Phase I study of the Syk inhibitor sovleplenib in relapsed or refractory mature B-cell tumors

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Abstract

Sovleplenib (HMPL-523) is a selective spleen tyrosine kinase (Syk) inhibitor with anti-tumor activity in preclinical models of B-cell malignancy. We conducted a dose-escalation and dose-expansion phase I study of sovleplenib in patients with relapsed/refractory mature B-cell tumors. Dose escalation followed a 3+3 design; patients received oral sovleplenib (200-800 mg once daily [q.d.] or 200 mg twice daily [b.i.d.], 28-day cycles). During dose expansion, patients were enrolled into four cohorts per lymphoma classification and treated at the recommended phase II dose (RP2D) (*clinicaltrials gov. Identifier: NCT02857998*). Overall, 134 Chinese patients were enrolled (dose escalation, N=27; dose expansion, N=107). Five patients experienced dose-limiting toxicities: one each of amylase increased (200 mg q.d.), febrile neutropenia (800 mg q.d.), renal failure (800 mg q.d.), hyperuricemia and blood creatine phosphokinase increased (200 mg b.i.d.) and blood bilirubin increased and pneumonia (200 mg b.i.d.). RP2D was determined as 600 mg (>65 kg) or 400 mg (≤65 kg) q.d.. The primary efficacy end point of independent review committee-assessed objective response rate in indolent B-cell lymphoma was 50.8% (95% confidence interval: 37.5-64.1) in 59 evaluable patients at RP2D (follicular lymphoma: 60.5%, marginal zone lymphoma: 28.6%, lymphoplasmacytic lymphoma/Waldenström macroglobulinemia, 0%). The most common (≥10% patients) grade ≥3 treatment-related adverse events in the dose-expansion phase were decreased neutrophil count (29.9%), pneumonia (12.1%) and decreased white blood cell count (11.2%). Pharmacokinetic exposures increased dose-proportionally with ascending dose levels from 200-800 mg, without observed saturation. Sovleplenib showed anti-tumor activity in relapsed/refractory B-cell lymphoma with acceptable safety. Further studies are warranted.

Introduction

Non-Hodgkin lymphomas (NHL) are the 12th most common cancer globally, with more than 544,000 diagnoses *per annum*.[1,2] In China, approximately 92,800 NHL cases are diagnosed annually, 64% of which are mature B-cell malignancies.[1,3] A fraction of patients with mature B-cell tumors are resistant to or relapse after current first-line therapies; therefore, an unmet need exists for new treatment options.[4,5]

Spleen tyrosine kinase (Syk) is a cytoplasmic protein tyrosine kinase that is ubiquitously expressed in hematopoietic cells, including B cells.[6] Syk mediates B-cell receptor (BCR) signaling, which is pivotal in the pathogenesis of B-cell lymphoma[7,8] and has been identified as an oncogenic driver in B-cell malignancies.[8] Targeting Syk signaling, which is upstream of both Bruton tyrosine kinase (BTK) and phosphoinositide 3-kinase (PI3Kδ), may overcome drug resistance to BTK inhibitors (BTKi) or PI3Kδ inhibitors in chronic lymphocytic leukemia (CLL).[9] Blocking Syk activity, using either small interfering RNA or a chemical inhibitor, leads to cell cycle arrest in diffuse large B-cell lymphoma (DLBCL) cells.[10] Syk inhibition also blocks cellular proliferation in follicular lymphoma (FL), mantle cell lymphoma (MCL) and Burkitt lymphoma.[11] Targeting the Syk pathway has demonstrated promise in the treatment of B-cell malignancies given the clinical activities of several Syk inhibitors in clinical trials;[9,12-22] however, to date, no Syk inhibitors are approved for lymphoma.

Sovleplenib (HMPL-523) is a novel, small-molecule, potent and highly selective oral Syk inhibitor.[23] Sovleplenib demonstrated a superior selectivity compared to R406 (the active metabolite of fostamatinib), especially against KDR and RET. *In vitro*, sovleplenib could effectively inhibit the phosphorylation of Syk and its downstream signaling molecule BLNK, ERK, AKT, PLCγ 1 and P38. Sovleplenib potently inhibited B-cell activation in human whole blood with a half maximal effective concentration (EC_{50}) of 0.157 μM and anti-IgD antibody induced B-cell activation in rat and mouse whole blood with EC_{50} of 0.546 and 1.000 μM, respectively. Moreover, sovleplenib inhibited cell survival in a panel of B-cell lymphoma cell lines, with a lower half maximal inhibitory concentration (IC_{50}) and an increased apoptotic rate in REC-1 cells compared with other Syk inhibitors.[24] We conducted a phase I study to determine the safety, tolerability, efficacy and pharmacokinetics of sovleplenib in patients with relapsed/refractory mature B-cell malignancies in China.

Methods

Study design

This multicenter, open-label phase I study with dose-escalation and dose-expansion phases was conducted in China between December 2016 and April 2021. Dose escalation employed a conventional 3+3 study design with doses from 200-800 mg once daily (q.d.). One additional regimen with a 200 mg twice-daily (b.i.d.) starting dose was explored. Dose expansion at the recommended phase II dose (RP2D) was conducted using a basket design for four cohorts: (A) CLL/small lymphocytic lymphoma (SLL), (B) aggressive B-cell lymphoma, (C) MCL and (D) indolent B-cell lymphoma. Patients received oral sovleplenib in 28-day cycles until progressive disease (PD), intolerable toxicity or consent withdrawal. Prophylactic antibiotics were not permitted.

The primary objective of the dose-escalation phase was to evaluate safety and determine the RP2D by the safety review committee (SRC). The primary objective of the dose-expansion phase was to evaluate safety and preliminary efficacy.

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. Ethical approval was obtained by the ethics committees. A list of ethics committees that approved the study is included in the *Online Supplementary Appendix*. All patients provided written informed consent.

Patients

Eligible adult patients had pathologically confirmed mature B-cell tumors that progressed or were ineligible for standard treatment (see *Online Supplementary Appendix*), including CLL/SLL, aggressive B-cell lymphoma (DLBCL, Richter syndrome and grade 3b FL), MCL or indolent B-cell lymphoma (marginal zone lymphoma [MZL], lymphoplasmacytic lymphoma/Waldenström macroglobulinemia [LPL/WM], grades 1, 2, 3a FL) in dose expansion; an Eastern Cooperative Oncology Group performance status of 0-1; and bidimensionally measurable disease at baseline in dose expansion (except CLL or LPL/WM patients). Patients with protocol-defined laboratory abnormalities or a history of clinically significant liver disease were excluded. Detailed eligibility criteria are listed in the *Online Supplementary Appendix*.

Assessments

Treatment-emergent adverse events (TEAE) were assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events v4.03. Tumor response was assessed according to modified IWCLL 2008 criteria for CLL/SLL, IWM-7 for LPL/WM and modified Cheson 2014 criteria for other B-cell lymphomas. Responses were assessed with enhanced computed tomography (CT) every 8 weeks for the first 24 weeks, and every 12 weeks thereafter. For DLBCL, MCL, FL, and other fluorodeoxyglucose-sensitive lymphoma, responses were assessed by positron emission tomography-computed tomography (PET-CT) with enhanced CT according to Cheson 2014 criteria. For pharmacokinetic analyses, plasma samples were collected at multiple time points (*Online Supplementary Appendix*). Plasma concentrations of sovleplenib and its metabolites were assessed using liquid chromatography-tandem mass spectrometry (LabCorp Drug Development, Shanghai, China), and biomarker concentrations were measured by MILLIPLEX human cytokine/chemokine panel assay (Millipore).

