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

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Supplementary Material

List of the ethics committees that approved the study

Name of ethics committee
Ethics Committee of Beijing Cancer Hospital
Ethics Committee of Fudan University Shanghai Cancer Center
Ethics Committee of Institute of Hematology & Blood Diseases Hospital
Ethics Committee of Tianjin Medical University Cancer Institute & Hospital
Ethics Committee of the First Affiliated Hospital of Soochow University
Ethics Committee of Guangdong General Hospital
Ethics Committee of Beijing Shijitan Hospital, Capital Medical University
Ethics Committee of Peking University Third Hospital
Ethics Committee of Harbin Medical University Cancer Hospital
Drug Clinical Trial Ethics Committee of the Fourth Hospital of Hebei Medical University
Clinical Trial Ethics Committee of the First Affiliated Hospital of Zhejiang University School of Medicine
Clinical Trial Ethics Review Committee of West China Hospital, Sichuan University
Ethics Committee of Henan Cancer Hospital
Ethics Committee of Zhejiang Cancer Hospital
Ethics Committee of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology
Ethics Committee of Hunan Cancer Hospital
Ethics Committee of Fujian Medical University Union Hospital
Ethics Committee of Jinan Central Hospital Affiliated to Shandong University

Inclusion and exclusion criteria

Inclusion criteria
Patients must meet all of the following conditions:
1. Have fully understood this study and voluntarily signed the informed consent form
2. Age ≥ 18 years
3. Patients with pathologically (immunophenotyping) confirmed mature B-cell tumors who have failed standard treatment (PD after treatment or no response to treatment) or who cannot tolerate standard treatment and cannot receive or do not have standard treatment [refer to 2016 World Health Organization (WHO) classification criteria for lymphocytic tumors, see Appendix 10 of the protocol (V5.0, September 19, 2018) for details]
4. Each cohort in the dose expansion phase had specific criteria as follows:
Cohort A: CLL/SLL
Cohort B: Aggressive B-cell lymphoma [including DLBCL, Richter's syndrome and FL (grade 3b)]
Cohort C: MCL
Cohort D: Indolent B-cell lymphoma [including MZL, LPL/WM, FL (grades 1, 2, 3a)]
5. Patients were required to have at least one bidimensionally measurable lesion during the dose expansion phase, with the exception of:
a) Patients with CLL
b) Patients with LPL/WM who have abnormal immunoglobulin (eg, IgM) elevations
6. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1
7. Expected survival of more than 24 weeks as judged by the investigator
8. Male or female patients of childbearing potential must agree to use effective contraceptive methods during the study and within 90 days after study drug administration, such as double-barrier contraceptive methods, condoms, oral or injectable contraceptives, intrauterine devices, etc. Postmenopausal women (>45 years of age and amenorrheic for more than 1 year) and surgically sterile women are not constrained to this cretirion.
Exclusion criteria
Any of the following criteria must be excluded from the study plan:
1. Pathologically confirmed primary central nervous system lymphoma
2. The following laboratory abnormalities were present:
a) Absolute neutrophil count $<1.5 \times 10^9$/L
b) Platelets $<75 \times 10^9$/L
c) Hemoglobin <9 g/dL
Note: In the dose expansion phase, if the investigator considers that the patient's above examination values are lower than the lower limit of the protocol due to bone marrow involvement by lymphoma, the results can be

discussed with the sponsor and agreed by the sponsor in writing
3. Serum total bilirubin (TBIL) greater than 1.5xthe upper limit of the normal reference range (ULN), with the exception of patients with:
a) Patients with Gilbert disease who have normal alanine aminotransferase (ALT) and aspartate aminotransferase (AST) and serum TBIL no greater than 3x ULN
4. ALT or AST 2.5x higher than ULN in the absence of liver lymphoma invasion; ALT or AST 5x higher than ULN in the presence of liver lymphoma invasion (the latter condition does not apply to the dose escalation phase)
5. Serum amylase or lipase above ULN
6. Serum creatinine greater than 1.5xthe ULN (except for subjects with normal creatinine clearance), or estimated creatinine clearance <50mL/min according to the Cockcroft-Gault formula
7. International normalized ratio (INR) higher than 1.5xthe ULN or activated partial thromboplastin time (aPTT) higher than 1.5x the ULN. Patients who are receiving anticoagulant therapy with warfarin, such as an INR between 2 and 3
8. Known history of clinically significant liver disease, including viral or other hepatitis or cirrhosis:
a) Chronic hepatitis B positivity was defined as positive hepatitis B surface antigen (HBsAg) serology
Patients with occult or pre-hepatitis B infection [defined as hepatitis B core antibody (HBcAb) positive, HBsAg negative] may be enrolled in case of negative polymerase chain reaction (PCR) test for hepatitis B virus (HBV) deoxyribonucleic acid (DNA); and these patients require monthly PCR test for HBV DNA
b) Hepatitis C positive was defined as positive hepatitis C virus (HCV) antibody serology
HCV antibody positive patients with negative PCR detection result of HCV ribonucleic acid (RNA) can be enrolled
9. Known human immunodeficiency virus (HIV) infection
10. Women who are pregnant (positive pregnancy test before medication) or breastfeeding
11. Congestive heart failure greater than or equal to New York Heart Association (NYHA) Class 2
12. Hereditary long QT syndrome or QTc >480 msec or taking drugs that may cause QT prolongation or torsades de pointes
13. Patients with other malignant tumors within the past 5 years, except for cutaneous basal cell carcinoma, breast carcinoma in situ and cervical carcinoma in situ treated with curative intent
14. Antineoplastic therapy, including chemotherapy, radiotherapy, hormone therapy, biological therapy [including chimeric antigen receptor T cell immunotherapy (CAR-T)] or immunotherapy
15. Patients who received herbal medicine before the study treatment
16. Administration of strong cytochrome P450 (CYP) 3A inhibitors or inducers and CYP3A, CYP1A2 or CYP2B6 substrates with narrow therapeutic windows less than one week or 3 half-lives (whichever is longer as the time period) from the start of study treatment [see Appendix 9 of the protocol (V5.0, September 19, 2018)]

