommended phase 2 dose (RP2D).

**CLL/SLL cohort**

Clinical safety and efficacy data in this report include patients with CLL/SLL (n=94) enrolled and treated in part 2, including 6 CLL/SLL patients enrolled to cohort 2a (Table 1). Twenty-two patients (23.4%) were treatment-naïve. The median number of prior therapies for previously treated patients was 2 (range, 1–9). Some patients had high-risk disease features, including adverse cytogenetics [del(11q), 23.3%; del(17p) and/or \( TP53 \) mutation, 19.1%]. Patients enrolled to the 320-mg once-daily
group (n=40) were given the option to change their treatment regimen to 160 mg twice daily after determination of the RP2D and schedule (Supplemental Table S10). With a median follow-up of 13.7 months (range, 0.4–30.5), 89 patients (94.7%) are continuing study treatment. Two patients (both with untransformed CLL) have discontinued treatment because of progressive disease (1 who previously attained a PR and 1 with a best response of stable disease), whereas 2 others discontinued because of AEs, and 1 for unspecified reasons.

Safety

Most AEs were of grade 1 or 2 severity (Table 2). Grade 3/4 AEs reported in more than 1 patient were neutropenia (n=6), anemia (n=2), pneumonia (n=2), and hypertension (n=2). One patient had febrile neutropenia (grade 3) and 1 patient had disseminated herpes zoster infection (grade 3). Atrial fibrillation (grade 2) occurred in 1 patient with a history of hypertension and hyperlipidemia. Only 1 patient with CLL/SLL (receiving concomitant aspirin) experienced major hemorrhage (grade 3 subcutaneous hemorrhage). Concomitant antiplatelet (aspirin, clopidogrel, or nonsteroidal anti-inflammatory drugs) and anticoagulant (unfractionated or low molecular weight heparin, direct thrombin inhibitors, or warfarin) medications were used by 16.0% and 8.5% of patients, respectively. The exposure-adjusted incidence rate for grade 3 petechiae/purpura/contusion was 0.086 per 100 person-months. There were no deaths in the CLL/SLL cohort.

Efficacy
Of the 94 patients with CLL/SLL, 78 were evaluable for response by virtue of having been enrolled at least 3 months before the data cutoff date or having progressed before that date. At a median follow-up of 13.7 months (range, 0.4–30.5), the ORR was 96.2% (95% CI, 89.2–99.2), including 2 patients (2.6%) who achieved a CR, 63 (80.8%) with PR, and 10 (12.8%) PR-L (Table 3). Early redistribution lymphocytosis was observed with return to baseline within 12 weeks in most patients (Figure 3C). All efficacy-evaluable patients with del(17p) or TP53 mutation responded (n=16; ORR=100% [95% CI, 79.4–100]). Response rates were comparable in treatment-naïve patients and those with relapsed/refractory disease (ORR 100% and 94.6%; CR rates 4.5% and 1.8%, respectively, Table 3). Likewise, reductions in lymph node disease burden observed in treatment-naïve patients (Figure 3A) and patients with relapsed/refractory disease (Figure 3B) were similar. There has been no incidence of Richter transformation. Median progression-free survival has not been reached and 12-month estimated progression-free survival is 100%; 2 patients have progressed at 15.3 and 16.4 months.

**Discussion**

Inhibition of BTK has proven remarkably effective as a mechanism-based therapeutic approach in B-cell malignancies, including CLL/SLL.\(^\text{23}\) Toxicities, some likely related to off-target effects, are the most frequent reason for treatment discontinuation in CLL patients treated with ibrutinib.\(^\text{7,11,24}\) The novel BTK inhibitor
zanubrutinib has improved specificity for BTK compared with ibrutinib, with preclinical data showing improved selectivity (Supplemental Table S1). Consistent with the favorable oral bioavailability in preclinical studies, oral administration of zanubrutinib achieved excellent plasma drug exposures with the RP2D of 160 mg twice daily. After adjusting for plasma protein binding (94.2% for zanubrutinib), this exposure is approximately 8-fold higher than that observed with ibrutinib 560 mg daily. Further, compared with acalabrutinib, another highly specific BTK inhibitor with demonstrated activity in CLL, zanubrutinib has a longer half-life (4 hours vs. 1 hour, respectively) leading to more sustained exposure. This heightened exposure translates to complete inhibition of BTK in lymph node biopsy specimens and is hypothesized to maximize the chances of achieving deep and sustained remissions.