Statistical analysis

The study planned to enroll 217-232 patients, with 27-42 during dose escalation and 190 during dose expansion based on adverse event (AE) assumptions (*Online Supple-*

mentary Appendix).

Patients who received ≥1 dose of sovleplenib were included in the safety set (SS). The efficacy-evaluable analysis set (EEAS) included all patients in the SS who had ≥1 valid postbaseline tumor evaluation. Objective response rate (ORR) and 95% confidence interval (CI) were calculated using the Clopper-Pearson method. Time to event was estimated using the Kaplan-Meier method. Analyses of time to response (TTR) and duration of response (DOR) were based on the EEAS, and analyses of time to progression (TTP) and progression-free survival (PFS) were based on the SS. *Post hoc* analyses of investigator-assessed tumor response were performed in CLL/SLL or FL according to prior treatment status.

The pharmacokinetic analysis set included patients who received ≥1 dose of sovleplenib with concentration data available. Pharmacokinetic parameters were analyzed with a non-compartmental model using Phoenix WinNonlin software (v8.1). Pharmacokinetic and biomarker analyses were summarized using descriptive statistics.

Results

Patients and demographics

Between December 15, 2016, and September 3, 2020, 166 patients were screened at 18 centers across China; 134 were enrolled and received sovleplenib (Figure 1).

Dose escalation

During dose escalation, 27 patients were enrolled (Figure 1). Among them, 23 (85.1%) were classified as Ann Arbor

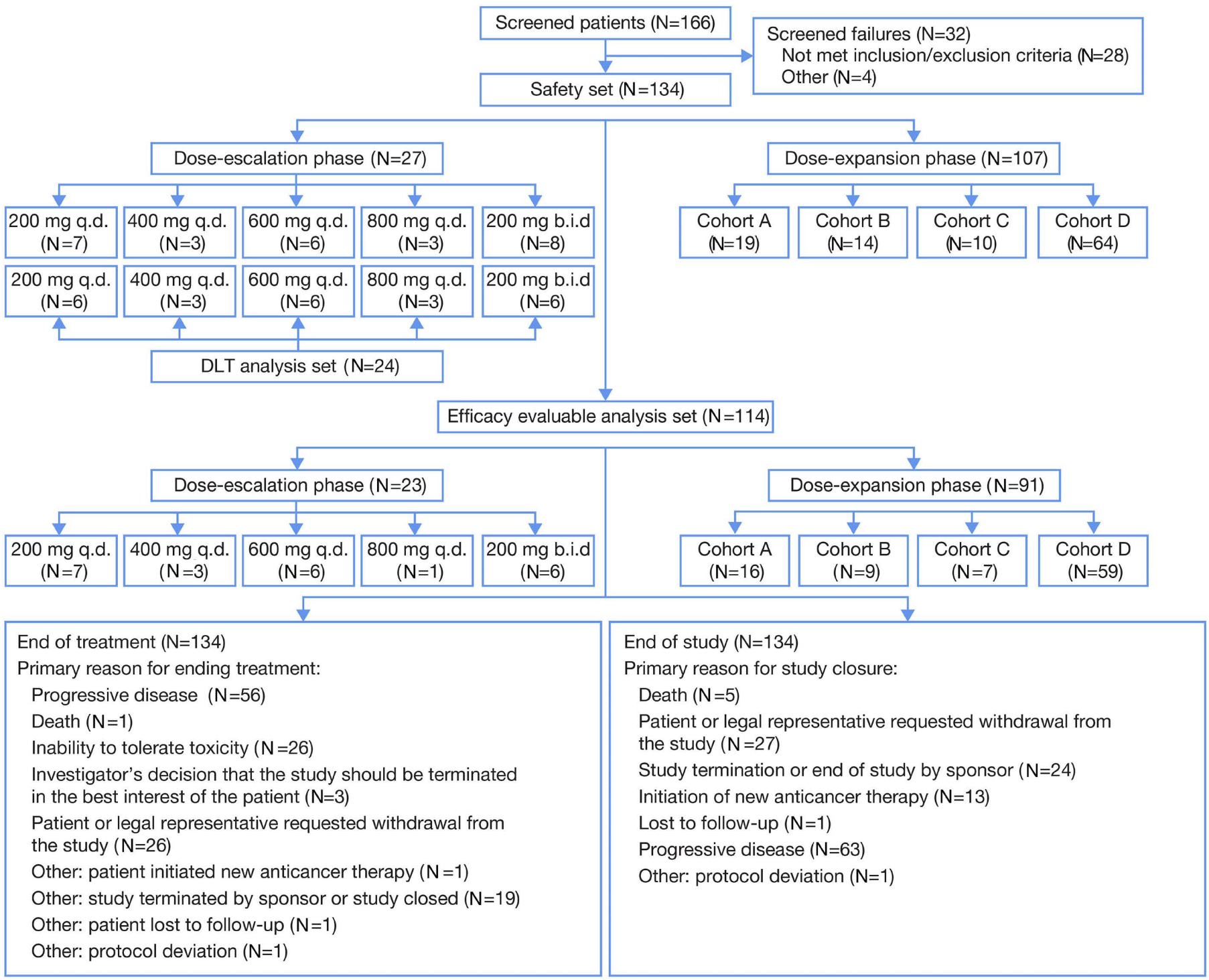

Figure 1. Patient disposition. The safety set (SS) includes all patients who have taken at least 1 dose of study drug. The efficacy-evaluable analysis set (EEAS) includes all patients in the SS who have at least 1 valid postbaseline tumor evaluation. b.i.d.: twice daily; DLT: dose-limiting toxicity; q.d.: once daily.

stage III or IV. The median time from diagnosis to first dose was 32.9 months (range, 5.4-104.3) (*Online Supplementary Table S1*). All patients had received previous anti-tumor treatment, with 13 (48.1%) having received ≥3 lines of treatment. Twenty-one (77.8%) patients had received previous anti-CD20 antibody treatment. All patients received ≥1 dose of sovleplenib, as follows: 200 mg q.d. (N=7), 400 mg q.d. (N=3), 600 mg q.d. (N=6), 800 mg q.d. (N=3), 200 mg b.i.d. (N=8). At data cutoff (April 30, 2021), all patients had discontinued treatment, most of them discontinued because of PD (N=12; 44.4%).

Dose expansion

During dose expansion, 107 patients were enrolled in cohorts A (N=19), B (N=14), C (N=10) or D (N=64). The number of enrolled patients being less than the planned sample size was due to difficulties in enrolling patients with CLL/SLL and indolent B-cell lymphoma. The median time from diagnosis to first dose was 37.3 months (range, 1.9-152.4) (Table 1). Of patients enrolled, 83 (77.6%) were classified as Ann Arbor stage III or IV. All patients received prior anti-tumor treatment, and 48 (44.9%) received ≥3 lines of treatment. Eighty-seven (81.3%) patients had received previous anti-CD20 antibody treatment. In cohort A, eight (42.1%) patients had received a prior BTKi, and two (10.5%) patients had a received prior BCL-2 inhibitor (Table 1). Other baseline demographic and disease characteristics are presented in *Online Supplementary Table S2*. One (0.9%)

Table 1. Baseline demographic and disease characteristics of the safety set in the dose-expansion phase.

