Activity of venetoclax in patients with relapsed or refractory chronic lymphocytic leukaemia: analysis of the VENICE-1 multicentre, open-label, single-arm, phase 3b trial

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Summary

Background Most patients with chronic lymphocytic leukaemia progress after treatment or retreatment with targeted therapy or chemoimmunotherapy and have limited subsequent treatment options. Response levels to the single-agent venetoclax in the relapsed setting is unknown. We aimed to assess venetoclax activity in patients with or without previous B-cell receptor-associated kinase inhibitor (BCRi) treatment.

Methods This multicentre, open-label, single-arm, phase 3b trial (VENICE-1) assessed activity and safety of venetoclax monotherapy in adults with relapsed or refractory chronic lymphocytic leukaemia, stratified by previous exposure to a BCRi. Eligible participants were aged 18 years or older with previously treated relapsed or refractory chronic lymphocytic leukaemia. Presence of del(17p) or *TP53* aberrations and previous BCRi treatment were permitted. Patients received 5-week ramp-up to 400 mg of oral venetoclax once daily and were treated for up to 108 weeks, with 2 years follow-up after discontinuation, or optional extended access. The primary activity endpoint was complete remission rate (complete remission or complete remission with incomplete marrow recovery) in BCRi-naive patients. Analyses used the intent-to-treat (ie, all enrolled patients, which coincided with those who received at least one dose of venetoclax). This study was registered with ClinicalTrials.gov, NCT02756611, and is complete.

Findings Between June 22, 2016, and March 11, 2022, we enrolled 258 patients with relapsed or refractory chronic lymphocytic leukaemia (180 [70%] were male; 252 [98%] were White; 191 were BCRi-naive and 67 were BCRi-pretreated). Median follow-up in the overall cohort was 49·5 months (IQR 47·2–54·1), 49·2 months (47·2–53·2) in the BCRi-naive group, and 49·7 months (47·4–54·3) in the BCRi-pretreated group. Of 191 BCRi-naive patients, 66 (35%; 95% CI 27·8–41·8) had complete remission or complete remission with incomplete marrow recovery. 18 (27%; 95% CI 16·8–39·1) of 67 patients in the BCRi-pretreated group had complete remission or complete remission with incomplete marrow recovery. Grade 3 or worse treatment-emergent adverse events were reported in 203 (79%) and serious adverse events were reported in 136 (53%) of 258 patients in the overall cohort. The most common treatment-emergent adverse event was neutropenia (96 [37%]) and the most common and serious adverse event was pneumonia (21 [8%]). There were 13 (5%) deaths reported due to adverse events; one of these deaths (autoimmune haemolytic anaemia) was possibly related to venetoclax. No new safety signals were identified.

Interpretation These data demonstrate deep and durable responses with venetoclax monotherapy in patients with relapsed or refractory chronic lymphocytic leukaemia, including BCRi-pretreated patients, suggesting that venetoclax monotherapy is an effective strategy for treating BCRi-naive and BCRi-pretreated patients.

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Introduction

Treatment with targeted agents, including B-cell receptor-associated kinase inhibitors (BCRis), has improved survival outcomes of individuals with chronic lymphocytic leukaemia.[1–3] However, BCRis need to be taken until disease progression, and are associated with long-term toxicities.[4,5] B-cell lymphoma-2 (BCL-2) protein, another therapeutic target, is overexpressed in chronic lymphocytic leukaemia.[6,7] Venetoclax, a first-in-class orally bioavailable BCL-2 inhibitor approved for the treatment of chronic lymphocytic leukaemia,[8] acts by inducing rapid apoptosis in chronic lymphocytic leukaemia cells.[6,9] This inhibitor has demonstrated deep and durable responses in patients with relapsed or refractory chronic lymphocytic leukaemia, including those with poor prognostic features.[10–12] Single-agent venetoclax can induce overall response rates of 65% or higher in these patients, with a manageable safety profile.[3,10,13] Although BCRi

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Research in context

Evidence before this study

We searched PubMed using the search terms "chronic lymphocytic leukemia", "clinical trials", "relapsed chronic lymphocytic leukemia", "refractory chronic lymphocytic leukemia", and "CLL and BCL-2" for studies published between Jan 1, 2011, and Dec 31, 2015, without language restrictions. At the time this study was initiated in 2016, venetoclax had received its first approval by the US Food and Drug Administration (FDA) as monotherapy in patients with chronic lymphocytic leukaemia with the 17p deletion (as detected by an FDA-approved test) who have received one or more previous therapies; venetoclax was also nearing approval for similar indications in the EU and Canada. The efficacy and safety data supporting approval of venetoclax monotherapy was derived from the following phase 1–2 studies of patients with relapsed or refractory chronic lymphocytic leukaemia: (1) the first-in-human study (NCT01328626) that enrolled 116 patients with relapsed or refractory chronic lymphocytic leukaemia who received target dosages of 150–1200 mg per day, in which patients had an overall objective response rate of 79%, with 20% of patients having either complete remission or complete remission with incomplete marrow recovery; (2) a single-arm phase 2 trial (NCT01889186) that enrolled 107 patients with relapsed or refractory chronic lymphocytic leukaemia, with 17p deletion, who received the eventual venetoclax label dose of 400 mg per day, that resulted in an overall response rate of 79% and complete remission or complete remission with incomplete marrow recovery rate of 8%; (3) and a phase 2 trial (NCT02141282) that evaluated 400 mg per day of venetoclax in patients with chronic lymphocytic leukaemia who had relapsed or were refractory to the B-cell receptor-targeted agents ibrutinib (n=41) or idelalasib (n=13), that resulted in an overall response rate of 61% and 50% and complete remission rate of 8% and 0%, respective to each previous therapy. The findings were broadly similar regardless of patient characteristics, including those often associated with poor chemoimmunotherapy outcomes, such as the presence of the 17p deletion or fludarabine resistance; however, there was a slightly lower overall response rate among the patients with previous B-cell receptor-associated kinase inhibitor (BCRi) therapy. Since venetoclax therapy in relapsed or refractory chronic lymphocytic leukaemia was, at that time, being further developed as a combination regimen with CD20 antibodies, this study (VENICE-I) was intended to provide data in a large population of patients with relapsed or refractory chronic lymphocytic leukaemia with diverse molecular features and previous treatment exposure.

