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ORIGINAL ARTICLE

Phase 1/2 study of venetoclax, a BCL-2 inhibitor, in Japanese patients with relapsed or refractory chronic lymphocytic leukemia and small lymphocytic lymphoma

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Abstract

Patients with relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) have limited treatment options. Venetoclax is a potent BCL-2 inhibitor that induces apoptosis in CLL cells. This open-label, phase 1/2 study (NCT02265731) evaluated the safety, pharmacokinetics, and efficacy of venetoclax in Japanese patients with R/R CLL/SLL. Patients enrolled in phase 1 received 400 mg/day venetoclax monotherapy. Patients enrolled in phase 2 received 400 mg/day venetoclax, plus rituximab. Venetoclax was administered with a weekly stepwise ramp-up in doses. In phase 2, efficacy was evaluated by objective response rate (ORR). Twelve patients were enrolled, six in each arm. The most common grade ≥ 3 adverse events were neutropenia (83%), lymphopenia (67%), leukopenia (33%), and thrombocytopenia (17%). Patients receiving venetoclax monotherapy achieved an ORR of 100%, including a complete remission (CR) rate of 17%. Patients receiving combination therapy had an ORR of 67% and a CR rate of 50%. The venetoclax pharmacokinetics profile in Japanese patients was similar to that of Western patients. Venetoclax 400 mg/day monotherapy or in combination with rituximab was well-tolerated and induced promising responses in Japanese patients with R/R CLL/SLL. Although patient numbers were small, the safety profile was largely consistent with other Western studies. Clinical trial registration: clinicaltrials.gov; NCT02265731.

Keywords BCL-2 · Chronic lymphocytic leukemia · Small lymphocytic lymphoma · Venetoclax

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Introduction

Among adult patients suffering from leukemia in the Western countries, chronic lymphocytic leukemia (CLL) is the most prevalent, accounting for approximately 30% of all leukemias [1], but is rarely found in Japan and other East Asian countries [2]. The incidence of CLL is 6.9 cases per 100,000 person-years in the non-Hispanic white population, vs. 1.4 cases in the Asian and Pacific Islander population [3]. Presentation of CLL can vary due to its genetic and pathologic heterogeneity, and there are documented differences between Asian and Western patients, including prevalence of mutations in the immunoglobulin heavy chain variable (*IGHV*) region, as well as other immunophenotypes [4–6]. However, the frequency of chromosomal rearrangements and mutations is fairly alike in both populations [6, 7], as is the efficacy of CLL treatments [8, 9].

There have been significant advances in the treatment of CLL/small lymphocytic lymphoma (SLL), but it remains an incurable disease as many patients will relapse or become refractory (R/R). Available therapies for patients with R/R CLL, such as the combination of rituximab and fludarabine, rituximab and bendamustine, or ofatumumab, have been associated with toxicities, provided limited disease control, or both [10–13]. More recent therapies, including B cell receptor signaling pathway inhibitor (BCRi) therapies such as ibrutinib and idelalisib, have demonstrated more favorable efficacy outcomes than other historically available treatments. However, patients who have failed BCRi treatment are an emerging subpopulation with a dismal prognosis [14, 15]. In Japan, treatment options for CLL are limited as many novel agents are not yet approved.

The BCL-2 protein is a negative regulator of the intrinsic apoptotic pathway, acting to sequester pro-apoptotic proteins such as BAX and BAK. CLL cells are highly dependent on BCL-2 for survival, and thus most patients with CLL are inherently sensitive to BCL-2 inhibition [16, 17]. Venetoclax is a highly selective, potent, oral BCL-2 inhibitor that induces apoptosis in CLL cells, alone or in combination with other therapeutic agents [18]. Pre-clinical studies have shown that the combination of venetoclax with anti-CD20 monoclonal antibodies, such as rituximab, is more effective than either agent alone, and in mouse xenograft models, the venetoclax and rituximab combination significantly improved tumor growth delay, tumor growth inhibition, and induced complete responses [18]. The increase in cell death may be due to the ability of anti-CD20 monoclonal antibodies to induce non-apoptotic cell death in some CLL cells, thus complementing the mechanism of action of venetoclax by targeting a different pathway [19].

Studies in Western countries have shown that venetoclax monotherapy or in combination with other agents is safe and efficacious in multiple patient populations with CLL. Phase 1 and 2 studies of venetoclax monotherapy have demonstrated high overall response rates in patients with R/R CLL and also among patients with confirmed deletion of chromosome arm 17p [20–22]. Further studies of venetoclax in combination with rituximab demonstrated durable and deep responses [23] and significantly increased progression-free survival (PFS) across all clinical and biological subgroups when administered as 2-year fixed duration treatment [24] in patients with R/R CLL. More recently, treatment naïve CLL patients receiving 12-month fixed duration treatment of venetoclax in combination with obinutuzumab demonstrated a significantly prolonged PFS when compared to patients treated with chlorambucil and obinutuzumab [25].