Parameter	CLL/SLL N=19	Aggressive B-cell lymphomas N=14	MCL N=10	Indolent B-cell lymphoma N=64	Total N=107
Age in years, median (range)	57.0 (33-78)	65.0 (40-74)	65.0 (56-73)	57.0 (30-77)	58.0 (30-78)
Sex: male, N (%)	13 (68.4)	4 (28.6)	9 (90.0)	36 (56.3)	62 (57.9)
Baseline ECOG score, N (%) 0 1	 7 (36.8) 12 (63.2)	 5 (35.7) 9 (64.3)	 4 (40.0) 6 (60.0)	 29 (45.3) 35 (54.7)	 45 (42.1) 62 (57.9)
Median time in months since diagnosis (range)	42.10 (4.1-152.4)	22.85 (3.8-107.2)	47.30 (15.3-135.5)	35.15 (1.9-152.2)	37.30 (1.9-152.4)
Time since last relapse or disease progression N of patients Months, median (range)	 17 1.05 (0.3-2.9)	 12 1.05 (0.5-2.1)	 9 1.91 (0.3-17.5)	 59 1.31 (0.2-42.6)	 97 1.28 (0.2-42.6)
Lines of last anti-tumor drug treatment, N (%) 1 line 2 lines ≥3 lines	 4 (21.1) 6 (31.6) 9 (47.4)	 4 (28.6) 1 (7.1) 9 (64.3)	 2 (20.0) 3 (30.0) 5 (50.0)	 22 (34.4) 17 (26.6) 25 (39.1)	 32 (29.9) 27 (25.2) 48 (44.9)
Median time in months from last systemic therapy to sovleplenib treatment (range)	2.05 (1.0-58.3)	2.55 (1.0-28.2)	6.00 (1.2-63.8)	5.90 (1.0-50.8)	3.80 (1.0-63.8)
Prior anticancer agents, N (%)	19 (100)	14 (100)	10 (100)	64 (100)	107 (100)
Chemotherapy, N (%) Alkylating agents Anthracycline Vinblastines Purine analogs	 18 (94.7) 9 (47.4) 7 (36.8) 12 (63.2)	 14 (100) 13 (92.9) 10 (71.4) 4 (28.6)	 10 (100) 10 (100) 5 (50.0) 2 (20.0)	 63 (98.4) 62 (96.9) 39 (60.9) 15 (23.4)	 105 (98.1) 94 (87.9) 61 (57.0) 33 (30.8)
Rituximab-based therapy, N (%) Anti-CD20 antibody	 12 (63.2)	 9 (64.3)	 9 (90.0)	 57 (89.1)	 87 (81.3)
BCR inhibitors, N (%)	8 (42.1)	3 (21.4)	3 (30.0)	5 (7.8)	19 (17.8)
Immunomodulators, N (%) BTK inhibitor Pi3K inhibitors BCL-2 inhibitor	5 (26.3) 8 (42.1) 0 2 (10.5)	1 (7.1) 3 (21.4) 0 0	0 2 (20.0) 1 (10.0) 0	12 (18.8) 4 (6.3) 3 (4.7) 0	18 (16.8) 17 (15.9) 4 (3.7) 2 (1.9)
Prior ASCT, N (%)	0	1 (7.1)	0	0	1 (0.9)

ASCT: autologous stem cell therapy; BCL-2: B-lymphocytoma-2; BCR: B-cell receptor; BTK: Bruton tyrosine kinase; CLL: chronic lymphocytic leukemia; DLBCL: diffuse large B-cell lymphoma; ECOG: Eastern Cooperative Oncology Group; IPI: International Prognostic Index; MCL: mantle cell lymphoma; Pi3K: phosphatidylinositol 3-kinase; SLL: small lymphocytic lymphoma.

patient had received autologous hematopoietic stem cell transplant. As of data cutoff (April 30, 2021), all patients had discontinued treatment; most of them discontinued because of PD (N=44; 41.1%).

Safety/adverse events

Dose escalation

The median duration of exposure was 3.2 months and 92.6% of patients had a relative dose intensity between 80% and 110%.

One patient, two patients, and two patients treated with 200 mg q.d., 200 mg b.i.d., and 800 mg q.d., respectively, experienced dose-limiting toxicity (DLT) events (definitions of DLT are stated in the *Online Supplementary Appendix*): grade 3 amylase increased (200 mg q.d., dose interruption, resolved without supportive or concomitant treatment), grade 4 hyperuricemia and blood creatine phosphokinase increased (200 mg b.i.d., dose interruption, unknown outcome), grade 3 blood bilirubin increased and pneumonia (200 mg b.i.d., treatment discontinuation due to pneumonia, both events resolved with supportive or concomitant treatment), grade 3 febrile neutropenia (800 mg q.d., dose interruption, resolved with supportive or concomitant treatment), and grade 3 renal failure (800 mg q.d., treatment discontinuation, resolved with supportive or concomitant treatment). The maximum tolerated dose was determined as 600 mg q.d., and the SRC determined this as the recommended dose for dose expansion on December 6, 2017. As of July 30, 2018, of 28 patients treated with 600 mg q.d., nine (32.1%) experienced grade ≥3 treatment-related AE (TRAE) during the first cycle of study treatment. In the exploratory analysis, patients who experienced treatment-related grade 3 AE had higher plasma exposure of sovleplenib and tended to have lower body weight (≤65 kg) *versus* those who experienced no drug-related grade ≥3 AE. In addition, drug exposure was body weight-dependent, evidenced by higher plasma sovleplenib concentration detected in patients with lower body weight. Therefore, weight-based dosing was introduced in the expansion cohort to reduce the risk of grade ≥3 AE in patients with lower body weight. The SRC recommended the RP2D of 600 mg q.d. in patients with a weight of >65 kg and 400 mg q.d. in those with a weight of ≤65 kg. If patients did not experience grade ≥2 AE at the starting dose of 400 mg q.d., after one or two treatment cycles the dose could be increased to 500 mg q.d. to maximize treatment efficacy. All (100%) patients experienced TEAE and, among them, 17 (63.0%) reported grade ≥3 TEAE. No fatal TEAE were reported. TEAE leading to treatment discontinuation occurred in five (18.5%) patients, including pneumonia in two (7.4%) patients (1 in 200 mg q.d. and 1 in 200 b.i.d.) and renal failure, malignant pleural effusion and anemia in one patient each. Pneumonia (1 patient in 200 mg b.i.d.), renal failure and anemia were considered possibly related to treatment, and the other TEAE were unlikely related. The event of malignant pleural effusion was resolved with closed thoracentesis drainage. All (100%) patients had TRAE (Table 2); 13 (48.1%) patients had grade ≥3 TRAE. Five patients experienced treatment-related serious AE, including pneumonia (N=2; 200 mg q.d. and 200 mg b.i.d.), upper respiratory infection (N=1; 200 mg q.d.), blood bilirubin increased (N=1; 200 mg b.i.d.), interstitial lung disease (N=1; 600 mg q.d.), renal failure (N=1; 800 mg q.d.) and febrile neutropenia (N=1; 800 mg q.d.). All treatment-related serious AE were grade 3 and recovered/resolved with symptomatic treatment, dose modification and/or dose discontinuation. Thirteen (48.1%) patients reported TEAE leading to dose interruption or reduction; most common (≥2 patients) were neutrophil count decreased (18.5%), white blood cell count decreased (11.1%), blood bilirubin increased (7.4%), pneumonia (7.4%) and febrile neutropenia (7.4%).