Added value of this study

To our knowledge, this phase 3b trial of venetoclax monotherapy is the largest and has the longest follow-up for any trial evaluating venetoclax monotherapy and demonstrated deep and durable responses and prolonged overall survival, irrespective of previous BCRi treatment. With dose modifications, the safety profile of venetoclax was manageable even given this extended period of follow-up, and many patients transitioned to an extension study to continue receiving venetoclax therapy.

Implications of all the available evidence

These data suggest that patients with relapsed or refractory chronic lymphocytic leukaemia, including those with previous BCRi exposure, can derive clinical benefit from venetoclax monotherapy, even over extended periods of time.

refractoriness can affect the rate and duration of response to venetoclax, data indicate venetoclax is efficacious even after BCRi failure.[3,13–15] The efficacy and safety of fixed-duration venetoclax combinations has been established in relapsed or refractory and previously untreated chronic lymphocytic leukaemia,[16–18] but long-term data on single-agent venetoclax treatment in relapsed or refractory chronic lymphocytic leukaemia, including BCRi relapsed or refractory chronic lymphocytic leukaemia, are sparse.

To our knowledge, VENICE-1 is the largest multicentre phase 3b trial designed to assess venetoclax monotherapy activity and safety in BCRi-naive and BCRi-pretreated patients with relapsed or refractory chronic lymphocytic leukaemia, irrespective of 17p deletion or *TP53* mutation status. Here, we report the VENICE-1 primary activity analyses and minimal residual disease responses.

Methods

Study design and participants

This open-label, single-arm, phase 3b study was conducted at 59 sites across 21 countries in Europe and North America (appendix pp 6, 25).

In countries where venetoclax was not commercially available, patients who continued to derive benefit after 2 years' treatment were able to extend treatment for up to 3 additional years in the extension phase of the trial. Patients were followed up for disease progression and survival for 2 years after venetoclax discontinuation.

Eligible participants were aged 18 years or older with previously treated relapsed or refractory chronic lymphocytic leukaemia (progression on previous treatment determined by investigator medical assessment), had a creatinine clearance rate of 50 mL per min or higher, and required treatment according to the 2008 modified International Workshop on Chronic Lymphocytic Leukaemia criteria. Presence of del(17p) or *TP53* aberrations and previous BCRi treatment were permitted. Patients who had developed Richter transformation or prolymphocytic leukaemia, and those who had received venetoclax previously, were not eligible. Before initiation of venetoclax, patients could not have received antineoplastic biological agents for 30 days or less; any anticancer therapy (except BCRi) or radiotherapy within five half-lives or 14 days; steroids

See Online for appendix

or strong or moderate cytochrome P450 3A (CYP3A) inducers for 7 days or less; or strong or moderate CYP3A inhibitors or BCRi for 3 days or less. Full inclusion and exclusion criteria are listed in the appendix (pp 2–3). Disease response was assessed at screening, and at weeks 24, 36, and 48. Assessment was conducted by the study investigator according to the 2008 modified International Workshop on Chronic Lymphocytic Leukaemia criteria. Laboratory tests were conducted at screening to assess eligibility and included a full blood chemistry and haematology panel.

The review boards of participating institutions approved the study protocol, which was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice. All patients provided written informed consent.

Procedures

The starting dose for venetoclax (AbbVie, North Chicago, IL, USA) was 20 mg orally once daily (tablet form), and the dose was increased weekly to 50 mg, 100 mg, and 200 mg, up to the target of 400 mg once daily, which was the dose administered for up to 108 weeks, unless earlier discontinuation or reduction occurred due to unacceptable toxicity, disease progression, or intolerability. Dose interruptions or dose reductions were applied for haematological and other toxicities related to venetoclax (appendix p 5). CT imaging was performed on all patients at screening and also at week 48, alongside bone marrow biopsy and aspirate to confirm response in patients with complete remission or complete remission with incomplete marrow recovery. Self-reported patient sex, race, and ethnicity were provided by the individual investigators.

Blood chemistry and haematology tests were also performed at 6–8 h and 24 h after the first dose increase in patients with low to high risk of tumour lysis syndrome.