Given the CLL treatment landscape in Japan, and as venetoclax is approved in the US and other countries for treatment of patients with CLL/SLL, we undertook a phase 1/2 study of venetoclax monotherapy and in combination with rituximab to evaluate safety, pharmacokinetics (PK), and efficacy in Japanese patients with R/R CLL/SLL, the results of which are reported here.

Materials and methods

Study design and participants

Study M13-834 (NCT02265731) was an open-label, multicenter phase 1/2 study of venetoclax mono- or combination therapy in Japanese patients, which comprised of four arms. Here, we report results from patients with CLL/SLL in Arms B and D. The primary objectives of Arm B were to evaluate the safety and PK of venetoclax (Ven) monotherapy in patients with R/R CLL/SLL. The secondary objectives were to evaluate preliminary efficacy of venetoclax on objective response rate (ORR), time to disease progression (TTP), and duration of overall response (DoR). The primary objectives of phase 2 (Arm D) were to evaluate the efficacy of venetoclax in combination with rituximab (VenR) in patients with R/R CLL as best ORR. The secondary objectives were to evaluate CR rate, partial response (PR) rate, DoR, PFS, and TTP. The safety and tolerability of venetoclax in combination with rituximab was also evaluated. Results from Arms A and C, both part of phase 1, are reported elsewhere [26].

Eligible patients (≥ 20 years) had an Eastern Cooperative Oncology Group (ECOG) performance score of ≤ 1. For Arm B, patients had relapsed following or were refractory to standard treatments, such as fludarabine- or alkylator-based treatments. For Arm D, patients had R/R disease to ≥ 1 line of therapy, with a diagnosis of R/R CLL as defined by the 2008 Modified International Workshop on Chronic Lymphocytic Leukemia (IWCLL) guidelines [27]. All patients

had to have adequate bone marrow, hepatic, and renal function, could not have undergone an allogeneic or autologous stem cell transplant, and could not have received strong or moderate CYP3A inhibitors or inducers (due to venetoclax being a CYP3A substrate) within 7 days prior to the first dose of study drug. The use of CYP3A inhibitors was also excluded during the venetoclax ramp-up period and until the dose limiting toxicity (DLT) assessment for a dose level was complete, and was considered cautionary afterwards.

This study was performed in accordance with the 1964 Declaration of Helsinki and its later amendments, and the International Conference on Harmonization Good Clinical Practice Guideline. All patients provided written informed consent prior to enrollment, and the study design was approved by the institutional review board/ethics committee of each participating institution.

Based on tolerability of venetoclax 400 mg in Arm B, the protocol was amended to add Arm D which enrolled patients with R/R CLL to investigate the combination therapy of venetoclax with rituximab.

Treatment

Patients with R/R CLL/SLL in Arm B received venetoclax monotherapy once a day orally until progression or other discontinuation criteria were met. A stepwise weekly dose ramp-up from a starting dose of 20 mg to the target 400 mg daily dose (20, 50, 100, 200, 400 mg) was used over 5 weeks, and the designated dose of 400 mg/day was used thereafter (Fig. 1a). Patients could continue receiving venetoclax for up to 2 years following the date of the last patient enrolled, provided they continued to tolerate the drug, had no evidence of disease progression, and did not meet any criteria for discontinuation.

Patients with R/R CLL in Arm D received oral venetoclax in combination with rituximab, with dosing in three periods: a ramp-up period from weeks 1 to 5; a combination therapy period from weeks 6 to 29; and a monotherapy period from week 30 onward (Fig. 1b). For the ramp-up, venetoclax was administered as described above for Arm B. During the combination therapy period, patients received venetoclax 400 mg daily from weeks 6–29 plus rituximab 375 mg/m^2 on week 6 day 1, followed by 500 mg/m^2 every 4 weeks until week 29 day 1 (six doses of rituximab in total). All patients received prophylactic uric acid reducing agents (e.g. allopurinol, febuxostat, or rasburicase) and intravenous hydration to mitigate the risk of tumor lysis syndrome (TLS). Patients received acetaminophen and diphenhydramine within 30–60 min prior to the start of rituximab infusion. A single dose of hydrocortisone (up to 100 mg or