Dose expansion

The median duration of exposure was 3.7 months (range, 0.1-35.7 months); 91.6% of patients had a relative dose intensity between 80% and 110%.

During dose expansion, 106 (99.1%) patients reported TEAE; among them, 105 (98.1%) were related to study drug (Table 2). The most common (≥30%) TRAE included neutrophil count decreased (60.7%), aspartate aminotransferase increased (51.4%), white blood cell count decreased (50.5%), alanine aminotransferase increased (44.9%), anemia (32.7%) and platelet count decreased (31.8%). The common grade ≥3 TRAE with an incidence of ≥5% included neutrophil count decreased (29.9%), pneumonia (12.1%), white blood cell count decreased (11.2%) and platelet count decreased (9.3%). Four (3.7%) patients (1 patient in cohort B and 3 patients in cohort D) experienced grade 1-2 blood lactate dehydrogenase increased; among these, two events were considered as treatment related. TEAE leading to death were reported in five (4.7%) patients, including one case each of sudden cardiac death, platelet count decreased, interstitial lung disease, pneumonia and acute kidney injury; all were considered treatment-related (possibly related). In addition, 20 (18.7%) patients experienced TEAE that led to treatment discontinuation, among which pneumonia (N=5; 4.7%) and interstitial lung disease (N=3; 2.8%) were most common. No notable difference was observed among cohorts for the incidence of TEAE leading to treatment discontinuation.

Tumor response

Dose escalation

Based on the EEAS (N=23), the overall ORR during dose escalation was 21.7% (95% CI: 7.5-43.7), where five patients (21.7%; 4 FL and 1 SLL) achieved partial response (PR), at 400 mg q.d. (1 PR), 600 mg q.d. (3 PR) and 200 mg b.i.d. (1 PR), and none achieved complete response (CR). In addition, nine (39.1%) achieved stable disease (SD). Of five responders, median TTR (mTTR) was 3.6 months (95% CI:

Table 2. Common treatment-emergent adverse events that related to study drug (any grade ≥20%) in the dose-escalation and dose-expansion phases.

Dose-escalation phase, N (%)	200 mg q.d. N=7		400 mg q.d. N=3		600 mg q.d. N=6		800 mg q.d. N=3		200 mg b.i.d. N=8		Total N=27	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
At least one TEAE related to study drug	7 (100)	3 (42.9)	3 (100)	1 (33.3)	6 (100)	3 (50.0)	3 (100)	3 (100)	8 (100)	3 (37.5)	27 (100)	13 (48.1)
Aspartate aminotransferase increased	1 (14.3)	0	1 (33.3)	0	5 (83.3)	0	2 (66.7)	0	4 (50.0)	0	13 (48.1)	0
White blood cell count decreased	3 (42.9)	0	3 (100)	0	3 (50.0)	1 (16.7)	1 (33.3)	0	3 (37.5)	0	13 (48.1)	1 (3.7)
Neutrophil count decreased	3 (42.9)	1 (14.3)	2 (66.7)	0	3 (50.0)	3 (50.0)	1 (33.3)	1 (33.3)	3 (37.5)	0	12 (44.4)	5 (18.5)
Alanine aminotransferase increased	1 (14.3)	0	2 (66.7)	0	4 (66.7)	0	1 (33.3)	0	3 (37.5)	0	11 (40.7)	0
Yellow skin	3 (42.9)	0	1 (33.3)	0	3 (50.0)	0	1 (33.3)	0	2 (25.0)	0	10 (37.0)	0
Platelet count decreased	1 (14.3)	0	1 (33.3)	0	3 (50.0)	0	1 (33.3)	0	2 (25.0)	0	8 (29.6)	0
Proteinuria	1 (14.3)	0	0	0	3 (50.0)	0	0	0	3 (37.5)	0	7 (25.9)	0
Amylase increased	1 (14.3)	1 (14.3)	0	0	1 (16.7)	0	2 (66.7)	0	2 (25.0)	0	6 (22.2)	1 (3.7)
Anemia	2 (28.6)	1 (14.3)	0	0	1 (16.7)	0	0	0	3 (37.5)	0	6 (22.2)	1 (3.7)

Dose-expansion phase, N (%)		CLL/SLL N=19		Aggressive B-cell lymphomas N=14		MCL N=10		Indolent B-cell lymphoma N=64		Total N=107	
		Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
At least one TEAE related to study drug	-	19 (100)	15 (78.9)	12 (85.7)	8 (57.1)	10 (100)	4 (40.0)	64 (100)	45 (70.3)	105 (98.1)	72 (67.3)
Neutrophil count decreased	-	13 (68.4)	7 (36.8)	3 (21.4)	1 (7.1)	6 (60.0)	2 (20.0)	43 (67.2)	22 (34.4)	65 (60.7)	32 (29.9)
Aspartate aminotransferase increased	-	9 (47.4)	0	5 (35.7)	0	5 (50.0)	0	36 (56.3)	0	55 (51.4)	0
White blood cell count decreased	-	6 (31.6)	2 (10.5)	2 (14.3)	0	3 (30.0)	0	43 (67.2)	10 (15.6)	54 (50.5)	12 (11.2)
Alanine aminotransferase increased	-	6 (31.6)	1 (5.3)	4 (28.6)	0	5 (50.0)	0	33 (51.6)	0	48 (44.9)	1 (0.9)
Anemia	-	9 (47.4)	3 (15.8)	5 (35.7)	0	3 (30.0)	1 (10.0)	18 (28.1)	1 (1.6)	35 (32.7)	5 (4.7)
Platelet count decreased	-	10 (52.6)	3 (15.8)	2 (14.3)	0	4 (40.0)	2 (20.0)	18 (28.1)	5 (7.8)	34 (31.8)	10 (9.3)

b.i.d.: twice daily; q.d.: once daily; CLL: chronic lymphocytic leukemia; MCL: mantle cell lymphoma; SLL: small lymphocytic lymphoma; TEAE: treatment-emergent adverse event.

1.9-not calculable [NC]) and median DOR (mDOR) was 11.0 months (95% CI: 4.7-NC). The median PFS (mPFS) was 8.3 months (95% CI: 1.8-16.5), and median TTP (mTTP) was 8.3 months (95% CI: 1.8-16.5).