17. Previous participation in other drug clinical studies less than 4 weeks from the last use of small molecule drugs or less than 8 weeks of macromolecular drugs (such as antibody drugs)
18. Prior treatment with any SYK inhibitor (e.g., fostamatinib)
19. Major surgery 4x before the first dose of study drug
20. Autologous stem cell transplantation within 6 months after the first dose of study drug
21. Previous allogeneic stem cell transplantation
22. Toxicity from prior anticancer therapy has not recovered to grade 0 or 1 (except alopecia)
23. Clinically significant active infection
24. History of acute myocardial infarction, unstable angina, stroke, or transient ischemic attack within 6 months prior to enrolment
25. Inability to take oral drugs, previous surgery or severe gastrointestinal diseases such as dysphagia, active gastric ulcer, etc., which in the opinion of the investigator may affect the absorption of the study drug
26. Insufficient compliance of patients participating in this clinical study as judged by the investigator
27. Any other disease, metabolic abnormality, physical examination abnormality or significant laboratory abnormality, which, in the judgment of the investigator, provides reasonable suspicion that the patient has a disease or condition that would make the use of the study drug inappropriate, or which would affect the interpretation of the study results or put the patient at high risk.

Sample collection for pharmacokinetic analysis

For pharmacokinetic analyses, plasma samples were collected at multiple timepoints: (within 0.5 h pre-dose; and 0.5 h, 1 h, 2 h, 4 h, 6 h, 8 h post-dose) on day 1, (within 0.5 h pre-dose) on day 2 and day 8, (within 0.5 h pre-dose; and 0.5 h, 1 h, 2 h, 4 h, 6 h, 8 h post-dose) on day 15, within 0.5 h pre-dose on day 16, (within 0.5 h pre-dose; and 0.5 h, 1 h, 2 h, 4 h, 6 h, 8 h post-dose) on day 28, (within 0.5 h pre-dose) on day 29 in dose escalation for QD cohorts; (within 0.5 h pre-dose; and 0.5 h, 1 h, 2 h, 4 h, 6 h, 8 h, 12 h post-dose) on day 1, (within 0.5 h pre-dose) on day 8, (within 0.5 h pre-dose; and 0.5 h, 1 h, 2 h, 4 h, 6 h, 8 h, 12 h post-dose) on day 15, (within 0.5 h pre-dose; and 0.5 h, 1 h, 2 h, 4 h, 6 h, 8 h, 12h post-dose) on day 28 in dose escalation for BID cohorts; (within 0.5 h pre-dose; and 0.5 h, 1 h, 2 h, 4 h, 6 h, 8 h post-dose) on day 1, (within 0.5 h pre-dose; and 0.5 h, 1 h, 2 h, 4 h, 6 h, 8 h post-dose) on day 15 in dose expansion for QD cohorts; (within 0.5 h pre-dose; and 0.5 h, 1 h, 2 h, 4 h, 6 h, 8 h, 12 h post-dose) on day 1, (within 0.5 h pre-dose; and 0.5 h, 1 h, 2 h, 4 h, 6 h, 8 h, 12 h post-dose) on day 15 in dose expansion for BID cohorts.

Sample size calculation for the dose expansion phase based on AE assumption

To further characterize the safety and efficacy of sovleplenib at the recommended phase II dose, approximately 190 patients were to be enrolled into four cohorts during dose expansion, this gives a probability of observing at least one such AE of 99.9%, 99.7%, 85.2%, and 61.4% for AEs with incidence rates of 5%, 3%, 1%, and 0.5%, respectively.

Definition of dose-limiting toxicities

Dose-limiting toxicities (DLTs) are defined as the following toxicities that occur within 28 days of the first dose of sovleplenib, and are considered by the investigator or sponsor to be reasonably related to treatment with sovleplenib:

- Any sovleplenib related grade 4 or higher adverse events (AEs), except:
    - Expected grade 4 lymphopenia associated with treatment effect
    - Grade 4 neutropenia (non-febrile neutropenia) alone, with recovery to grade 1 to 3 without colony-stimulating factor support, and to ≤ grade 2 after that
- Any sovleplenib related grade 3 AE except:
    - Grade 3 lymphopenia expected to be associated with treatment effect
    - Grade 3 neutropenia but not febrile neutropenia and recovery to grade 2 or lower without colony-stimulating factor support
    - Grade 3 thrombocytopenia that does not result in bleeding and that resolves to grade 2 or less without transfusion/platelet therapy
    - Grade 3 or greater nausea/vomiting, diarrhea, constipation, and electrolyte imbalance that decrease to grade 2 or less within 3 days of appropriate supportive care

The DLT analysis set (DLTS) included all DLT-evaluable patients, defined as those who received ≥75% of the prescribed dose of sovleplenib and had the most basic safety evaluation within the DLT evaluation window (cycle 1, days 1–28), or who developed a DLT during the DLT evaluation window.