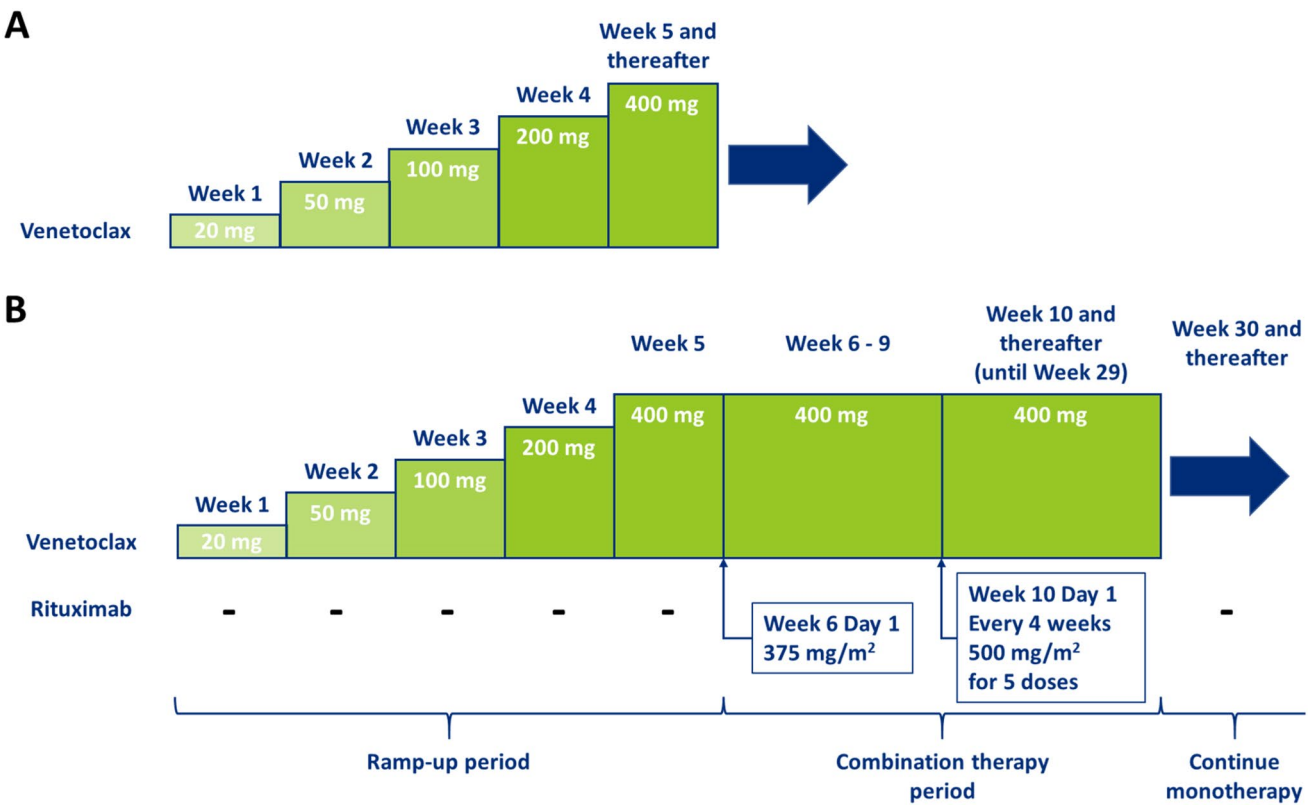

Fig. 1 Dosing schematics for **a** venetoclax monotherapy arm and **b** venetoclax plus rituximab combination therapy arm

an equivalent dose of methylprednisolone) was also administered beginning with the first infusion. On days when both venetoclax and rituximab were given, venetoclax was taken at least 30 min prior to starting the rituximab infusion. For the subsequent monotherapy period, venetoclax 400 mg/day only was administered to patients from week 30 onward, for up to 2 years as described above.

In either arm, any dose modifications for safety management were made per protocol. Patients who discontinued rituximab due to related toxicity may have continued to receive venetoclax at the investigator's discretion. Furthermore, to mitigate the risk of TLS, a known risk for venetoclax, all patients followed the guidelines for management of TLS as per protocol (supplemental methods) as well as other studies [24]. In addition, anti-infective prophylaxis was recommended as clinically indicated in an individual patient, including appropriate prophylaxis for viral, fungal, bacterial, or pneumocystis infections.

Safety and tolerability assessments

Dose limiting toxicities for Arm B were determined during the ramp-up period plus 3 weeks (21 days or until completion of week 7) of study drug administration. Patients in Arm B were evaluated for tolerability by the protocol defined dose of 400 mg/day. There was no dose escalation in Arm B. For Arm D, the period until completion of week 9 was defined as the DLT evaluation period. Though the primary objective of Arm D was to evaluate the efficacy with ORR, safety and tolerability of the combination therapy of venetoclax and rituximab were also assessed. Tolerability in both arms were evaluated based on the DLT criteria defined in protocol. Additional details on DLTs can be found in the Supplemental methods.

Safety assessments for all patients included adverse event (AE) monitoring, vital signs, physical examination, 12-lead electrocardiography, multiple gated acquisition scan/2-dimensional echocardiogram, and laboratory assessments. AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v4.03 [28].

Efficacy assessment

For Arm B (Ven), preliminary efficacy was evaluated by ORR, TTP, and DoR. For Arm D (VenR), efficacy was measured by ORR as the primary objectives, and CR rate, PR rate, DoR, PFS, and TTP as the secondary objectives. Responses were assessed in Arm B on day 1 of week 6, 16, 24, 36, 48 and every 24 weeks thereafter, and in Arm D on day 1 of week 6, 14, 22, 30 and every 12 weeks thereafter. Tumor response was assessed based on the modified 2008 IWCLL National Cancer Institute-Working Group (NCI-WG) Guidelines, with the addition of CT imaging or MRI (if medically indicated) as defined in the study procedures [27] for patients with CLL, or based on International Working Group criteria [29] for patients with SLL. In this study, PR was confirmed $\geq$ 49 days apart for objective response. DoR was defined as the time from first documented objective response to disease progression/relapse, as assessed by the investigator, or death. PFS was defined as the time from the first dose of the study drug to disease progression or death. TTP was defined as the time from first dose to disease progression.