Dose expansion

Cohort A: chronic lymphocytic leukemia/small lymphocytic lymphoma

Among CLL/SLL patients in the EEAS (N=16), ORR was 56.3% (95% CI: 29.9-80.2) per investigator assessments (Table 3; *Online Supplementary Figure S1*). The mean best percentage change in tumor burden from baseline in CLL/SLL patients was -66.58 (± 30.80%) (*Online Supplementary Figure S1*). mTTR was 1.9 months (95% CI: 1.8-1.9) and mDOR was 13.1 months (95% CI: 1.8-NC). In the SS (N=16), mPFS was 14.9 months (95% CI: 3.7-NC; *Online Supplementary Figure S2*).

Cohort B: aggressive B-cell lymphomas

Among aggressive B-cell lymphoma patients in the EEAS (N=9), ORR was 33.3% (95% CI: 7.5-70.1) per investigator assessments (Table 3; *Online Supplementary Figure S1*). The mean best percentage change in tumor burden from baseline in aggressive B-cell lymphoma patients was 21.90% (± 87.407%) (*Online Supplementary Figure S1*). In the SS (N=14), mTTP was 1.9 months (95% CI: 0.8-9.1) and mPFS was 1.9 months (95% CI: 0.8-9.1; *Online Supplementary Figure S2*).

Cohort C: mantle cell lymphoma

Among MCL patients in the EEAS (N=7), the ORR was 28.6% (95% CI: 3.7-71.0) per investigator assessments, and two (28.6%) patients achieved PR (Table 3; *Online Supplementary Figure S1*). The mean best percentage change in tumor burden from baseline in MCL patients was -9.8% (± 28.265%) (*Online Supplementary Figure S1*). Kaplan-Meier plots of PFS are provided in *Online Supplementary Figure S2*.

Cohort D: indolent B-cell lymphoma

Per independent review committee assessments, eight (13.6%) patients in the EEAS for cohort D (N=59) achieved CR and 22 (37.3%) patients achieved PR; the overall ORR was 50.8% (95% CI: 37.5-64.1; Table 3; Figure 2). In addition, 26 (44.1%) achieved SD. mTTR was 2.7 months (95% CI: 1.8-3.7), and mDOR was 15.7 months (95% CI: 7.4-NC). In the SS (N=64), mTTP was 12.0 months (95% CI: 8.2-NC), and mPFS was 12.0 months (95% CI: 6.3-NC). FL patients (grade 1, 2, 3a; EEAS, N=43) achieved an IRC-assessed ORR of 60.5% (95% CI: 44.4-75.0); with seven (16.3%) patients achieved CR and 19 (44.2%) patients achieved PR. The mDOR was not reached and 14 (32.6%) maintained SD. Among FL patients in the SS (N=47), mTTP was 12.0 months (95% CI: 8.2-NC) and mPFS was 11.0 months (95% CI: 6.3-NC). Among 14 MZL patients in the EEAS, the IRC-assessed ORR was 28.6% (95% CI: 8.4-58.1).

Tumor response per investigator assessments (Table 3; *Online Supplementary Figures S1-3*) was consistent with that per IRC assessments in cohort D.

The mean best percentage change in tumor burden from baseline based on investigator assessment was similar to that based on IRC assessment (Figure 2). Among 57 patients with change in tumor burden from baseline, the

Table 3. Anti-tumor activity of sovleplenib based on the efficacy evaluable analysis set in the dose-expansion phase.

Dose-expansion phase	CLL/SLL N=19	Aggressive B-cell lymphomas N=14	MCL N=10	Indolent B-cell lymphoma N=64	Total N=107
Efficacy evaluable (INV/IRC[a]), N CR PR/PR-L SD PD	16 1 4/4 6 1	9 1 2/0 1 5	7 0 2/0 4 1	59 INV 3, IRC 8 INV 25/0, IRC 22/0 INV 23[b], IRC 26 INV 8, IRC 2	91 5 33/4 34[b] 15
Not evaluable, N	0	0	0	INV 0, IRC 1	0
ORR % (95% CI)	56.3 (29.9-80.2)	33.3 (7.5-70.1)	28.6 (3.7-71.0)	INV 47.5 (34.3-60.9) IRC 50.8 (37.5-64.1)	46.2 (35.6-56.9)
Median DOR in months (95% CI)	13.1 (1.8-NC)	5.3 (3.7-NC)	4.6 (1.9-NC)	INV 13.9 (6.4-NC) IRC 15.7 (7.4-NC)	13.1 (6.5-NC)
Median PFS in months (95% CI)[c]	14.9 (3.7-NC)	1.9 (0.8-9.1)	3.7 (0.9-NC)	INV 8.3 (5.5-16.6) IRC 12.0 (6.3-NC)	8.2 (5.5-12.0)
Median TTR in months (95% CI)	1.9 (1.8-1.9)	1.9 (1.8-NC)	1.9 (1.9-NC)	INV 2.0 (1.9-3.6) IRC 2.7 (1.8-3.7)	1.9 (1.9-2.0)

[a]IRC: tumor response in the indolent B-cell lymphoma cohort was assessed by the independent review committee (IRC) and investigators (INV), and in the other cohorts was assessed by the INV. [b]Including 1 patient with minor response. [c]Median progression-free survival (PFS) was evaluated from the safety set. CI: confidence interval; CLL: chronic lymphocytic leukemia; CR: complete response; DOR: duration of response; MCL: mantle cell lymphoma; NC: not calculable; ORR: objective response rate; PD: progressive disease; PR: partial response; PR-L: partial response with increased lymphocyte count; SD: stable disease; SLL: small lymphocytic lymphoma; TTR: time to response.