The constant BTK inhibition across blood and tissue compartments with zanubrutinib was associated with a favorable toxicity profile, in keeping with the drug’s high selectivity for BTK. Specifically, the relative sparing of EGFR from inhibition likely explains the lower rates of diarrhea and rash observed with zanubrutinib (~20%, with no grade ≥3 AEs, compared with 42%–51% for ibrutinib [Table 2]). Furthermore, although the mechanisms behind the major bleeding and atrial fibrillation associated with ibrutinib are not fully understood, these toxicities were infrequent, with each having been reported in only 1 patient in the current study. Lower-grade bleeding was still observed, most likely due to the on-target effect of BTK inhibition on platelet function, which is a class effect of all BTK inhibitors. However, zanubrutinib’s relative sparing of other kinases relevant to
hemostasis, such as TEC, may favorably influence the incidence and severity of bleeding, consistent with our preliminary observations. In support of the hypothesis that highly specific BTK inhibition may lead to better drug tolerance, we note that only 2 patients in the CLL/SLL cohorts ceased study drug because of AEs. Additionally, lower rates of AEs have also been reported in patients treated with acalabrutinib.

A unique aspect of this study is the detailed evaluation of the extent of BTK inhibition in lymph nodes. To our knowledge, a systematic evaluation of target inhibition in nodal tissues has not been undertaken with other BTK inhibitors. Notably, zanubrutinib achieves complete or near complete occupancy of BTK in lymph nodes at the RP2D. As BTK is irreversibly bound by all BTK inhibitors in clinical use, recovery of BTK function is solely a function of new protein synthesis. Therefore, it is not surprising that twice-daily dosing of zanubrutinib was more efficient in maintaining continuous BTK blockade in lymph nodes (100% median occupancy at trough plasma concentrations), and this led to the selection of 160 mg twice daily, rather than 320 mg once daily, as the RP2D on pharmacodynamic grounds. No clear differences in efficacy or safety were evident between the daily and split dose regimens. However, the power of the study to detect such differences was low given the high response rates with both regimens.

The clinical activity of zanubrutinib in CLL/SLL patients in this study was notable, with high ORRs in patients with treatment-naïve (100%) and relapsed/refractory (93%) disease. Response rates with zanubrutinib were similarly high in patients regardless of high-risk cytogenetic features. Complete responses were uncommon
at this early timepoint, consistent with previous experience with other BTK inhibitors.\textsuperscript{5,12,14,23,28} Longer follow-up is needed to more precisely determine the final complete remission rate and response duration for this CLL/SLL cohort. The fact that zanubrutinib and ibrutinib share the same binding site on BTK as ibrutinib suggests that cells bearing the C481S mutation may emerge with longer follow up.

In this first-in-human study, zanubrutinib demonstrated encouraging activity in patients with relapsed/refractory and treatment-naïve CLL/SLL, with good tolerability. Two ongoing randomized studies of zanubrutinib versus ibrutinib (NCT03053440 and NCT03734016) aim to determine whether consistent, continuous BTK blockade with a selective inhibitor results in fewer off-target effects and translates into improvements in disease control.
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Authorship