Pharmacokinetics

For Arm B (Ven), blood samples for the venetoclax PK assay were collected at the following times: weeks 1–5, 8 h post-dose on day 1 of each cycle; week 7 day 1, 0 h (pre-dose) and 2, 3, 4, 6, 8 h post-dose; week 7 day 2, 0 h (pre-dose); and weeks 8, 12, 16, 24, 0 h (pre-dose) on day 1 of each cycle. For Arm D (VenR), blood samples were collected at the following times: week 1–5, 8 h post-dose on day 1 of each cycle; week 6 day 1, 0 h (pre-dose); week 10 day 1, 0 h (pre-dose), 2, 4, 6, 8 h post-dose; and weeks 14, 18, 26, 0 h (pre-dose) on day 1 of each cycle.

Values for the PK parameters of venetoclax, including the maximum observed plasma concentration (C_{max}), the time to C_{max} (peak time, T_{max}) and the area under the plasma concentration–time curve over a 24-h dose interval ($AUC_{0–24}$) were determined using noncompartmental methods for doses administered on the intensive PK day (i.e., week 7 day 1 for Arm B or week 10 day 1 for Arm D). Venetoclax concentrations at 24 h were imputed using 0-h concentrations to calculate $AUC_{0–24}$. No adjustments for covariates were provided.

Statistical analyses

Patients who received at least one dose of venetoclax were included in the analyses. Unless otherwise noted, statistical significance was determined by a two-sided p value ≤ 0.05. Descriptive statistics were provided for baseline demographic variables and summarized with means, medians, standard deviation (SD), and ranges, with frequencies and percentages included as necessary. In phase 2 (Arm D), based on other Japanese CLL studies, the threshold of ORR was set at 20% and the lower limit of 95% confidence interval (CI) of response was confirmed to be above 20% to demonstrate efficacy of venetoclax. For ORR, the proportion of patients with a response of CR, CR with incomplete bone marrow recovery (CRi), confirmed nodular PR (nPR), or confirmed PR was estimated and provided with the corresponding 95% CI. The CR rate was defined as the proportion of patients with CR or CRi, and the PR rate was defined as

the proportion of patients with nPR or PR; both estimates included the 95% CI. TTP, DoR, and PFS were analyzed by Kaplan–Meier methodology. Median PFS time was calculated and presented with 95% CI.

Results

Patient demographics and characteristics

Six patients each were enrolled in the Ven (phase 1, Arm B) and VenR (phase 2, Arm D) arms. The median age was 72 years (range, 38–73) in the Ven arm and 64 years (range, 55–77) in the VenR arm. In both arms, 10 (83%) patients had CLL and 2 (17%) had SLL. Ten (83%) patients received ≤ 3 prior lines of therapy, 2 (17%) received 6 or more prior lines, and 4 (33%) received prior BCRi therapy (Table 1).

Disposition

As of the data cut-off of 18 July 2018, 8 (67%) patients remained active on study. The median time on venetoclax was 21.9 months (range, 9.5–29.5) and 7.5 months (2.7–9.5) in the Ven and VenR arms, respectively. Median duration of venetoclax treatment was substantially longer for patients in the Ven vs VenR arm, as the VenR arm (phase 2) began enrollment after the Ven arm (phase 1). In the VenR arm, the median number of rituximab treatments was 6 (range, 2–6). In the Ven arm, one patient discontinued venetoclax due to progressive disease on 76.1 weeks and one patient discontinued venetoclax for an AE of myelodysplastic syndrome, unrelated to venetoclax, which resulted in the patient's death more than 30 days after the last dose of study drug on 41.3 weeks. Two patients had an AE resulting in venetoclax interruption (one patient with hyperphosphatemia; one patient with a large intestinal ulcer and sepsis), and one patient had an AE of neutropenia leading to venetoclax reduction and dose delay. In the VenR arm, one patient discontinued venetoclax due to progressive disease on 19.3 weeks and one patient discontinued for an AE of grade 4 thrombocytopenia, related to venetoclax on 11.7 weeks. Three patients had AEs leading to venetoclax interruption (one patient with neutropenia; one patient with hyperphosphatemia; one patient with bacterial pneumonia, purpura, and increased alanine aminotransferase levels), and two patients had AEs resulting in dose reduction (one patient with neutropenia; one patient with bacterial pneumonia, neutropenia, and increased alanine aminotransferase levels).

Safety profile

All patients experienced at least one AE (Table 2). The most common AEs of any grade in the Ven arm were neutropenia in 6 (100%) patients, lymphopenia in 5 (83%), and thrombocytopenia, constipation, cough, pyrexia, stomatitis, and weight decreased in 2 patients (33%) each. In the VenR arm, the major AEs were neutropenia in 5 (83%) patients, lymphopenia, leukopenia, nausea, and increased aspartate aminotransferase in 4 (67%) patients each, thrombocytopenia and malaise in 3 (50%) patients each, and hot flush/flash in 2 (33%) patients. Nine of the 11 patients in both arms with neutropenia received G-CSF support to control their neutropenia and were able to continue study treatment. There were no fatal outcomes due to neutropenia.