Each patient could withdraw from the study at any time. Investigators could also discontinue a patient from

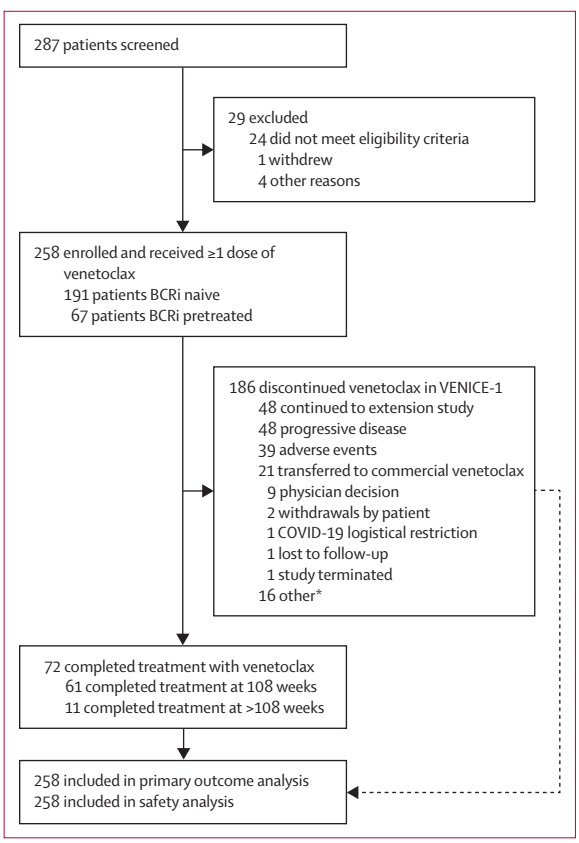


Figure 1: **Study profile**
*Other includes receiving a medication or therapy not allowed by the protocol, receiving compassionate use venetoclax, death, stem-cell transplantation, thrombocytopenia, and withdrawal of consent.

	All patients (N=258)	BCRi-naive group (n=191)	BCRi-pretreated group (n=67)
Age			
Median age (IQR), years	68 (61–72)	68 (61–74)	69 (63–75)
≥65 years	164 (64%)	118 (62%)	46 (69%)
Sex			
Male	180 (70%)	136 (71%)	44 (66%)
Female	78 (30%)	55 (29%)	23 (34%)
Race			
White	252 (98%)	186 (97%)	66 (99%)
Black or African American	3 (1%)	3 (2%)	0
Asian	2 (1%)	1 (1%)	1 (1%)
Other	0	0	0
Missing	1 (<1%)	1 (1%)	0
Ethnicity			
Not Hispanic or Latino	248 (96%)	181 (95%)	67 (100%)
Hispanic or Latino	9 (3%)	9 (5%)	0
Missing	1 (<1%)	1 (1%)	0
Eastern Cooperative Oncology Group performance status			
0	142 (55%)	110 (58%)	32 (48%)
1	95 (37%)	67 (35%)	28 (42%)
2	21 (8%)	14 (7%)	7 (10%)
Previous lines of chronic lymphocytic leukaemia-directed treatments			
1	106 (41%)	101 (53%)	5 (7%)
2	64 (25%)	47 (25%)	17 (25%)
≥3	88 (34%)	43 (23%)	45 (67%)
Median (IQR) number of previous lines of anti-chronic lymphocytic leukaemia	2 (1–3)	1 (1–2)	3 (2–4)
Previous ibrutinib failure			
First line	3 (1%)	NA	3 (4%)
Second line and beyond	47 (18%)	NA	47 (70%)
Not reported	208 (81%)	191 (100%)	17 (25%)
Previous idelalisib failure			
First line	3 (1%)	NA	3 (4%)
Second line and beyond	24 (9%)	1 (1%)*	23 (34%)
Not reported	231 (90%)	190 (99%)	41 (61%)
Previous fludarabine treatment	157 (61%)	112 (59%)	45 (67%)

(Table 1 continues on next page)

	All patients (N=258)	BCRi-naive group (n=191)	BCRi-pretreated group (n=67)
(Continued from previous page)			
Mutation presence (centrally assessed)†			
IGHV mutational status			
Mutated	42 (16%)	30 (16%)	12 (18%)
Unmutated	111 (43%)	86 (45%)	25 (37%)
Missing or indeterminate	105 (41%)	75 (39%)	30 (45%)
17p deletion‡			
Present	35 (14%)	20 (11%)	15 (22%)
Absent	137 (53%)	107 (56%)	30 (45%)
Missing or indeterminate	86 (33%)	64 (33%)	22 (33%)
TP53 mutation			
Present	42 (16%)	28 (15%)	14 (21%)
Absent	131 (51%)	100 (52%)	31 (46%)
Missing or indeterminate	85 (33%)	63 (33%)	22 (33%)
Genomic complexity category			
High	35 (14%)	21 (11%)	14 (21%)
Low	36 (14%)	31 (16%)	5 (8%)
Non-complex	101 (39%)	75 (39%)	26 (39%)
Missing	86 (33%)	64 (34%)	22 (33%)
Absolute lymphocyte count, ×10⁹/L			
<25	122 (47%)	86 (45%)	36 (54%)
≥25–<100	92 (36%)	71 (37%)	21 (31%)
≥100	40 (16%)	32 (17%)	8 (12%)
Not reported§	4 (2%)	2 (1%)	2 (3%)
Largest lymph node diameter, cm			
<5	165 (64%)	121 (63%)	44 (66%)
5–<10	56 (22%)	43 (23%)	13 (19%)
≥10	31 (12%)	23 (12%)	8 (12%)
Not reported§	6 (2%)	4 (2%)	2 (3%)

Data are n (%) unless otherwise stated. BCRi=B-cell receptor pathway inhibitor. NA=not applicable. *Patient discontinued during ramp-up and before any post-baseline disease assessment. †Mutation data were not mandatory for inclusion into the study. ‡Determined by array comparative genomic hybridisation. §Values were not recorded ≤24 h before venetoclax initiation.