Contribution: Together with BeiGene authors (L.W., L.H., and J.H.), C.S.T., J.T., J.F.S., S.O., and A.W.R. were responsible for study design, and R.E., J.H., S.O., and C.S.T. contributed to data interpretation and analysis. All investigators (C.S.T., J.T., J.A.B., G.C., D.G., R.H., P.B.J., P.M., J.M., S.O., J.F.S., D.S., A.T., and A.W.R.) and their respective research teams reviewed patient records and contributed to data collection. BeiGene authors (Y.Z., Y.Y., Z.S., Y.O., and L.W.) confirmed assay validation and data accuracy and compiled data for summation and analysis. Y.Z., Y.Y., Z.S., Y.O., and L.W. performed data analysis and interpretation. C.S.T., A.W.R., R.E., J.H., and J.H. contributed to the first draft of the manuscript; C.S.T., R.E., and J.H. further contributed to final manuscript writing. BeiGene was involved in study design, compilation of data, and statistical analysis. The corresponding author, C.S.T., had final responsibility to submit for publication. All authors had full access to all of the data. All authors carefully reviewed the manuscript and approved the final version.
Conflict-of-interest disclosure: C.S.T. reports research funding, personal fees, and other from BeiGene during the conduct of the study; personal fees from Janssen and Pharmacyclics outside the submitted work. G.C. reports research funding from BeiGene during the conduct of the study; served on an advisory board for AbbVie Pty Ltd and received travel grants from Amgen Australia and Takeda Australia outside the submitted work. P.M. reports personal fees and non-financial support from Novartis, Roche, Janssen, Amgen, and Celgene outside the submitted work. J.M. reports personal fees from Gilead/Kite Pharma, Pharmacyclics/Janssen, Bayer, Alexion, Pfizer, Juno/Celgene, Bristol-Myers Squibb, Genentech, and Kyowa outside the submitted work. S.O. reports research funding from BeiGene during the conduct of the study. J.F.S. reports grants, personal fees, and other from AbbVie and Janssen; personal fees and other from Acerta and Sunesis outside the submitted work. D.S. reports grants from BeiGene during the conduct of the study; grants from Amgen, Acerta, Pharmacyclics, Millennium, Sanofi, and BeiGene; grants and personal fees from AbbVie, Janssen, Roche, Celgene, and MSD outside the submitted work. A.W.R. reports research funding from BeiGene during the conduct of the study; grants from AbbVie and Janssen, other from Genentech outside the submitted work; and is an employee of the Walter and Eliza Hall Institute which receives milestone and royalty payments relating to venetoclax. R.E., Z.T., L.H., J.H., and W.N. are employees of BeiGene USA. L.W. is an employee of BeiGene Beijing. Y.Y. is an employee of BeiGene Shanghai. J.T., D.G., R.H., P.B.J., A.T., and J.A.B. have nothing to disclose.
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References


Table 1. Demographics and baseline disease characteristics for all patients in part 1, cohort 2a, and patients with CLL/SLL in part 2

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Dose escalation* (Part 1; n=17)</th>
<th>Cohort 2a (Part 2; n=39)</th>
<th>CLL/SLL† (Part 2; n=94)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range), y</td>
<td>67 (41–85)</td>
<td>69 (24–87)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>42 (75.0)</td>
<td>73 (77.7)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>14 (25.0)</td>
<td>21 (22.3)</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>45 (80.4)</td>
<td>86 (91.5)</td>
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<tr>
<td>Black or African American</td>
<td>0</td>
<td>1 (1.1)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>9 (16.1)</td>
<td>4 (4.3)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>2 (3.6)</td>
<td>3 (3.2)</td>
<td></td>
</tr>
<tr>
<td>ECOG performance status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>27 (48.2)</td>
<td>47 (50.0)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>24 (42.9)</td>
<td>42 (44.7)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>5 (8.9)</td>
<td>5 (5.3)</td>
<td></td>
</tr>
<tr>
<td>Prior treatment status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment-naïve</td>
<td>1 (1.8)</td>
<td>22 (23.4)</td>
<td></td>
</tr>
<tr>
<td>Relapsed or refractory</td>
<td>55 (98.2)</td>
<td>72 (76.6)</td>
<td></td>
</tr>
<tr>
<td>Cytogenetics, n/N evaluable</td>
<td>2 (0–7)</td>
<td>2 (1–9)†</td>
<td></td>
</tr>
<tr>
<td>----------------------------</td>
<td>---------</td>
<td>---------</td>
<td></td>
</tr>
<tr>
<td>del(17p) or TP53 mutation</td>
<td>–</td>
<td>18/94 (19.1)</td>
<td></td>
</tr>
<tr>
<td>del(11q)</td>
<td>–</td>
<td>17/73 (23.3)</td>
<td></td>
</tr>
<tr>
<td>Unmutated IgHV</td>
<td>–</td>
<td>14/21 (66.7)</td>
<td></td>
</tr>
<tr>
<td>Bulky disease (&gt;10 cm)</td>
<td>0</td>
<td>5 (5.3)</td>
<td></td>
</tr>
</tbody>
</table>

Values shown are n (%) unless otherwise indicated.

CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; ECOG, Eastern Cooperative Oncology Group; IgHV, immunoglobulin variable-region heavy chain.

*Includes the following B-cell malignancies histologies: CLL/SLL (n=4), Waldenström macroglobulinemia (n=4), mantle cell lymphoma (n=6), diffuse large B-cell lymphoma (n=2), and hairy cell leukemia (n=1).

†Includes 6 patients also included in cohort 2a.

‡Relapsed or refractory patients only.

§Prior therapies included purine nucleoside analogues (fludarabine and pentostatin), alkylating agents (cyclophosphamide and chlorambucil), anti-CD20 antibodies (rituximab, ofatumumab, and obinutuzumab) and bendamustine either alone or in combination; anthracycline-based regimens (eg, CHOP) and/or CVP; alemtuzumab; and lenalidomide. Three patients had prior exposure to a BCL-2 inhibitor (venetoclax or navitoclax) and 2 patients received prior therapy with a phosphoinositide 3-kinase inhibitor (idelalisib or duvelisib).

ǁDenominators are the number of patients with valid assessments.
Table 2. Adverse events occurring in patients with CLL/SLL in part 2

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Any grade</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any event, n (%)</td>
<td>89 (94.7)</td>
<td>34 (36.2)</td>
</tr>
<tr>
<td>Contusion</td>
<td>33 (35.1)</td>
<td>0</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>31 (33.0)</td>
<td>0</td>
</tr>
<tr>
<td>Cough</td>
<td>24 (25.5)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>20 (21.3)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>18 (19.1)</td>
<td>0</td>
</tr>
<tr>
<td>Back pain</td>
<td>14 (14.9)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Hematuria</td>
<td>14 (14.9)</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>13 (13.8)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>13 (13.8)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Rash</td>
<td>12 (12.8)</td>
<td>0</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>11 (11.7)</td>
<td>0</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>11 (11.7)</td>
<td>0</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>10 (10.6)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Petechiae</td>
<td>8 (8.5)</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>7 (7.4)</td>
<td>0</td>
</tr>
<tr>
<td>Purpura</td>
<td>7 (7.4)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>7 (7.4)</td>
<td>6 (6.4)</td>
</tr>
<tr>
<td>Condition</td>
<td>No. (%)</td>
<td>No. (%)</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>----------</td>
<td>---------</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>7 (7.4)</td>
<td>2 (2.1)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>7 (7.4)</td>
<td>0</td>
</tr>
<tr>
<td>Limb injury</td>
<td>6 (6.7)</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>5 (5.3)</td>
<td>0</td>
</tr>
<tr>
<td>Basal cell carcinoma</td>
<td>5 (5.3)</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>5 (5.3)</td>
<td>0</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>5 (5.3)</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>5 (5.3)</td>
<td>0</td>
</tr>
<tr>
<td>Post-procedural contusion</td>
<td>5 (5.3)</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5 (5.3)</td>
<td>2 (2.1)</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>5 (5.3)</td>
<td>1 (1.1)</td>
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<tr>
<td>Nasopharyngitis</td>
<td>5 (5.3)</td>
<td>0</td>
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<tr>
<td>Squamous cell carcinoma of the skin</td>
<td>5 (5.3)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Anemia</td>
<td>3 (3.2)</td>
<td>2 (2.1)</td>
</tr>
</tbody>
</table>

All adverse events occurring in ≥5% of patients and grade ≥3 adverse events occurring in 2 or more patients are reported.

CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma.
Table 3. Response rates in evaluable patients with CLL/SLL in part 2

<table>
<thead>
<tr>
<th>Best response, n (%) [95% CI]</th>
<th>Treatment-naïve (n=22)</th>
<th>Relapsed or refractory (n=56)</th>
<th>Total (N=78)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>22 (100)</td>
<td>53 (94.6)</td>
<td>75 (96.2)</td>
</tr>
<tr>
<td></td>
<td>[84.56–100]</td>
<td>[85.13–98.88]</td>
<td>[89.17–99.2]</td>
</tr>
<tr>
<td>CR</td>
<td>1 (4.5)</td>
<td>1 (1.8)</td>
<td>2 (2.6)</td>
</tr>
<tr>
<td>PR</td>
<td>18 (81.8)</td>
<td>45 (80.4)</td>
<td>63 (80.8)</td>
</tr>
<tr>
<td>PRL</td>
<td>3 (13.6)</td>
<td>7 (12.5)</td>
<td>10 (12.8)</td>
</tr>
<tr>
<td>SD</td>
<td>0</td>
<td>2 (3.6)</td>
<td>2 (2.6)</td>
</tr>
<tr>
<td>PD</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Missing/Not evaluable</td>
<td>0</td>
<td>1 (1.8)</td>
<td>1 (1.3)</td>
</tr>
</tbody>
</table>

Sixteen patients were not included because the first protocol-specified response assessment time point of 3 months from treatment start date had not been reached and progression had not been observed.

CI, confidence interval; CR, complete response; ORR, overall response rate; PD, progressive disease; PR, partial response; PRL, partial response with lymphocytosis; SD, stable disease.
Figures

Figure 1. Plasma concentration-time profile of zanubrutinib after initial doses of 40, 80, 160, and 320 mg once daily and 160 mg twice daily in part 1 and cohort 2a patients. Lines represent mean plasma concentration and error bars indicate standard deviation.

*For the 160-mg twice-daily dose group, patients received only the morning dose (half of the daily dose) for the 24-hour pharmacokinetic evaluation on day 1 of week 1. BID, twice daily; QD, once daily.

Figure 2. BTK occupancy in (A) PBMCs and (B) nodal tissue. Data for individual patients at each time point are shown. Patient numbers and the percentage of patients with >95% BTK occupancy are noted. Triangles indicate percentages of BTK occupancy in PBMCs of patients predose, at 4 and 24 hours after zanubrutinib treatment on day 1 of week 1 (W1D1), predose on day 3 of week 1 (W1D3), and day 1 of week 2 (W2D1). BTK occupancy in lymph node biopsy specimens was assessed at baseline and predose on W1D3 and calculated as 1−([free BTK on day 3 predose] × [total BTK at screening])/([free BTK at screening] × [total BTK on day 3 predose]). Median values are shown as lines through the individual triangles. BID, twice daily; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; QD, once daily; WM, Waldenström macroglobulinemia.
Figure 3. Reductions in the sum of the products of perpendicular diameters of target lymph nodes in patients with (A) treatment-naïve or (B) relapsed/refractory CLL/SLL; (C) kinetics of lymphocytosis Data indicate median percentage change in lymphocyte counts and 95% CIs. ALC, absolute lymphocyte count; CR, complete response; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable disease; SPD, sum of the products of lymph node diameters as assessed by computed tomography scan.
Zanubrutinib Concentration, ng/mL

Time, hours

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Phase 1 study of selective BTK inhibitor zanubrutinib in B-cell malignancies and safety and efficacy evaluation in CLL

Constantine Si Lun Tam, Judith Trotman, Stephen Opat, Jan A Burger, Gavin Cull, David J Gottlieb, Rosemary Anne Harrup, Patrick Johnston, Paula Marlton, Javier Munoz, John F. Seymour, David R Simpson, Alessandra Tedeschi, Rebecca Elstrom, Yiling Yu, Zhiyu Tang, Lynn Han, Jane Huang, William Novotny, Lai Wang and Andrew W. Roberts

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