All patients had at least one AE considered to be venetoclax-related (Table 3). In the Ven arm, the most common AEs related to venetoclax treatment were neutropenia occurring in 6 (100%), lymphopenia in 5 (83%) and thrombocytopenia in 2 (33%) patients. In the VenR arm, common AEs related to treatment were nausea in 4 (67%), neutropenia in 4 (67%), lymphopenia and leukopenia in 3 (50%) patients each. In the VenR arm, 5 (83.3%) patients experienced an AE with a reasonable possibility of relationship to rituximab, and two patients had infusion-related reactions related to rituximab. No DLTs were reported in Ven arm. In VenR arm, one patient had DLTs of grade 3 bacterial pneumonia and grade 3 increased alanine aminotransferase levels.

Serious AEs were reported in 4 (33%) patients, two from each arm. In the Ven arm, both patients had multiple AEs. One patient had herpes zoster, sepsis, and a large intestinal ulcer; the other had myelodysplastic syndrome, febrile neutropenia, pneumonia, and septic shock. In the VenR arm, one patient had progressive disease, and the other had bacterial pneumonia. Infections and infestations of any grade AE were reported in 3 (50%) patients in each Ven and VenR arm. Two (33.3%) patients in each arm experienced a ≥ grade 3 infections, and there were no fatal AEs of infection and no patient who discontinued venetoclax due to infection. No events of laboratory or clinical TLS were reported. No Richter's transformation was observed.

Efficacy

Patients receiving Ven achieved an ORR of 100% (1 CR, 5 PR) and patients receiving VenR achieved an ORR of 66.7% (3 CR, 1 PR) (Fig. 2). The CR rate (CR + CRi) was 16.7% (95% CI 0.4–64.1) for Ven and 50.0% (95% CI 11.8–88.2) for VenR. The PR rate was 83.3% (95% CI 35.9–99.6) for Ven and 16.7% (95% CI 0.4–64.1) for VenR. Among patients achieving PR or better, 4/6 receiving Ven and 3/4 receiving VenR achieved PR early on at the week 6 day 1 assessment, corresponding to completion timing of the ramp-up period. Two patients with 17p deletion achieved a best response of either CR (one patient receiving Ven) or PR (one receiving Ven). Four patients receiving prior BCRi achieved a best response of either CR (two patients receiving VenR) or PR

Table 1 Patient demographics and baseline characteristics

	Arm B (Ven), $n=6$	Arm D (VenR), $n=6$	All patients, $N=12$
Sex			
Female	2 (33)	1 (17)	3 (25)
Male	4 (67)	5 (83)	9 (75)
Age, median (range)	72 (38–73)	64 (55–77)	70 (38–77)
Diagnosis			
CLL	4 (67)	6 (100)	10 (83)
SLL	2 (33)	0	2 (17)
ECOG performance score			
0	3 (50)	4 (67)	7 (58)
1	3 (50)	2 (33)	5 (42)
No. of prior lines of therapy*			
1	3 (50)	1 (17)	4 (33)
2	2 (33)	1 (17)	3 (25)
3	0	3 (50)	3 (25)
≥6	1 (17)	1 (17)	2 (17)
Prior BCRi therapy			
Ibrutinib	1 (17)	1 (17)	2 (17)
Idelalisib	0	1 (17)	1 (8)
Ibrutinib + idelalisib	0	1 (17)	1 (8)
Rai stage at diagnosis			
1	1 (25)	2 (33)	3 (30)
2	1 (25)	1 (17)	2 (20)
3	1 (25)	1 (17)	2 (20)
4	1 (25)	2 (33)	3 (30)
Missing	2**	0	2**
Binet stage at diagnosis			
A	1 (25)	0	1 (10)
B	2 (50)	4 (67)	6 (60)
C	1 (25)	2 (33)	3 (30)
Missing	2*	0	2*
TLS risk category***			
Low	2 (33)	0	2 (17)
Medium	3 (50)	5 (83)	8 (67)s
High	1 (17)	1 (17)	2 (17)
β2 microglobulin			
≤3.5 μg/mL	2 (67)	1 (100)	3 (75)
>3.5 μg/mL	1 (33)	0	1 (25)
Missing	3	5	8
IGHV mutations			
Yes	2 (100)	0	2 (100)
No	0	0	0
Missing	4	6	10
p53 mutation			
Yes	0	1 (100)	1 (25)
No	2 (67)	0	2 (50)
Indeterminate	1 (33)	0	1 (25)
Missing	3	5	8
17p deletion			
Deleted	2 (50)	1 (17)	3 (30)
Not deleted	2 (50)	5 (83)	7 (70)
Missing	2	0	2

Table 1 (continued)

	Arm B (Ven), $n=6$	Arm D (VenR), $n=6$	All patients, $N=12$
11q deletion			
Deleted	0	0	0
Not deleted	0	3 (100)	3 (100)
Missing	6	3	9