Table 1: **Demographic and disease characteristics**

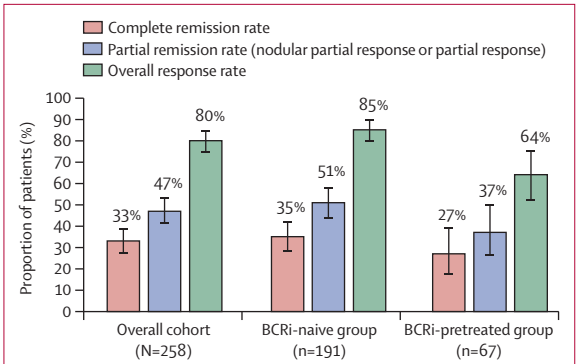


Figure 2: **Response rates for patients with relapsed or refractory chronic lymphocytic leukaemia treated with venetoclax monotherapy at week 48**
BCRi=B-cell receptor pathway inhibitor. Partial response needed to be confirmed later than 7 weeks or more for overall response.

study drug treatment at any time if the investigator considered it necessary for any reason. Such reasons included unsatisfactory response to therapy requirement for other cancer treatment during the study period, unacceptable toxicity, the patient became pregnant while on study, drug protocol non-compliance, and determination that it is in the patient's best interest.

Quality of life was assessed using the EuroQol 5 Dimensions 5 Levels Questionnaire (EQ-5D-5L), the Functional Assessment of Cancer Therapy–Leukemia (FACT-Leu) questionnaire, and the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) scale (appendix p 4).

Methods for minimal residual disease and molecular assessments are detailed in the appendix (pp 3–4). Array-based genomic complexity status was defined by numbers of copy number aberrations: non-complex (0–2), low (3–4), or high (≥5), as has been previously defined.[17]

Adverse events were monitored and recorded throughout the study. Recommended dose modifications are in the appendix (p 5). Safety analyses were performed on patients who received at least one dose of venetoclax. Safety evaluations included drug exposure, adverse events, serious adverse events, deaths, and laboratory parameters. Adverse event analyses only included treatment-emergent adverse events with onset on or after first dose and 30 days less after the last dose. Adverse event severity was rated according to NCI Common Terminology Criteria for Adverse Event (v4.03).

Outcomes

The primary efficacy endpoint was complete remission rate (defined as the proportion of patients who had a complete remission or complete remission with incomplete marrow recovery as their best response [per investigator assessment] based on the 2008 modified International Workshop on Chronic Lymphocytic Leukaemia criteria) in BCRi-naive patients.

Secondary efficacy endpoints were complete remission or complete remission with incomplete marrow recovery in BCRi-pretreated patients, progression-free survival (days from first dose to earliest disease progression or death), overall response rate (complete remission, complete remission with incomplete marrow recovery, nodular partial remission, or partial remission rates), duration of response (days from first response to earliest recurrence or progressive disease), time to progression (days from first dose to earliest disease progression), and overall survival (days from first dose to death). Exploratory efficacy endpoints were assessment of minimal residual disease and rate of minimal residual disease negativity (defined as the proportion of patients with <1 chronic lymphocytic leukaemia cell per 10 000 leukocytes [$<10^{-4}$] in peripheral blood and bone marrow). Patient-reported quality of life, assessed through the FACT-Leu, FACIT-F, and EQ-5D-5L

instruments, was an additional efficacy endpoint; scores for all quality of life assessments were calculated according to their respective scoring manuals.

Statistical analysis

At protocol initiation, a sample size of 250 patients was calculated to provide approximately 90% power (based on an exact test for single proportions using a two-sided alpha of 5%) to reject the null hypothesis of 6% in favour of an alternative hypothesis that the complete remission rate for venetoclax monotherapy is 12% (doubling of the complete remission rate). Before readout, the primary hypothesis was revised and a sample size of 190 patients who had not previously received BCRi therapy was required to reject the null hypothesis of a complete remission or complete remission with incomplete marrow recovery rate of 6% or less at approximately 80% power on the basis of an exact test for single proportions using a two-sided alpha of 5%. As the study aimed to enrol approximately 250 patients, up to 60 patients with previous BCRi treatment could be included, allowing descriptive reporting of outcomes for this subgroup within the trial population.

Analyses were performed on the overall cohort and prespecified subgroups (BCRi-naive and BCRi-pretreated groups). Primary efficacy analysis was conducted once all patients had completed a week-48 disease assessment in the intention-to-treat population. All enrolled patients who received at least one dose of venetoclax were included; patients who had not had complete remission or complete remission with incomplete marrow recovery at week 48 were considered non-responders in the calculation of the complete remission rate. Complete remission or complete remission with incomplete marrow recovery rates and overall response rates were evaluated using point estimates and corresponding 95% CIs were calculated on the basis of binomial distribution.