Supplementary Table S1: Baseline demographics and disease characteristics in the safety set in the dose-escalation phase

Parameter	**200 mg QD (*n* = 7)**	**400 mg QD (*n* = 3)**	**600 mg QD (*n* = 6)**	**800 mg QD (*n* = 3)**	**200 mg BID (*n* = 8)**	**Total (*n* = 27)**
Age, years						
Median (range)	58.0 (49-72)	56.0 (33-68)	62.0 (44-70)	47.0 (30-49)	50.0 (36-64)	56.0 (30-72)
Age category, *n* (%)						
<65 years	5 (71.4)	2 (66.7)	4 (66.7)	3 (100)	8 (100)	22 (81.5)
≥65 years	2 (28.6)	1 (33.3)	2 (33.3)	0	0	5 (18.5)
Sex, *n* (%)						
Male	5 (71.4)	1 (33.3)	5 (83.3)	2 (66.7)	3 (37.5)	16 (59.3)
Female	2 (28.6)	2 (66.7)	1 (16.7)	1 (33.3)	5 (62.5)	11 (40.7)
Histologic subtype						
CLL	2 (28.6)					2 (7.4)
SLL			1 (16.7)	1 (33.3)		2 (7.4)
DLBCL	1 (14.3)		1 (16.7)	1 (33.3)	2 (25.0)	5 (18.5)
MCL	2 (28.6)			1 (33.3)	1 (12.5)	4 (14.8)
MZL	1 (14.3)		1 (16.7)		1 (12.5)	3 (11.1)
LPL			1 (16.7)			1 (3.7)
FL	1 (14.3)	3 (100.0)	2 (33.3)		4 (50.0)	10 (37.0)
Baseline ECOG score, n (%)						
0	4 (57.1)	1 (33.3)	3 (50.0)	3 (100)	3 (37.5)	14 (51.9)
1	3 (42.9)	2 (66.7)	3 (50.0)	0	5 (62.5)	13 (48.1)
Time (months) since initial disease diagnosis to first dose of sovleplenib						
Median (range)	38.60 (5.4-104.3)	47.50 (17.1-74.8)	37.70 (22.8-50.4)	27.00 (24.2-63.3)	31.30 (15.3-65.3)	32.90 (5.4-104.3)
Ann Arbor staging, *n* (%)						
II	0	0	0	0	1 (12.5)	1 (3.7)
III	2 (28.6)	2 (66.7)	4 (66.7)	1 (33.3)	3 (37.5)	12 (44.4)
IV	3 (42.9)	1 (33.3)	2 (33.3)	1 (33.3)	4 (50.0)	11 (40.7)
Not done	0	0	0	1 (33.3)	0	1 (3.7)
Not applicable	2 (28.6)	0	0	0	0	2 (7.4)
Prognostic risk groups for chronic lymphocytic leukemia/small cell lymphoma, *n* (%)						
Intermediate risk (Rai stage I, II or Binet stage B)	2 (28.6)	0	0	0	0	2 (7.4)
Mantle cell lymphoma prognostic score risk group, *n* (%)						
Low Risk (0-3)	0	0	0	1 (33.3)	1 (12.5)	2 (7.4)
Intermediate risk (4-5)	2 (28.6)	0	0	0	0	2 (7.4)
Follicular lymphoma prognostic score risk group, *n* (%)						
Low Risk (0 or 1)	0	0	2 (33.3)	0	0	2 (7.4)
Intermediate risk (2)	0	2 (66.7)	0	0	3 (37.5)	5 (18.5)
High Risk (3-5)	1 (14.3)	1 (33.3)	0	0	1 (12.5)	3 (11.1)
Other lymphoma IPI prognostic score risk groups, *n* (%)						
Low Risk (0 or 1)	0	0	0	0	1 (12.5)	1 (3.7)
Intermediate-Low Risk (2)	3 (42.9)	0	1 (16.7)	0	2 (25.0)	6 (22.2)
Intermediate-High Risk (3)	0	0	1 (16.7)	2 (66.7)	0	3 (11.1)
No. of lines of last antitumor drug treatment, *n* (%)						
Lines 1	1 (14.3)	1 (33.3)	1 (16.7)	1 (33.3)	0	4 (14.8)
Lines 2	2 (28.6)	0	3 (50.0)	0	5 (62.5)	10 (37.0)

Lines ≥3	4 (57.1)	2 (66.7)	2 (33.3)	2 (66.7)	3 (37.5)	13 (48.1)
Time (months) since end of last anti-tumor drug treatment to first dose of sovleplenib						
Median (range)	4.75 (1.4-29.3)	12.50 (5.1-16.9)	9.45 (1.1-20.6)	2.15 (1.2-3.1)	4.10 (1.0-18.8)	5.10 (1.0-29.3)
Prior Anti-Tumor treatment, *n* (%)						
Chemotherapy:						
Alkylating agent	7 (100)	3 (100)	6 (100)	3 (100)	8 (100)	27 (100)
Anthracycline	7 (100)	3 (100)	5 (83.3)	3 (100)	8 (100)	26 (96.3)
Vinblastines	6 (85.7)	2 (66.7)	5 (83.3)	3 (100)	8 (100)	24 (88.9)
Purine analogues	1 (14.3)	1 (33.3)	0	1 (33.3)	2 (25.0)	5 (18.5)
R (rituximab) based therapy:						
CD20 monoclonal antibody	5 (71.4)	2 (66.7)	4 (66.7)	3 (100)	7 (87.5)	21 (77.8)
Immunomodulators	2 (28.6)	0	2 (33.3)	0	1 (12.5)	5 (18.5)
Prior autologous hematopoietic stem cell transplant, *n* (%)	1 (14.3)	0	0	0	1 (12.5)	2 (7.4)