Data shown as *n* (%). Percentages were calculated based on non-missing values

BCRi B cell receptor pathway inhibitor, *CLL* chronic lymphocytic leukemia, *ECOG* Eastern Cooperative Oncology Group, *R* rituximab, *SLL* small lymphocytic lymphoma, *TLS* tumor lysis syndrome, *Ven* venetoclax

*No patients received four or five lines of prior therapy

**Both patients had stage four SLL

***TLS risk categories were defined as follows: Low [any lymph node (LN) < 5 cm and absolute lymphocyte count (ALC) $< 25\times10^9$/L]; Medium [any LN 5 cm to < 10 cm or ALC $\geq 25\times10^9$/L]; High [any LN ≥ 10 cm or any LN ≥ 5 cm and ALC $\geq 25\times10^9$/L]

Table 2 Treatment-emergent adverse events (TEAEs)

TEAE	Arm B (Ven), $n=6$		Arm D (VenR), $n=6$		All patients, $N=12$	
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Any TEAE	6 (100)	6 (100)	6 (100)	6 (100)	12 (100)	12 (100)
Neutropenia	6 (100)	5 (83)	5 (83)	5 (83)	11 (92)	10 (83)
Lymphopenia	5 (83)	4 (67)	4 (67)	4 (67)	9 (75)	8 (67)
Leukopenia	1 (17)	0	4 (67)	4 (67)	5 (42)	4 (33)
Thrombocytopenia	2 (33)	0	3 (50)	2 (33)	5 (42)	2 (17)
Nausea	1 (17)	0	4 (67)	0	5 (42)	0
Aspartate aminotransferase increased	0	0	4 (67)	0	4 (33)	0
Constipation	2 (33)	0	1 (17)	0	3 (25)	0
Cough	2 (33)	0	1 (17)	0	3 (25)	0
Hot flush/flash	1 (17)	0	2 (33)	0	3 (25)	0
Malaise	0	0	3 (50)	0	3 (25)	0
Pyrexia	2 (33)	0	1 (17)	0	3 (25)	0
Stomatitis	2 (33)	0	1 (17)	0	3 (25)	0
Weight decreased	2 (33)	0	1 (17)	0	3 (25)	0

All data shown as *n* (%). Includes TEAEs of any grade in ≥ 25% of patients

Table 3 Treatment-emergent adverse events (TEAEs) having a reasonable possibility of being venetoclax related

TEAE	Arm B (Ven), $n=6$		Arm D (VenR), $n=6$		All patients, $N=12$	
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Any TEAE	6 (100)	6 (100)	6 (100)	6 (100)	12 (100)	11 (92)
Neutropenia	6 (100)	5 (83)	4 (67)	4 (67)	10 (83)	9 (75)
Lymphopenia	5 (83)	4 (67)	3 (50)	3 (50)	8 (67)	7 (58)
Nausea	1 (17)	0	4 (67)	0	5 (42)	0
Leukopenia	1 (17)	0	3 (50)	3 (50)	4 (33)	3 (25)
Thrombocytopenia	2 (33)	0	2 (33)	2 (33)	4 (33)	2 (17)
Hot flush	1 (17)	0	2 (33)	0	3 (25)	0

All data shown as *n* (%). Includes TEAEs of any grade in ≥ 25% of patients

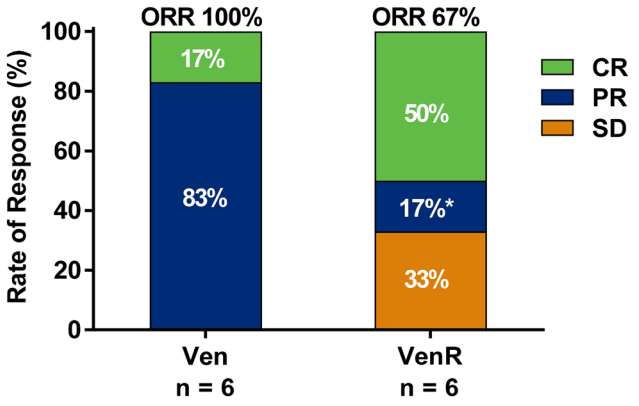

Fig. 2 Objective response rate (ORR) for patients treated with Ven or VenR. *CR* complete remission, *PR* partial remission, *R* rituximab, *SD* stable disease, *Ven* venetoclax. *PR needed to be confirmed not less than 49 days apart for objective response according to the study protocol. One patient receiving VenR had an unconfirmed PR due to progression prior to assessment and was included in the SD category

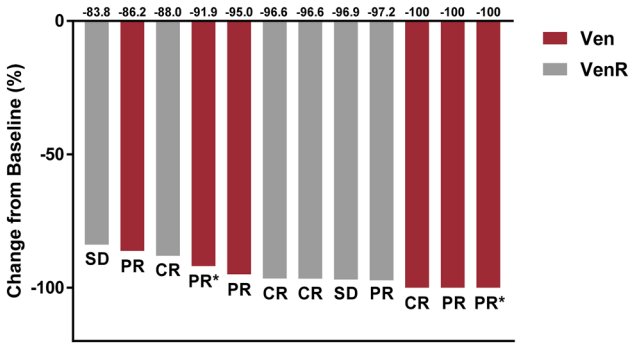

Fig. 3 Maximum lymph node response in all patients. Number at the top indicates the percent change from baseline in lymph node size. Confirmed objective response for each patient is indicated at the bottom of the column. *CR* complete remission, *PR* partial remission, *R* rituximab, *SD* stable disease, *Ven* venetoclax. All patients had CLL except for those with a asterisk (*), indicating the patient had SLL