All time-to-event endpoints were analysed for the whole study period using Kaplan–Meier methodology; patients who did not have an event (progressive disease or death, where appropriate) were censored at their last adequate disease assessment date (or last known alive date for overall survival). Descriptive statistics were calculated for baseline demographics and clinical characteristics, quality of life, and safety events.

Additional post-hoc efficacy analyses (univariate and multivariable) were conducted to assess prominent prognostic factors (*IGHV* status, *TP53* status, del[17p] status, or genomic complexity) on outcomes. These analyses were conducted in patients with available baseline molecular results (patients without a specimen or inconclusive results were excluded). Odds ratios (ORs), hazard ratios (HRs), and rate ratios (RRs) were calculated using univariate, multiple logistic, and Cox proportional hazards regressions.

Main data analysis was performed using SAS (v9.4) software; exploratory analyses were done using R (v4.3.1).

The study was registered with ClinicalTrials.gov, NCT02756611.

Role of the funding source

The funder of the study had a role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

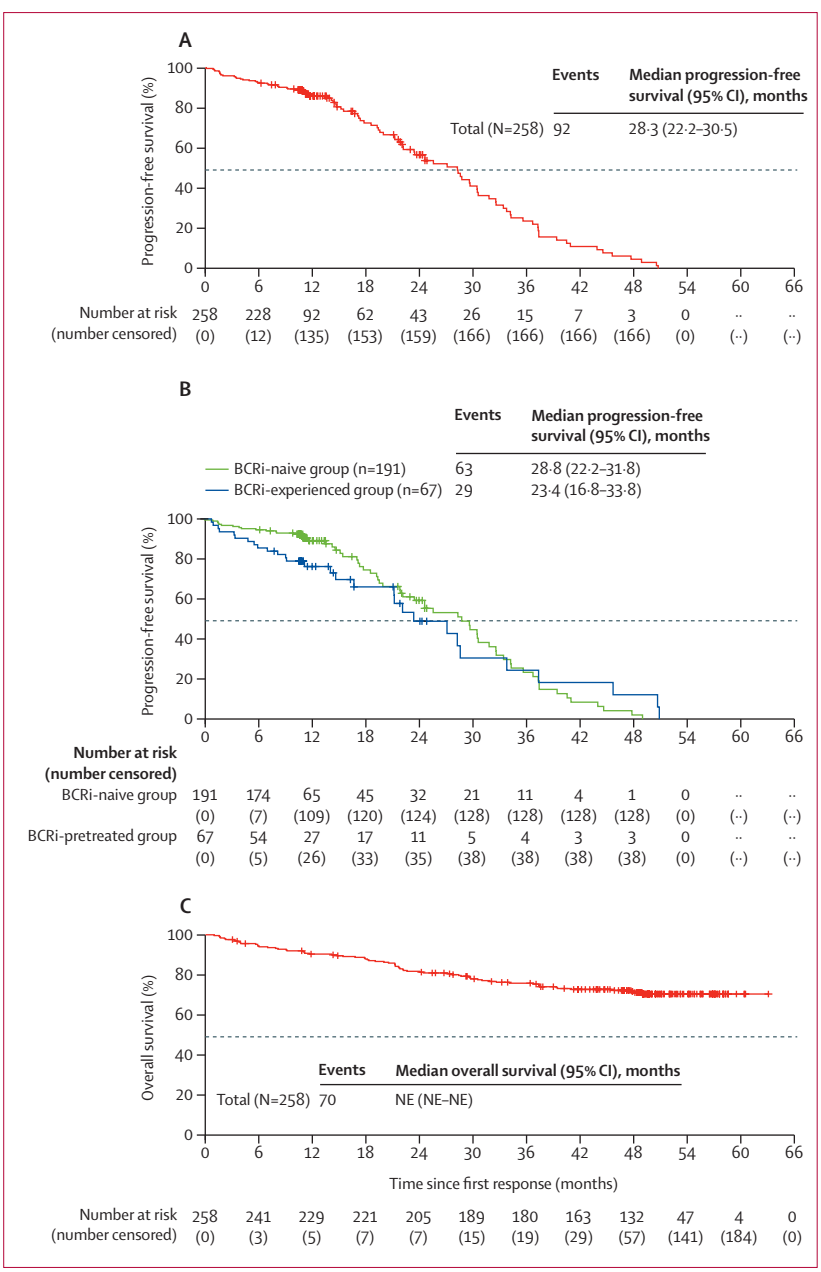
Between June 22, 2016, and March 11, 2022, 287 patients were screened and 258 patients with relapsed or refractory chronic lymphocytic leukaemia were enrolled; 191 were BCRi-naive and 67 were BCRi-pretreated (appendix pp 6, 8). The most common reasons for