Supplementary Table S2: Additional 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)**
Prognostic risk groups for chronic lymphocytic leukemia/small cell lymphoma, n (%)					
Intermediate risk (Rai stage I, II or Binet stage B)	7 (36.8)	0	0	0	7 (6.5)
High risk (Rai stage III, IV or Binet stage C)	7 (36.8)	0	0	0	7 (6.5)
Mantle cell lymphoma prognostic score risk group, n (%)					
Low risk (0-3)	0	0	3 (30.0)	0	3 (2.8)
Intermediate risk (4-5)	0	0	6 (60.0)	0	6 (5.6)
High risk (6-11)	0	0	1 (10.0)	0	1 (0.9)
Follicular lymphoma prognostic score risk group, n (%)					
Low risk (0 or 1)	0	0	0	8 (12.5)	8 (7.5)
Intermediate risk (2)	0	1 (7.1)	0	20 (31.3)	21 (19.6)
High risk (3-5)	0	2 (14.3)	0	18 (28.1)	20 (18.7)
Waldenström macroglobulinemia prognostic score risk group, n (%)					
Intermediate risk (2 risk factors or age >65 years only)	0	0	0	1 (1.6)	1 (0.9)
High risk (>2 risk factors)	0	0	0	1 (1.6)	1 (0.9)
Other lymphoma IPI prognostic score risk groups, n (%)					
Low risk (0 or 1)	1 (5.3)	4 (28.6)	0	2 (3.1)	7 (6.5)
Intermediate-low risk (2)	2 (10.5)	2 (14.3)	0	8 (12.5)	12 (11.2)
Intermediate-high risk (3)	1 (5.3)	3 (21.4)	0	4 (6.3)	8 (7.5)
High risk (4-5)	1 (5.3)	1 (7.1)	0	1 (1.6)	3 (2.8)

Supplementary Table S3: Antitumor activity of Sovleplenib in subgroups of patients with CLL/SLL or FL in the dose-expansion phase (assessed by investigator).

Dose-expansion stage (CLL/SLL)	Prior BTKi	BTKi naive	Prior BTKi or prior ≥3 lines	Total	Dose-expansion stage (FL)	Prior anti-CD20	Anti-CD20 naïve	Prior Pi3K inhibitor	Pi3K inhibitor naïve	Prior ≥2 lines (incl. anti-CD20)	Total
Safety population	9	10	13	19		43	4	6	41	30	47
Efficacy evaluable	8	8	10	16		39	4	6	37	27	43
CR/CRi	0	1	0	1		2	1	0	3	1	3
PR/PR-L	4	4	5	8		21	2	4	19	15	23
ORR (95% CI), %	50.0 (15.7–84.3)	62.5 (24.5–91.5)	50.0 (18.7–81.3)	56.3 (29.9–80.3)		59.0 (42.1–74.4)	75.0 (19.4–99.4)	66.7 (22.3–95.7)	59.5 (42.1–75.3)	59.3 (38.8–77.6)	60.5 (44.4–75.0)
DCR (95% CI), %	87.5 (47.3–99.7)	100 (63.1–100.0)	90 (55.5–99.8)	93.8 (69.8–99.8)		87.2 (72.6–95.7)	100.0 (39.8–100.0)	66.7 (22.3–95.7)	91.9 (78.1–98.3)	88.9 (70.8–97.7)	88.4 (74.9–96.1)
mDOR (95% CI)	14.7 (1.9–NC)	13.1 (1.8–NC)	14.7 (1.8–NC)	13.1 (1.8–NC)		14.8 (5.6–NC)	Not reached (8.3–NC)	5.5 (1.9–NC)	Not reached (6.5–NC)	9 (3.6–NC)	14.8 (6.5–NC)
mTTR (95% CI)	1.9 (1.9–NC)	1.9 (1.8–NC)	1.9 (1.9–NC)	1.9 (1.8–1.9)		1.9 (1.9–3.6)	5.5 (1.8–NC)	1.9 (1.8–NC)	2.0 (1.9–5.5)	1.9 (1.9–5.5)	1.9 (1.9–3.6)
mPFS (95% CI) [a]	16.5 (1.6–NC)	13.8 (3.5–NC)	16.5 (1.6–NC)	14.9 (3.7–NC)		8.3 (5.5–16.6)	Not reached (3.7–NC)	5.5 (1.8–NC)	12.0 (6.3–NC)	8.2 (5.5–16.6)	11.0 (6.3–16.6)

[a]Median PFS was evaluated from the safety population.
BTKi: Bruton tyrosine kinase inhibitor; CR: complete response; CRi: CR with incomplete bone marrow recovery; FL: follicular lymphoma; mDOR: median duration of response; mTT: median time to progression; NC: not calculable; ORR: objective response rate; PD: progressive disease; PFS: progression-free survival; Pi3K: phosphatidylinositol 3-kinase; PR: partial response; PR-L: PR with increased lymphocyte count; SD: stable disease.

Supplementary Table S4: Summary of pharmacokinetic parameters of sovleplenib based on the pharmacokinetic analysis set in the dose escalation phase