(one receiving Ven, one receiving VenR). The maximum lymph node response for each patient is shown in Fig. 3. For two patients with SD, one achieved PR but not confirmed per protocol criteria, including in SD category, and the other discontinued study treatment due to hematological AEs even though lymph node size was significantly decreased. Median TTP, DoR, and PFS were not reached for either arm as of the data cut-off date.

Pharmacokinetics

All available data were included in PK concentration summaries and statistical analyses, except for two patients who did not have intensive samples for calculation of PK estimates. The median time to peak venetoclax concentrations

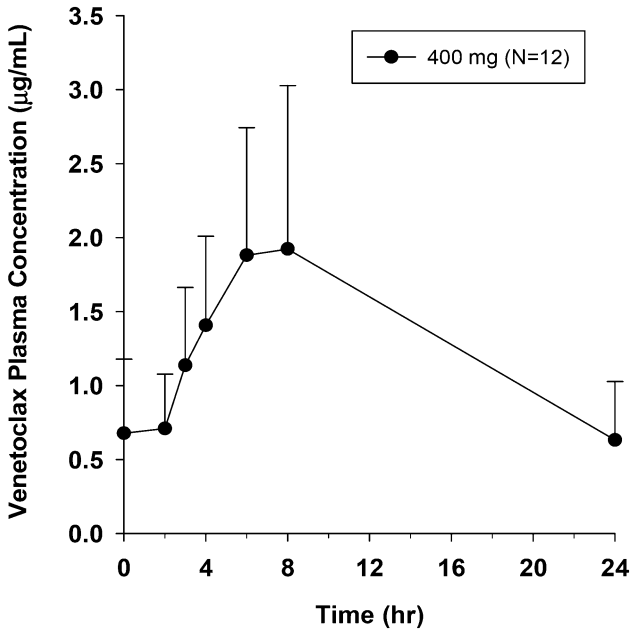

Fig. 4 Mean + SD venetoclax plasma concentration–time profiles in all patients in linear scale; *Hr* hour, *SD* standard deviation

was 6 h after the dose, and the mean C_{max} and $AUC_{0–24}$ at the 400 mg dose were 2.08 µg/mL and 31.0 µg h/mL, respectively (Fig. 4; Table 4). The mean pre-dose concentrations of venetoclax across visits at 400 mg ranged from 0.547 to 0.951 µg/mL (Supplementary Table S1). The mean and SD post-dose (8 h) venetoclax plasma concentrations are provided in Supplementary Table S2.

Discussion

Venetoclax 400 mg monotherapy or in combination with rituximab was well tolerated in Japanese patients with R/R CLL/SLL. An ORR of 100% and 66.7%, and CR rates of 16.7% and 50.0% were observed in patients treated with Ven and VenR, respectively, suggesting that both treatment regimens are efficacious in this population. In both arms, most responders (four patients treated with Ven and three patients treated with VenR) achieved PR at completion of the ramp-up period (5 weeks).

In this study, two patients with 17p deletion achieved response including one CR. Efficacy of venetoclax with or without rituximab in patients with 17p deletion was in line with the observation in the MURANO study, in which VenR regimen showed clearly higher 2-year PFS rate compared to bendamustine plus rituximab in the subgroup of patients 17p deletion. However, efficacy of venetoclax in the present phase 1/2 study should be interpreted with caution because of limited number of patients and missing genetic data.

Table 4 Mean ± SD (geometric mean, %CV) pharmacokinetic parameters of venetoclax

Venetoclax dose	*N*	T_{max}[a] (h)	C_{max} (μg/mL)	$AUC_{0–24}$ (μg × h/mL)	Dose normalized C_{max} (ng/mL)/mg	Dose normalized $AUC_{0–24}$ (ng h/mL)/mg
400 mg	12	6.0 (4.0–8.0)	2.08 ± 1.04 (1.87, 50)	31.0 ± 15.5 (27.6, 50)	5.20 ± 2.60 (4.68, 50)	77.5 ± 38.7 (69.0, 50)

$AUC_{0–24}$ area under the concentration–time curve from 0 to 24 h, *C_{max}* maximum observed concentration, *CV* coefficient of variation, *SD* standard deviation, *T_{max}* time to maximum observed plasma concentration

[a]T_{max} presented as median (range)