	All patients (N=258)	BCRi-naive group (n=191)	BCRi-pretreated group (n=67)
Best response			
Complete remission	76 (29%)	59 (31%)	17 (25%)
Complete remission with incomplete marrow recovery	8 (3%)	7 (4%)	1 (1%)
Nodular partial remission	5 (2%)	5 (3%)	0
Partial remission	117 (45%)	92 (48%)	25 (37%)
Stable disease	17 (7%)	11 (6%)	6 (9%)
Progressive disease	9 (3%)	3 (2%)	6 (9%)
No post-baseline disease assessment	26 (10%)	14 (7%)	12 (18%)
Complete remission rate (complete remission or complete remission with incomplete marrow recovery), n (%; 95% CI)	84 (33%; 26·9–38·6)	66 (35%; 27·8–41·8)	18 (27%; 16·8–39·1)
Partial remission rate (nodular partial remission or partial remission), n (%; 95% CI)	122 (47%; 41·1–53·6)	97 (51%; 43·5–58·1)	25 (37%; 25·8–50·0)
Overall response rate (complete remission or complete remission with incomplete marrow recovery, nodular partial remission, or partial remission),* n (%; 95% CI)	206 (80%; 74·4–84·6)	163 (85%; 79·5–90·0)	43 (64%; 51·5–75·5)

Data are n (%) unless otherwise stated. BCRi=B-cell receptor inhibitor. *Partial remission was confirmed later than 7 weeks or more for objective response.

Table 2: **Summary of response rates at week 48 (intention-to-treat population)**

venetoclax discontinuation were enrolment into the extension study (48 [19%] of 258 patients; whereby patients were recorded as having discontinued venetoclax treatment in VENICE-1 so they could receive venetoclax in the subsequent study) and progressive disease (48 [19%] patients) and adverse events (39 [15%;]; figure 1). Median duration of treatment exposure was 108 weeks (IQR 73·7–190·0) in the overall cohort, 110 weeks (85·9–202·1) in the BCRi-naive group, and 107 weeks (24·3–119·6) in the BCRi-pretreated group. Median follow-up in the overall cohort was 49·5 months (IQR 47·2–54·1), 49·2 months (47·2–53·2) in the BCRi-naive group, and 49·7 months (47·4–54·3) in the BCRi-pretreated group.



(Figure 3 continues on next page)

Patients were predominantly male (180 [70%]) and White (252 [98%]) with a median age of 68 years (IQR 61–74; table 1). Median number of previous chronic lymphocytic leukaemia therapies was 2 (IQR 1–3) in the overall cohort, 1 (1–2) in the BCRi-naive group, and 3 (2–4) in the BCRi-pretreated group. Among 67 patients with previous BCRi treatment, 50 (75%) patients had received ibrutinib, 26 (39%) patients had received idelalisib, and two patients had received acalabrutinib; 11 patients had received both ibrutinib and idelalisib. 82 reasons were recorded for the discontinuation of the 78 BCRi treatments; 23 were progressive disease and 47 were toxicities. Median treatment duration of previous BCRi was 9·0 months (IQR 4·0–20·7; n=67). Centrally assessed *IGHV* mutation mutations were reported for 42 (27%) of 153 patients, del(17p) for 35 (20%) of 172 patients, and *TP53* mutations for 42 (24%) of 173 patients with mutation data in the overall cohort; 35 (20%) of 172 patients with data for genomic complexity had high genomic complexity (≥5 copy number aberrations). Concordance rates for centrally assessed and locally assessed genomic characteristics are listed in the appendix (p 8).

In the overall cohort, complete remission or complete remission with incomplete marrow recovery rate at week 48 was 84 (33%) of 258 patients (95% CI 26·9–38·6; figure 2). The complete remission or complete remission with incomplete marrow recovery rate in BCRi-naive patients (primary endpoint) was 35% (66 of 191 patients; 95% CI 27·8–41·8), with an RR of 1·29 (95% CI 0·76–2·17). The complete remission or complete remission with incomplete marrow recovery rate was 27% (18 of 67 patients; 95% CI 16·8–39·1) in the BCRi-pretreated group. The complete remission or complete remission with incomplete marrow recovery rate was similar across subgroups based on sex, race, age group, Eastern Cooperative Oncology Group performance status, previous number of therapies, absolute lymphocyte count, and baseline node size (appendix p 26). Overall complete remission or complete remission with incomplete marrow recovery rate was 28% (11 of 39 patients) and 38% (35 of 93 patients) in patients with and without a *TP53* mutation, and 27% (12 of 44 patients) and 34% (59 of 172 patients) in patients with and without del(17p) per investigator-assessed mutation status. Complete remission or complete remission with incomplete marrow recovery rates were similar regardless of number of previous therapies in the overall population (one therapy, 34% [36 of 106 patients]; two therapies, 33% [21 of 64 patients]; and more than two therapies, 31% [27 of 88 patients]). The overall response rate was 80% (206 of 258 patients) overall, 85% (163 of 191 patients) in the BCRi-naive group, and 64% (43 of 67 patients) in the BCRi-pretreated group (table 2). Post-hoc analyses of the effect of prognostic factors—namely, *IGHV* and *TP53*

mutations, del17p, and genomic complexity status, as centrally assessed at study entry on clinical outcomes—are reported in the appendix (pp 9–10, 28–31).

The overall median duration of response for patients who had a response (n=205; one patient included in the overall response rate analysis was excluded from the duration of response analysis due to a data collection discrepancy that could not be resolved) was 25·1 months (95% CI 19·4–28·6). The median duration of response was 24·4 months (95% CI 18·1–27·9) in the BCRi-naive group (n=162) and 28·6 months (95% CI 16·8–45·3) in the BCRi-pretreated population (n=43; appendix p 32). The overall time to progression (n=258) was 28·3 months (95% CI 23·4–32·6; appendix p 32). Median time to progression was 24·6 months (95% CI 21·9–30·6) for the BCRi-naive group (n=191) and 33·8 months (95% CI 23·4–not estimable) for the BCRi-pretreated group (n=67).