Visit week	PK parameters	Units	Dose				
			200 mg BID	**200 mg QD**	**400 mg QD**	**600 mg QD**	**800 mg QD**
C1D1	T_{max}	h	3.88 (1.97, 4.00), 8	4.00 (3.98, 5.97), 7	4.00 (1.97, 4.00), 3	4.02 (2.00, 8.00), 6	3.98 (1.97, 4.02), 3
	C_{max}	ng/mL	65.9 (33.8), 8	63.3 (46.5), 7	175 (36.4), 3	196 (33.5), 6	259 (128.1), 3
	AUC_{0-t}	h·ng/mL	460 (28.9), 8	635 (27.5), 7	1680 (32.6), 3	1970 (41.6), 6	2810 (92.1), 3
	AUC_{0-inf}	h·ng/mL	433 (-), 1	837 (27.8), 5	2150 (35.5), 3	2060 (34.7), 4	-
	$T_{1/2}$	h	7.36 (1.29), 8	9.47 (2.37), 6	9.82 (1.82), 3	9.70 (1.37), 4	14.2 (2.60), 3
C1D15	T_{max}	h	1.98 (1.95, 4.00), 7	4.00 (1.98, 6.00), 5	3.97 (3.88, 4.03), 3	3.98 (2.00, 5.97), 6	3.00 (2.00, 4.00), 2
	C_{max}	ng/mL	129 (38.4), 7	96.8 (36.7), 5	256 (5.6), 3	314 (31.8), 6	450 (30.2), 2
	AUC_{0-t}	h·ng/mL	1120 (39.1), 7	1020 (44.0), 5	3030 (20.0), 3	3660 (39.5), 6	5450 (19.8), 2
	AUC_{0-tau}	h·ng/mL	1120 (39.2), 7	902 (35.6), 4	3140 (22.7), 3	3790 (43.4), 6	5580 (23.1), 2
	C_{min}	ng/mL	58.5 (46.0), 7	15.0 (64.5), 5	50.6 (38.2), 3	67.1 (58.6), 6	93.2 (16.9), 2
	$T_{1/2}$	h	10.0 (2.50), 7	9.31 (1.63), 4	12.8 (2.21), 3	12.0 (2.78), 5	10.8 (0.190), 2
	$ARAUC_{0-tau}$	-	2.52 (0.782), 7	1.51 (0.596), 4	1.85 (0.360), 3	1.89 (0.0865), 4	2.64 (1.94), 2
C1D28	T_{max}	h	2.02 (2.00, 5.97), 4	4.00 (2.05, 5.95), 5	4.00 (3.98, 8.17), 3	3.98 (2.00, 5.93), 5	5.97 (5.97, 5.97), 1
	C_{max}	ng/mL	117 (34.2), 4	87.8 (38.2), 5	223 (14.8), 3	304 (34.3), 5	323 (-), 1
	AUC_{0-t}	h·ng/mL	996 (34.2), 4	1070 (38.7), 5	3000 (20.1), 3	3760 (36.7), 5	4210 (-), 1
	AUC_{0-tau}	h·ng/mL	996 (34.2), 4	1060 (45.0), 4	2890 (27.5), 2	4370 (30.3), 4	-
	C_{min}	ng/mL	50.8 (37.9), 4	19.3 (53.8), 5	58.8 (56.5), 3	63.2 (65.6), 5	79.6 (-), 1
	$T_{1/2}$	h	7.16 (0.463), 3	12.1 (2.17), 4	11.0 (0.898), 2	11.4 (2.44), 3	-
	$ARAUC_{0-tau}$	-	1.97 (0.159), 4	1.55 (0.281), 4	1.75 (0.345), 2	1.84 (0.146), 2	-

Note: T_{max} is median (minimum, maximum), $t_{1/2}$ is arithmetic mean (standard deviation), other parameters are geometric means (geometric% coefficient of variation); data after the parentheses indicate patient number for the specific parameter.

Supplementary Table S5: Summary of pharmacokinetic parameters of sovleplenib based on the pharmacokinetic analysis set in the dose-expansion phase

Visit week	Variable	Units	Dose	
			400 mg QD	**600 mg QD**
C1D1	T_{max}	h	4.00 (1.88, 5.95), 31	3.98 (0.983, 8.00), 71
	C_{max}	ng/mL	144 (46.1), 31	182 (54.3), 71
	AUC_{0-t}	h·ng/mL	839 (71.0), 31	1320 (76.5), 71
	AUC_{0-inf}	h·ng/mL	2240 (73.0), 5	2960 (44.6), 20
	$T_{1/2}$	h	7.91 (3.18), 7	9.44 (2.43), 28
C1D15	T_{max}	h	3.98 (1.87, 7.75), 22	3.94 (1.87, 6.05), 34
	C_{max}	ng/mL	221 (46.6), 22	320 (47.3), 34
	AUC_{0-t}	h·ng/mL	2910 (43.8), 22	4320 (51.6), 34
	AUC_{0-tau}	h·ng/mL	2910 (43.8), 22	4320 (51.6), 34
	C_{min}	ng/mL	57.4 (48.8), 22	87.2 (63.6), 34
	$T_{1/2}$	h	12.2 (3.87), 19	12.2 (3.15), 25
	$ARAUC_{0-tau}$	-	2.65 (0.149), 3	1.88 (0.549), 3
C1D28	T_{max}	h	3.88 (3.83, 4.00), 3	4.00 (1.97, 8.00), 24
	C_{max}	ng/mL	307 (3.7), 3	296 (52.5), 24
	AUC_{0-t}	h·ng/mL	3760 (11.4), 3	3900 (55.8), 24
	AUC_{0-tau}	h·ng/mL	3750 (12.1), 3	4410 (49.3), 16
	C_{min}	ng/mL	71.0 (7.6), 3	76.6 (70.6), 24
	$T_{1/2}$	h	12.1 (0.535), 3	14.4 (3.39), 15
	$ARAUC_{0-tau}$	-	1.55 (0.391), 2	2.01 (1.04), 14

Note: T_{max} is median (minimum, maximum), $t_{1/2}$ is arithmetic mean (standard deviation), other parameters are geometric means (geometric % coefficient of variation); data after the parentheses indicate patient number for the specific parameter.