All four patients who were treated with prior BCRi therapy, demonstrated CR or PR. Overall, the safety profile was largely consistent with Western patient populations in other studies [24, 30], and no Japanese-specific safety concerns were observed. The observed AEs were consistent with the known safety profile of venetoclax, as well as with AEs expected in an elderly, heavily pretreated patient population with hematological malignancies. Although TLS is a known risk of venetoclax treatment, there were no events of either laboratory or clinical TLS. All patients received TLS prophylaxis per protocol, which included ramp-up dosing, dose interruptions, and other standard-of-care methods according to the TLS risk as defined in the guidelines for management [31]. Neutropenia, a known on-target effect and identified risk of venetoclax [32], occurred in 11/12 (92%) patients in both arms but was manageable with standard care, which included dose modification and growth factor support (based on physician decision per protocol). In this study, anti-infection prophylaxis was recommended as clinically indicated but no specific agents were mandatory. All patients received some anti-infection prophylaxis. Prophylaxis for anti-pneumocystis pneumonia and herpes zoster were also administrated in most patients. The venetoclax PK profile of Japanese patients with CLL was consistent with that observed in the Western population [33, 34]. Previous analyses [35–37] from other trials have demonstrated that venetoclax PK is associated with efficacy and safety outcomes in CLL patients, which further suggests that efficacy and safety findings in phase 2 and 3 studies [21, 24, 25] conducted primarily in Western populations would be similar in the Japanese population as well.

Study limitations include that the study did not include any comparator arm, and thus no comparison to other standard treatment regimens can be made. Furthermore, only a small number of patients were involved, as this was a phase 1/2 study comprised of multiple hematologic malignancies in the multi-arm phase 1 portion, and the phase 2 portion had only one arm of patients with CLL. Minimal residual disease (MRD), is considered as a robust surrogate for long-term outcome such as PFS and overall survival for CLL patients [24, 38]. However, MRD data were not available during the preparation of this manuscript.

In conclusion, the study results suggest that venetoclax monotherapy and in combination with rituximab are effective and well-tolerated treatment options for Japanese patients with R/R CLL/SLL.

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Data availability AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual and trial-level data (analysis data sets), as well as other information (e.g., protocols and Clinical Study Reports), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications. This clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time and the data will be accessible for 12 months, with possible extensions considered. For more information on the process, or to submit a request, visit the following link: https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html.

Compliance with ethical standards

Conflict of interest Koji Izutsu: Honoraria from Eisai, MSD, Kyowa-Kirin, Takeda, Janssen, Dainihon Sumitomo, Mundipharma, Nihon Mediphysics, Chugai, AbbVie, AstraZeneca, Bayer, Ono, Celgene; research funding from Eisai, Janssen, Mundipharma, Chugai, AstraZeneca, AbbVie, Bayer, Ono, Gilead, Zenyaku, Celgene, Solasia, Symbio, Astellas, Astellas Amgen, Bayer, Daiichi Sankyo. Kazuhito Yamamoto: Research funding from AbbVie, ARIAD Pharmaceuticals, AstraZeneca, Bayer, Celgene, Chugai, Eisai, Gilead Sciences, Incyte, MSD, Mundipharma, Nippon Shinyaku, Novartis, Ono, Solasia Pharma, SymBio, Takeda, Zenyaku; honoraria from Chugai, Mundipharma, Takeda. Koji Kato: Honoraria from Chugai, Takeda, MSD, Kyowa-Kirin, Janssen, Celgene, Ono, Mundi, Dainippon-Sumitomo; consulting or advisory role for Novartis, Eisai, Janssen, Celgene; research funding from Chugai, Takeda, Kyowa-Kirin, AbbVie, Novartis, Eisai, Janssen, Celgene, Ono. Takayuki Ishikawa: Investigator in AbbVie-sponsored clinical trials. Noriko Fukuhara: Research funding from AbbVie, Bayer, Eisai, Gilead, Janssen, Ono, Takeda; honoraria

from Kyowa Hakko Kirin. Yasuhito Terui: Honoraria from Chugai, Takeda, Janssen, Celgene, Ono, Mundi, Novartis, Eisai, Takeda; research funding from BMS. Ilseung Choi: Investigator in AbbVie-sponsored clinical trials. Kathryn Humphrey: Employee of Roche and may own stock or stock options. Su Young Kim, Sumiko Okubo, Natsumi Ogawa, Yasuko Nishimura, Ahmed Hamed Salem: Employees of AbbVie and may own stock or stock options. Dai Maruyama: Research funding from Chugai Pharma, Ono Pharmaceutical, Celgene, Janssen, GlaxoSmithKline, Eisai, Mundipharma, Takeda, AbbVie, MSD, Astellas Pharma, Amgen, Astellas, BioPharma, Otsuka, Novartis, Nippon Boehringer Ingelheim, Pfizer, Solasia Pharma, Bayer, Zenyaku Kogyo, AstraZeneca; honoraria from Zenyaku Kogyo, Eisai, Takeda, Mundipharma, Janssen, Kyowa Hakko Kirin, Celgene, Fujifilm, Chugai Pharma, MSD, Ono Pharmaceutical. AbbVie/Genentech: AbbVie and Genentech sponsored the study (NCT02265731), contributed to the study design, analysis, interpretation of the data, and participated in the writing, review, and approval of the manuscript. All authors had access to data. Venetoclax (ABT-199/GDC-0199) is being developed in collaboration between AbbVie and Genentech.

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