In the overall cohort (n=258), 92 (36%) patients had progression-free survival events, with a median progression-free survival of 28·3 months (95% CI 22·2–30·5; figure 3A). In the BCRi-naive group 63 (33%) of 191 had progression-free survival events and in the BCRi-pretreated group 29 (43%) of 67 had progression-free survival events, and median progression-free survival was 28·8 months (95% CI 22·2–31·8) and 23·4 months (95% CI 16·8–33·8), respectively (figure 3B). In the overall cohort 70 (27%) of 258 died, 45 (24%) of 191 BCRi-naive died and 25 (37%) of 67 patients died in the BCRi-experienced group, and; median overall survival was not reached in the overall, BCRi-naive or BCRi-experienced populations (figure 3C and D). Five-year survival estimates were 71% (95% CI 65·0–76·5), 75% (95% CI 67·5–80·6), and 61% (95% CI 47·7–71·6) for the overall, BCRi-naive, and BCRi-experienced patients, respectively.

For the overall cohort, patients showed a mean improvement of 8·5 points (SD 14·4; 95% CI 6·5–10·5; n=204) in the EQ-5D-5L visual analogue score (VAS); this improvement decreased to 7·1 points (14·6; 4·8–9·4; n=156) by week 108. In the BCRi-naive group and BCRi-pretreated group, mean improvements in EQ-5D-5L VAS scores were 8·6 (14·5; n=164) and 8·0 (14·2; n=43), respectively, at week 48, and 7·3 (14·4; n=124) and 6·1 (15·8; n=32), respectively, at week 108. FACT-Leu subscale scores also improved at week 48 in the overall cohort, BCRi-naive group, and BCRi-pretreated group (mean scores of 6·8 [SD 8·0], n=202; 6·5 [8·2], n=161; and 7·8 [7·2], n=41, respectively) and at week 108 (6·0 [9·1], n=153; 6·2 [8·8], n=122; and 5·2 [10·3], n=31, respectively); similarly, the FACT-Leu trial outcome index showed improvements at week 48 in overall (9·8 [14·2]; n=201), BCRi-naive (9·0 [14·5]; n=160), and BCRi-experienced (13·0 [12·7]; n=201) populations, and changes were maintained at week 108. FACT-Leu general total score improvements were seen at week 48 in the overall cohort (5·5 [12·3], n=200) and in the BCRi-naive group and BCRi-pretreated group (4·8 [12·2; n=160] and 8·0 [12·7; n=40], respectively) and all were maintained at week 108. At week 48, patients had a mean improvement of 4·9 points (SD 9·4; 95% CI 3·6–6·2; n=205) from baseline in the FACIT-F score, which decreased by week 108 to 3·3 points (10·0; 95% CI 1·7–4·8; n=154).

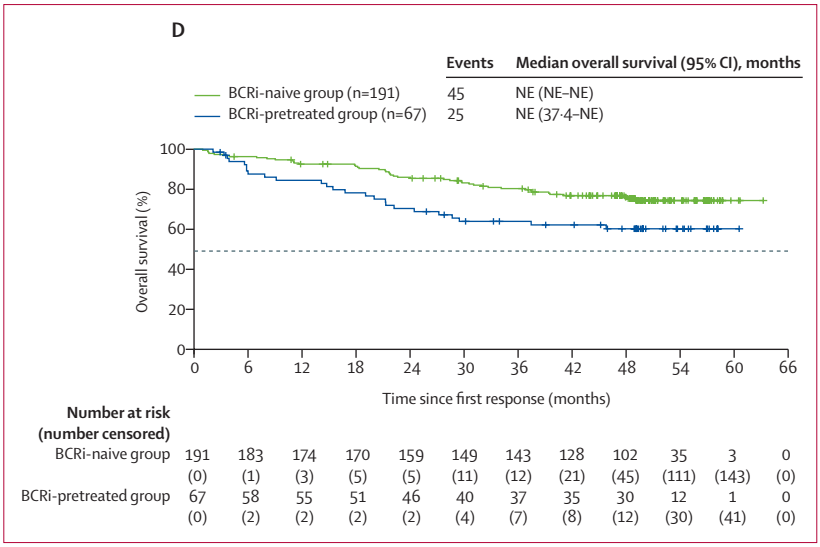


Figure 3: **Progression-free survival for the overall population (A) and by previous BCRi exposure (B), and overall survival for the overall population (C) and by previous BCRi exposure (D)**
BCRi=B-cell receptor pathway inhibitor. NE=not estimable.

198 patients had at least one on-therapy peripheral blood minimal residual disease assessment, with 60 patients missing at least one assessment. 104 of 258 patients (40% of intent-to-treat population, 53% of patients with minimal residual disease assessments) and 99 of 206 responders (48% of intent-to-treat population, 50% of patients with minimal residual disease assessments) had undetectable minimal residual disease by peripheral blood assessment. Of the 84 patients with complete remission or complete remission with incomplete marrow recovery and known minimal residual disease, 46 (55%) had undetectable minimal residual disease by peripheral blood assessment. 76 patients had a bone marrow minimal residual disease assessment, including 51 of 84 patients with complete remission or complete remission with incomplete marrow recovery. Among the 84 patients who had a complete remission or complete remission with incomplete marrow recovery, 23 (27%) were determined to be undetectable minimal residual disease by bone marrow; rates of undetectable minimal residual disease were similar for the BCRi-naive group (26%; n=17) and BCRi-pretreated group (33%; n=6).