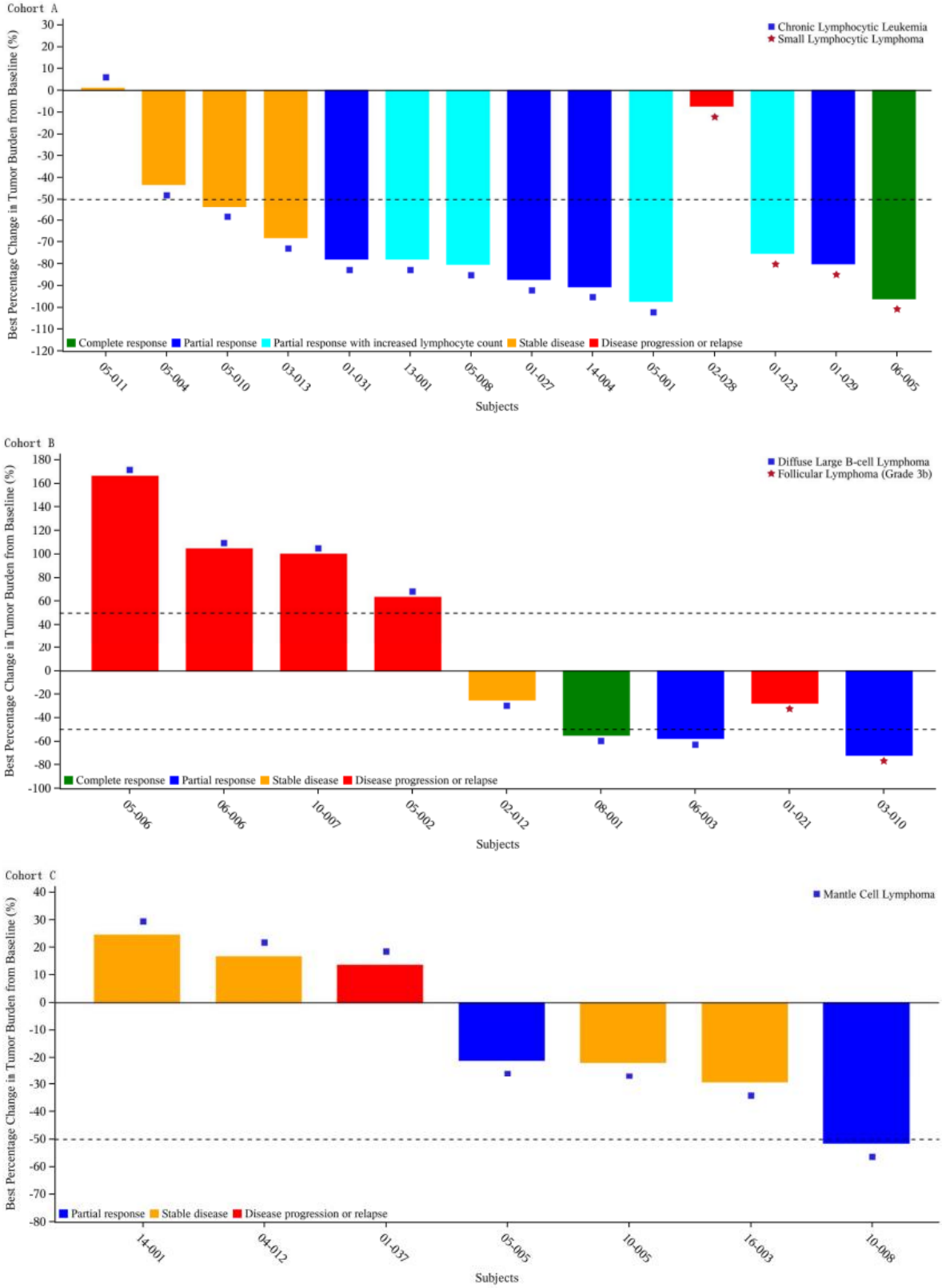
Supplementary Table S6 Summary of pharmacokinetic parameters of sovleplenib metabolites, M1 and M44, following once daily oral administration of 400 mg or 600 mg of sovleplenib