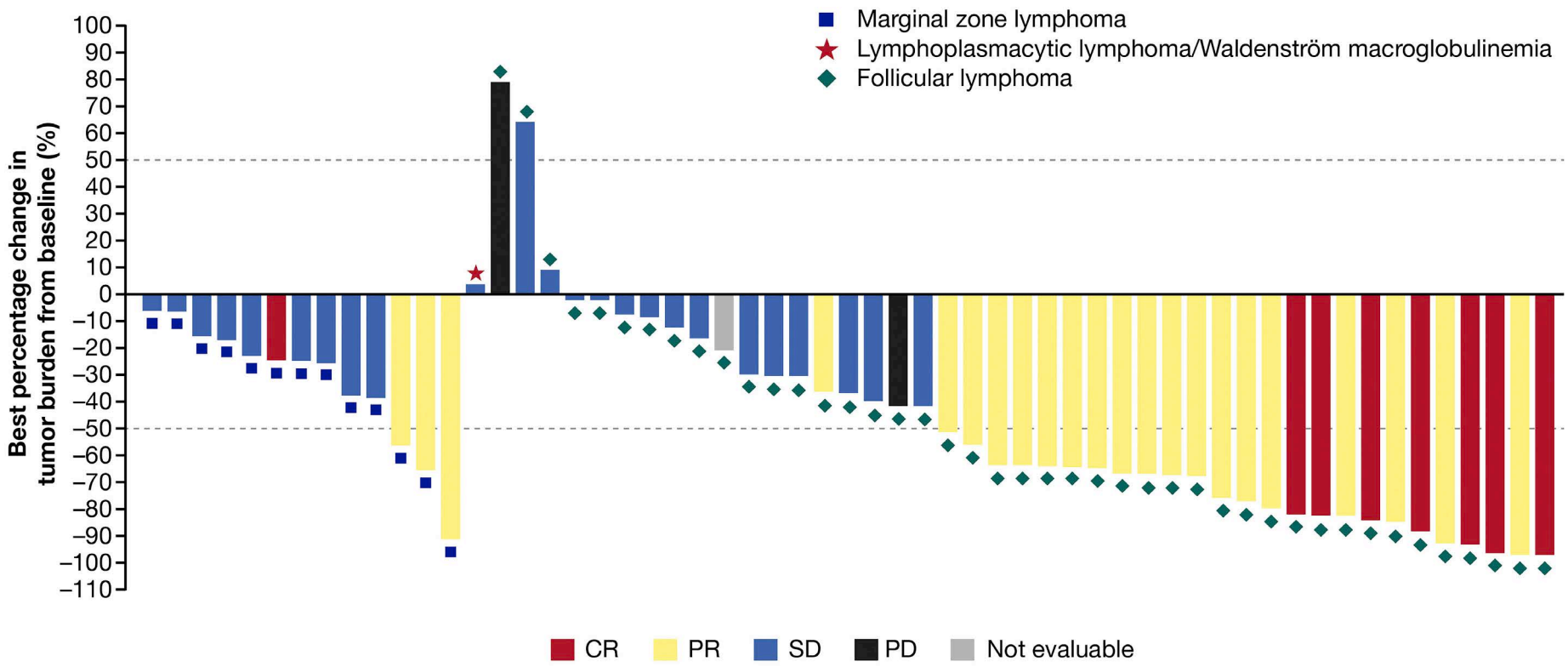

Figure 2. Best percentage change in tumor burden from baseline according to independent review committee assessments based on the efficacy-evaluable analysis set in the indolent B-cell lymphoma cohort. CR: complete response; PD: progressive disease: PR: partial response; SD: stable disease.

mean best percentage change was -44.08% (±37.748%).

Chronic lymphocytic leukemia/small lymphocytic lymphoma and follicular lymphoma subgroup analysis

Consistent anti-tumor activity was observed across CLL/SLL subgroups defined by prior treatment with BTKi or lines of prior treatment (*Online Supplementary Table S3*). CLL/SLL patients who had received prior BTKi (EEAS, N=8) and those who were BTKi-naive (EEAS, N=8) had ORR of 50% (95% CI: 15.7-84.3) and 62.5% (95% CI: 24.5-91.5), respectively, with mDOR of 14.7 months (95% CI: 1.9-NC) and 13.1 months (95% CI: 1.8-NC; Figure 3). mPFS was 16.5 months (95% CI: 1.6-NC) in CLL/SLL patients who had received prior BTKi and 13.8 months (95% CI: 3.5-NC) in those who were BTKi-naive. In patients with prior BTKi or ≥3 prior lines (EEAS, N=10), five achieved PR/PR with increased lymphocyte count (PR-L), with an ORR of 50% (95% CI: 18.7-81.3), mPFS of 16.5 months (95% CI: 1.6-NC) and mDOR of 14.7 months (95% CI: 1.8-NC).

Among 43 efficacy-evaluable FL patients, the ORR was 60.5% (95% CI: 44.4-75.0), with an mDOR of 14.8 months (95% CI: 6.5-NC), mTTR of 1.9 months (95% CI: 1.9-3.6) and mPFS of 11.0 months (95% CI: 6.3-16.6; *Online Supplementary Table S3;* Figure 4). Subgroup analysis revealed that patients who had received ≥2 lines (including anti-CD20) of treatment (EEAS, N=27) had an ORR of 59.3% (95% CI: 38.8-77.6), mPFS of 8.2 months (95% CI: 5.5-16.6) and mDOR of 9.0 months (95% CI: 3.6-NC). Anti-CD20-naive FL patients (EEAS, N=4) reported a higher ORR (75%, 95% CI: 19.4-99.4) than those without prior anti-CD20 treatment (59%, 95% CI: 42.1-74.4). An mDOR of 14.8 months (95% CI: 5.6-NC) and mTTR of 1.9 months (95% CI: 1.9-3.6) was recorded in FL patients with anti-CD20 treatment history. mPFS in prior anti-CD20–treated FL patients was 8.3 months (95% CI: 5.5-16.6).

Pi3K inhibitor–treated FL patients (EEAS, N=6) had an ORR of 66.7% (95% CI: 22.3-95.7) *versus* Pi3K inhibitor-naive patients (EEAS, N=37, 59.5% [95% CI: 42.1-75.3]). Those previously treated with a Pi3K inhibitor had an mDOR of 5.5 months (95% CI: 1.9-NC), and mTTR of 1.9 months (95% CI: 1.8-NC). mPFS in Pi3K inhibitor-naive patients was 12.0 months (95% CI: 6.3-NC) *versus* 5.5 months (95% CI: 1.8-NC) in patients previously treated with a Pi3K inhibitor.

Pharmacokinetics

After continuous q.d. oral administration (200-800 mg), the median T_{max} for sovleplenib was between 3.00 and 5.97 hours, arithmetic mean $t_{1/2}$ was 7.91-14.4 hours and the mean accumulation ratio range was 1.51-2.65 (*Online Supplementary Table S4*). Exposures increased with dose increase in the dose range of 200-800 mg q.d., but linear relationship between dose and C_{max}/AUC_{0-t} from dose escalation was not concluded. The steady state of sovleplenib was reached within 7 days in most dose cohorts. The geometric mean (geometric% CV) of C_{max} on day 15 was 221 (46.6%) and 320 (47.3%) ng/mL at 400 and 600 mg q.d., respectively; and the geometric mean (geometric% CV) of AUC_{0-tau} at 400 and 600 mg q.d. on day 15 was 2,910 (43.8%) and 4,320 (51.6%) h·ng/mL, respectively. The mean concentration-time profiles of sovleplenib at steady state are presented in *Online Supplementary Figure S3*. Pharmacokinetic parameters of sovleplenib and its metabolites are presented in *Online Supplementary Tables S5 and S6*, respectively.