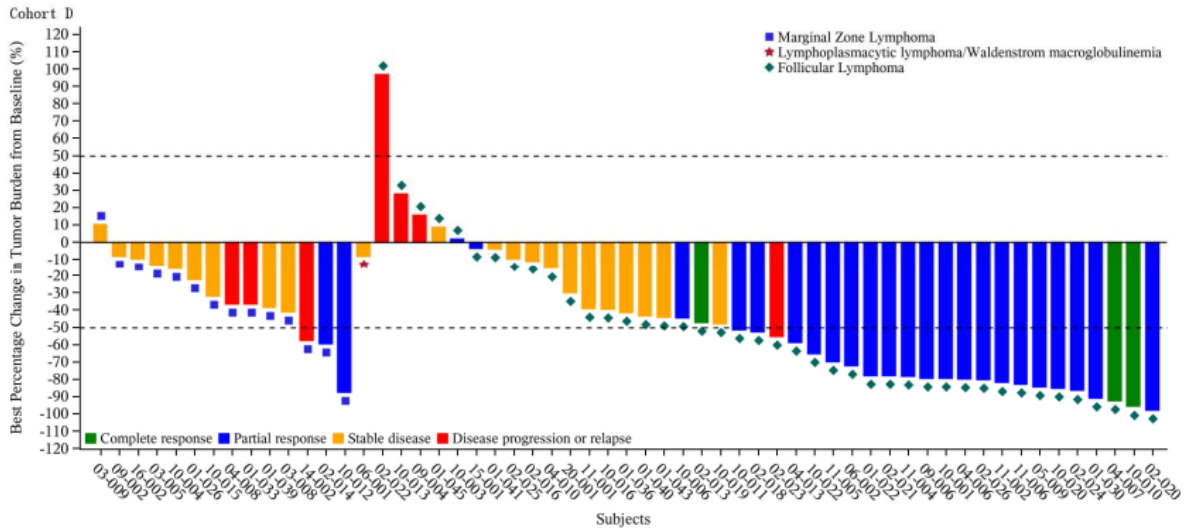
M1 metabolite				
Visit week	**PK parameters**	**Unit**	**400 mg**	**600 mg**
C1D1	T_{max}	h	3.98 (1.88, 6.08), 31	3.98 (1.95, 8.00), 71
	C_{max}	ng/mL	78.7 (64.8), 31	96.4 (78.4), 71
	AUC_{0-t}	h·ng/mL	390 (69.7), 31	572 (87.3), 71
	MRT	h	5.14 (31.4), 31	6.46 (35.3), 71
	$t_{1/2}$	h	6.55 (3.78), 9	8.45 (3.08), 25
	M/P_AUC_{0-t}	-	0.268 (0.0875), 31	0.253 (0.0813), 71
C1D15	T_{max}	h	3.83 (1.88, 7.75), 22	3.94 (1.87, 6.02), 34
	C_{max}	ng/mL	130 (45.1), 22	130 (49.0), 34
	AUC_{0-t}	h·ng/mL	1490 (32.5), 22	1610 (41.2), 34
	AUC_{0-tau}	h·ng/mL	1490 (32.5), 22	1610 (41.2), 34
	$t_{1/2}$	h	14.9 (5.80), 19	14.2 (4.76), 27
	AR_AUC_{0-tau}	-	3.25 (1.25), 5	-
	M/P_AUC_{0-t}	-	0.311 (0.0744), 22	0.258 (0.0793), 34
C1D28	T_{max}	h	3.88 (3.83, 4.00), 3	4.00 (1.97, 8.00), 24
	C_{max}	ng/mL	134 (52.5), 3	146 (41.6), 24
	AUC_{0-t}	h·ng/mL	1510 (38.0), 3	1630 (41.1), 24
	AUC_{0-tau}	h·ng/mL	1500 (39.0), 3	1770 (40.3), 17
	$t_{1/2}$	h	13.2 (2.71), 3	13.8 (6.43), 16
	AR_AUC_{0-tau}	-	1.78 (0.787), 2	2.27 (1.21), 16

	M/P_AUC_{0-t}	-	0.269 (0.0795), 3	0.266 (0.0779), 24
M44 Metabolite				
C1D1	T_{max}	h	2.00 (0.917, 4.10), 31	2.02 (0.500, 8.00), 71
	C_{max}	ng/mL	75.5 (65.5), 31	87.5 (91.7), 71
	AUC_{0-t}	h·ng/mL	302 (75.4), 31	428 (101.7), 71
	MRT	h	3.75 (31.2), 31	4.75 (31.6), 71
	$t_{1/2}$	h	3.03 (2.09), 23	4.28 (2.29), 50
	M/P_AUC_{0-t}	-	0.158 (0.0895), 31	0.157 (0.111), 71
C1D15	T_{max}	h	1.93 (0.950, 5.83), 22	2.88 (0.933, 6.02), 34
	C_{max}	ng/mL	76.8 (72.5), 22	85.1 (76.2), 34
	AUC_{0-t}	h·ng/mL	397 (77.7), 22	533 (69.5), 34
	AUC_{0-tau}	h·ng/mL	398 (77.2), 22	533 (69.5), 34
	t1/2	h	10.3 (8.69), 20	8.40 (3.41), 31
	AR_AUC_{0-tau}	-	1.52 (0.626), 17	1.41 (0.505), 17
	M/P_AUC_{0-t}	-	0.0724 (0.0589), 22	0.0629 (0.0275), 34
C1D28	T_{max}	h	1.97 (1.95, 3.88), 3	3.90 (1.00, 8.00), 24
	C_{max}	ng/mL	63.6 (36.1), 3	98.9 (82.8), 24
	AUC_{0-t}	h·ng/mL	402 (66.5), 3	635 (89.6), 24
	AUC_{0-tau}	h·ng/mL	401 (66.5), 3	611 (95.5), 21
	$t_{1/2}$	h	8.41 (2.03), 3	7.35 (2.48), 20
	AR_AUC_{0-tau}	-	0.552 (0.179), 2	1.31 (0.609), 20
	M/P_AUC_{0-t}	-	0.0555 (0.0336), 3	0.0928 (0.0823), 24

Note: Median (min, max) presented for T_{max}; mean (SD) presented for $t_{1/2}$, AR, and M/P; and geometric mean (%CV) was reported for other parameters; data after the parentheses indicate patient number for the specific parameter.

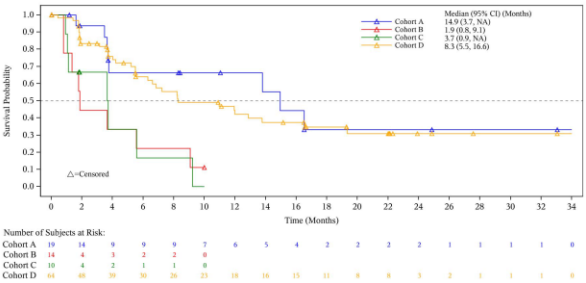
Supplementary Figure S1: Best percentage change in tumor burden from baseline according to investigator assessments in the efficacy evaluable analysis set in the dose-expansion phase
A-D



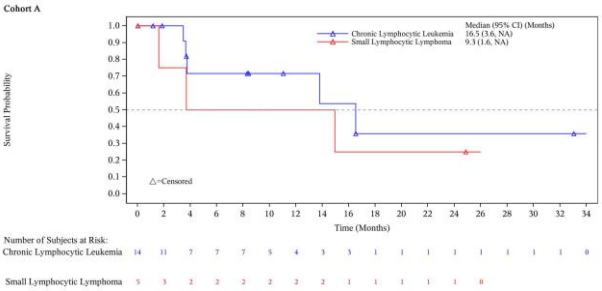

Cohort D
Best Percentage Change in Tumor Burden from Baseline (%)
Marginal Zone Lymphoma
Lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia
Follicular Lymphoma
Complete response
Partial response
Stable disease
Disease progression or relapse
Subjects

Supplementary Figure S2: Kaplan-Meier plots of progression-free survival as per investigator assessments based on the safety set in the dose-expansion phase

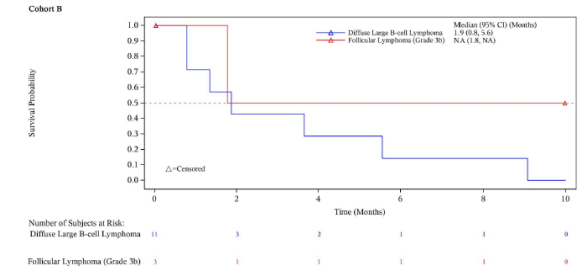
A (Overall)



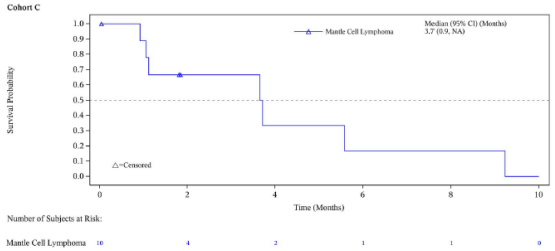
B (Cohort A)



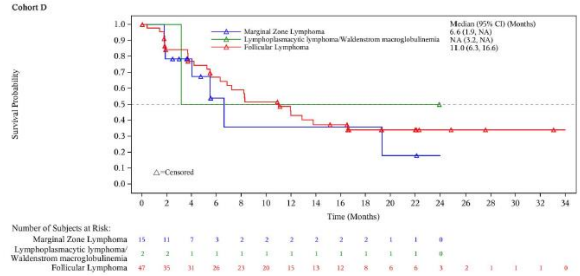
C (Cohort B)



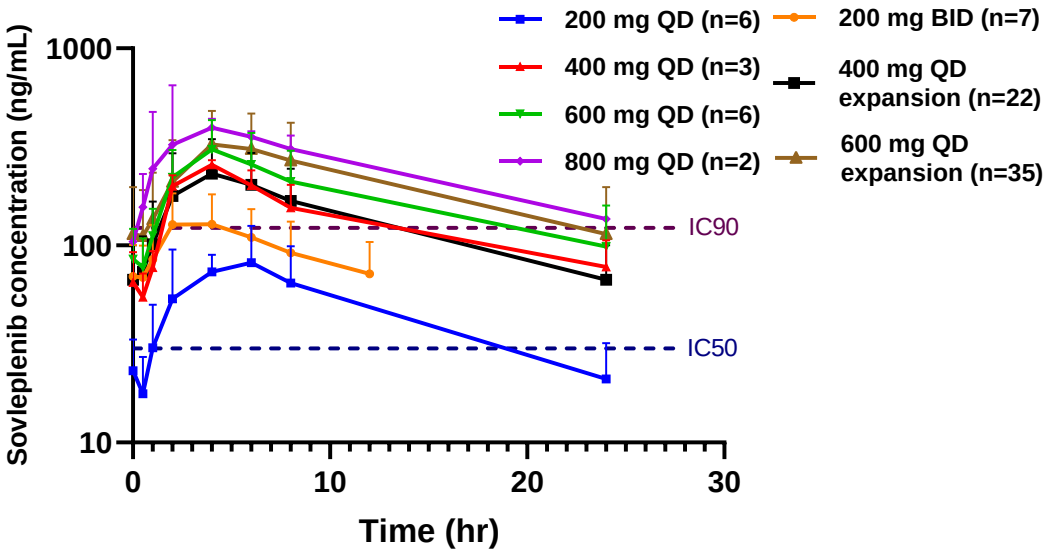
D (Cohort C)



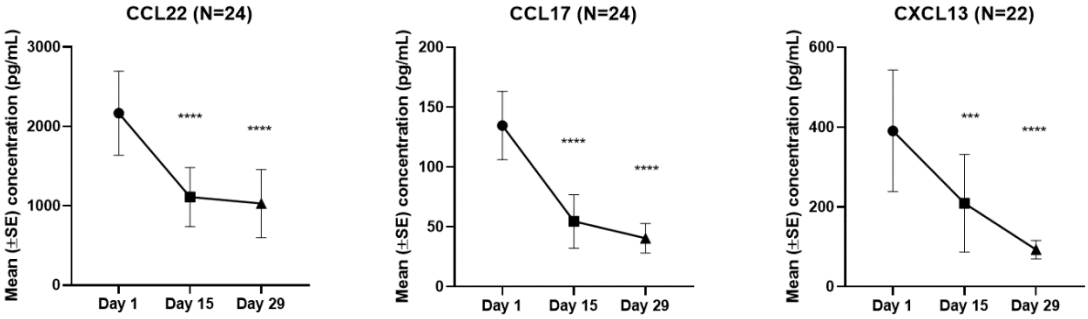
E (Cohort D)



Supplementary Figure S3: Mean plasma concentration-time curves of sovleplenib at steady state



Supplementary Figure S4: CLL22, CCL17, CXCL13 biomarker analysis during dose expansion



Supplementary Figure S5: CCL22, CCL17 and CXCL13 biomarker analysis during dose expansion with respect to cohorts A, B and D