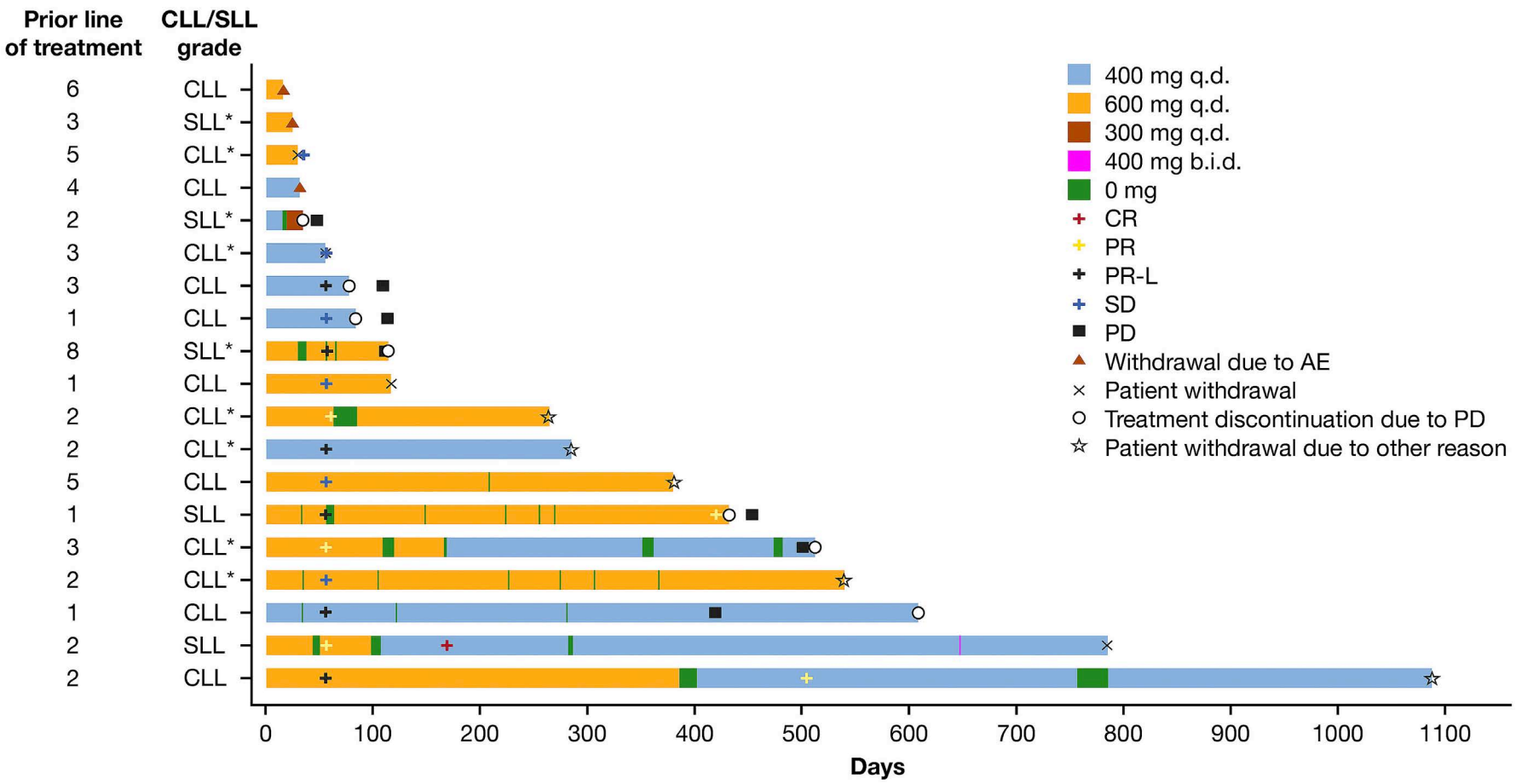

Figure 3. Duration of treatment in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma in the dose-expansion phase. CLL: chronic lymphocytic leukemia; SLL: small lymphocytic lymphoma; b.i.d.: twice daily; AE: adverse event; CR: complete response; PD: progressive disease; PR: partial response; PR-L: PR with increased lymphocyte count; q.d.: once daily; SD: stable disease.

Biomarker analysis

During dose expansion, sovleplenib induced reductions in plasma levels of CCL22, CCL17 and CXCL13 chemokines compared with baseline (*Online Supplementary Figure S4*). A similar trend was observed in separate analysis with cohorts A, B and D (*Online Supplementary Figure S5*). Consistent reduction was also observed with sovleplenib treatment during dose escalation (*data not shown*). Moreover, decreased levels of CCL3 and CCL4 in three of four CLL patients were observed, but not in other NHL subtypes (*data not shown*).

Discussion

This phase I study examined safety, tolerability and preliminary efficacy of sovleplenib in relapsed/refractory B-cell tumors. The RP2D was determined to be 600 mg q.d. in patients >65 kg and 400 mg q.d. in patients ≤65 kg. Clinical responses were observed in CLL/SLL, DLBCL, MCL, MZL, LPL/WM and FL, including in heavily pretreated patients.

The safety profile of sovleplenib was consistent with other Syk inhibitors; most toxicities were manageable, with no new safety concerns.[12,14,18,25]

Most common TEAE included neutropenia, leukopenia, anemia and platelet count decreased, with similar toxicities across cohorts. Some of the common toxicities reported for other Syk inhibitors, such as diarrhea, nausea, dyspepsia, headache, hypertension and fatigue, were less frequent in our study.[12,16,21] Although in patients treated with fostamatinib diarrhea was a DLT event (21%) or one of the most common TRAE (41%),[12,16] it was not a DLT of sovleplenib. The incidence of diarrhea was 3.7% in the dose escalation and 9.3% in the dose expansion. Pneumonia and interstitial lung disease were reported in the current study; pulmonary toxicities were also seen with entospletinib.[17,18,26] The safety profile may be attributable to the high target specificity of sovleplenib, which leads to low off-target adverse effects. Five patients who experienced probably sovleplenib-related TEAE leading to death had other confounding factors, including previous primary diseases and disease progression.

A challenge in treating B-cell malignancies is the heterogeneity of pathogenesis due to the complex nature of B-cell signaling and diversity of aberrant B-cell constitutive activation.[27] This study showed that sovleplenib has anti-tumor activity in lymphomas of different histology, including FL, CLL, SLL, indolent B-cell lymphoma, DLBCL and MCL. In a heavily pretreated population, the ORR in FL (grade 1, 2, 3a) was 60.5%. ORR in other cohorts ranged from 28.6% in both MCL and DLBCL cohorts to 56.3% in the CLL/SLL cohort.

The anti-tumor activity of sovleplenib was particularly noted in cohort D, where the overall IRC-assessed ORR was 50.8%, mDOR was 15.7 months, and mPFS was 12.0 months. More specifically, significant anti-tumor activity was demonstrated in FL patients with an IRC-assessed ORR of 60.5%,

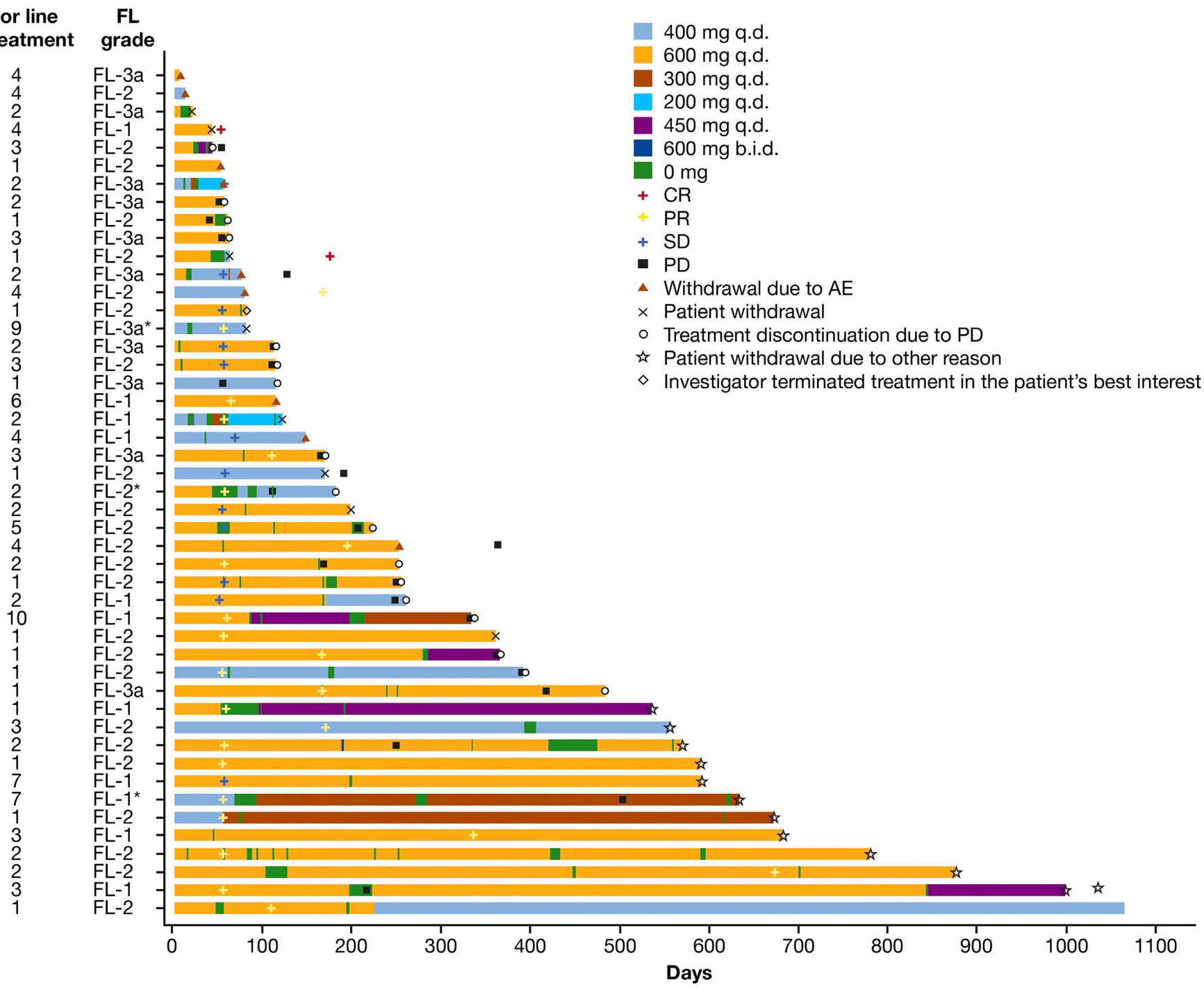

Figure 4. Duration of treatment in patients with follicular lymphoma in the dose-expansion phase. FL: follicular lymphoma; b.i.d.: twice daily; AE: adverse event; CR: complete response; PD: progressive disease; PR: partial response; PR-L: PR with increased lymphocyte count; q.d.: once daily; SD: stable disease.

mPFS of 11.0 months and mDOR not reached, indicating that this malignancy is distinctly susceptible to Syk inhibition. The Syk/FLT3 inhibitor TAK-659 has also been shown to achieve a high ORR of 89%, albeit in a small cohort (N=14) of FL patients.[12,18,25] In contrast, modest anti-tumor activity in FL patients treated with entospletinib or fostamatinib was noted, with ORR of 10% and 17%, respectively, and mPFS of 4.6 and 5.7 months, respectively. The differences in ORR may be due to different prior treatment regimens, such as 96.9% *versus* 33.3% of patients with MZL, LPL/WM and FL (grades 1, 2, 3a) receiving prior anthracycline in our study *versus* that in entospletinib.[18] Half of the FL patients in the study of TAK-659 had underwent prior autologous transplant.[12,18,25] Our subgroup analysis indicated that FL patients with prior Pi3K inhibitor treatment also experienced an encouraging tumor response (ORR, 66.7%; mDOR, 5.5 months; mPFS, 5.5 months), as did patients who received prior anti-CD20 monoclonal antibody therapy (ORR, 59%; mDOR, 14.8 months; mPFS, 8.3 months). This could indicate that sovleplenib may be an option after anti-CD20, or indeed Pi3K inhibitor, treatment failure given that Syk signaling is upstream of Pi3K during BCR activation.[28] Sovleplenib-mediated anti-tumor activity was also encouraging in CLL/SLL, with an ORR of 56.3%, mDOR of 13.1 months and mPFS of 14.9 months. Previous Syk inhibitor studies with entospletinib, cerdulatinib and fostamatinib demonstrated ORR results of 33-61% in CLL/SLL patients, with an mPFS of 5.6-13.8 months.[12,17,27] Current CLL/SLL first-line therapy includes chemotherapy, anti-CD20 immunotherapy, BTKi and BCL-2 inhibitors. In CLL/SLL patients previously treated with BTKi, or or received ≥3 lines of treatments, sovleplenib showed a notable anti-tumor activity, with an ORR of 50%, mDOR of 14.7 months and mPFS of 16.5 months; therefore, sovleplenib may be explored as

a potential subsequent treatment option in patients who cannot tolerate or become resistant to BTKi.

The target inhibition based on the IC_{50} indicated that the onset dose of sovleplenib was 400 mg q.d.. At 400 and 600 mg q.d., the coverage time of target inhibition was over 24 hours according to the IC_{50}.

Microenvironment-related biomarkers may predict clinical outcomes.[29] BCR activation and co-stimulation by $CD40^+$ T cells promote the secretion of CCL17 and CCL22, where these two chemokines could potentially induce trans-endothelial migration of activated T cells.[30] Monocyte-derived nurse-like cells attract and protect leukemic CLL cells through secretion of chemokines, such as CXCL12 and CXCL13, thus promoting CLL disease progression, as demonstrated in CLL animal models.[30,31] While in our study, a distinct reduction in CCL22, CCL17 and CXCL13 was observed in cohorts A, B and D, which indicates the contribution of sovleplenib to the tumor microenvironment.[17,32,33] Sovleplenib reduced biomarker levels consistently during dose escalation; however, a statistically significant dose-dependent correlation was not observed, similar to previous results seen in a dual SYK/JAK inhibitor.[34]

Limitations of this study include its single-arm design, small sample size and enrollment of Chinese patients only. Additionally, long-term overall survival data were not collected.

In conclusion, sovleplenib demonstrated acceptable tolerability in B-cell lymphomas patients; encouraging anti-tumor activities were observed, especially in CLL/SLL and FL. Further research is warranted to determine potential biomarkers to select patients that may be primed to benefit from Syk inhibitors in relapsed/refractory B-cell malignancies.

Disclosures

HY, SFu, SFan, QX, JW, XJ, GD, WS are employees of HUTCHMED Limited.

Contributions

HY, SFan and JZ conceptualized and designed the study. HY, SFu, SFan, QX, JW, XJ, GD and WS provided administrative support for study conduct. YS, JC, QZ, CL, LQ, JQ, HZhang, WL, LL, HJ, KZ, WZ, LZhang, DL, LZou, HYang, WQ, HZ and JH provided provision of study material or patients. YS, JC, QZ, CL, LQ, JQ, HZhang, WL, LL, HJ, KZ, WZ, LZhang, DL, LZou, HYang, WQ, HZ and JH performed the research and collected the data. QX analyzed the data. HY, SFu, SFan, QX, JW, XJ and GD interpreted the results. All authors had full access to study data, drafted, reviewed and approved the manuscript for submission.

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Data-sharing statement

Individual data will not be made available.

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