A listing of all adverse events of any grade are detailed in the appendix (p 12; grade 3–5 and grade 1 and 2 ≥10%) and in table 3. Of 258 patients, 254 (98%) had a treatment-emergent adverse event of any grade; most frequently reported were neutropenia (112 [43%]), diarrhoea (100 [39%]), and nausea (69 [27%]). Grade 3 or worse

	Grade 1 or 2			Grade 3			Grade 4			Grade 5		
	All patients (N=258)	BCRi-naive group (n=191)	BCRi-pretreated group (n=67)	All patients (N=258)	BCRi-naive group (n=191)	BCRi-pretreated group (n=67)	All patients (N=258)	BCRi-naive group (n=191)	BCRi-pretreated group (n=67)	All patients (N=258)	BCRi-naive group (n=191)	BCRi-pretreated group (n=67)
Any adverse event	245 (95%)	178 (93%)	67 (100%)	105 (41%)	89 (47%)	16 (24%)	85 (33%)	49 (26%)	36 (54%)	13 (5%)	11 (6%)	2 (3%)
Blood and lymphatic system disorders	72 (28%)	54 (28%)	18 (27%)	71 (28%)	62 (32%)	9 (13%)	55 (21%)	33 (17%)	22 (33%)	1 (<1%)	1 (1%)	0
Anaemia	28 (11%)	19 (10%)	9 (13%)	32 (12%)	21 (11%)	11 (16%)	2 (1%)	2 (1%)	0	0	0	0
Febrile neutropenia	1 (<1%)	1 (1%)	0	11 (4%)	4 (2%)	7 (10%)	6 (2%)	3 (2%)	3 (4%)	0	0	0
Neutropenia	16 (6%)	12 (6%)	4 (6%)	57 (22%)	49 (26%)	8 (12%)	39 (15%)	22 (12%)	17 (25%)	0	0	0
Thrombocytopenia	23 (9%)	18 (9%)	5 (7%)	14 (5%)	13 (7%)	1 (1%)	19 (7%)	11 (6%)	8 (12%)	0	0	0
Cardiac disorders	16 (6%)	7 (4%)	9 (13%)	9 (3%)	6 (3%)	3 (4%)	2 (1%)	2 (1%)	0	3 (1%)	3 (2%)	0
Eye disorders	28 (11%)	22 (12%)	6 (9%)	3 (1%)	3 (2%)	0	1 (<1%)	0	1 (1%)	0	0	0
Gastrointestinal disorders	158 (61%)	112 (59%)	46 (69%)	22 (9%)	17 (9%)	5 (7%)	1 (<1%)	0	1 (1%)	0	0	0
Abdominal pain	21 (8%)	12 (6%)	9 (13%)	3 (1%)	2 (1%)	1 (1%)	0	0	0	0	0	0
Constipation	33 (13%)	18 (9%)	15 (22%)	1 (<1%)	1 (1%)	0	0	0	0	0	0	0
Diarrhoea	91 (35%)	67 (35%)	24 (36%)	9 (3%)	7 (4%)	2 (3%)	0	0	0	0	0	0
Nausea	67 (26%)	46 (24%)	21 (31%)	2 (1%)	1 (1%)	1 (1%)	0	0	0	0	0	0
General disorders and administration site conditions	118 (46%)	80 (42%)	38 (57%)	14 (5%)	7 (4%)	7 (10%)	1 (<1%)	0	1 (1%)	2 (1%)	2 (1%)	0
Asthenia	31 (12%)	20 (11%)	11 (16%)	1 (<1%)	0	1 (1%)	0	0	0	0	0	0
Fatigue	40 (16%)	24 (13%)	16 (24%)	6 (2%)	3 (2%)	3 (4%)	0	0	0	0	0	0
Pyrexia	49 (19%)	33 (17%)	16 (24%)	4 (2%)	3 (2%)	1 (1%)	1 (<1%)	0	1 (1%)	0	0	0
Infections and infestations	163 (63%)	120 (63%)	43 (64%)	45 (17%)	29 (15%)	16 (24%)	6 (2%)	6 (3%)	0	2 (1%)	2 (1%)	0
Nasopharyngitis	38 (15%)	30 (16%)	8 (12%)	1 (<1%)	0	1 (1%)	0	0	0	0	0	0
Pneumonia	17 (7%)	15 (8%)	2 (3%)	18 (7%)	10 (5%)	8 (12%)	2 (1%)	2 (1%)	0	0	0	0
Upper respiratory tract infection	47 (18%)	36 (19%)	11 (16%)	2 (1%)	1 (1%)	1 (1%)	0	0	0	0	0	0
Injury, poisoning, and procedural complications	58 (23%)	39 (20%)	19 (28%)	6 (2%)	3 (2%)	3 (4%)	0	0	0	0	0	0
Investigations	97 (38%)	71 (37%)	26 (39%)	28 (11%)	16 (8%)	12 (18%)	21 (8%)	11 (6%)	10 (15%)	0	0	0
Weight decreased	23 (9%)	12 (6%)	11 (16%)	1 (<1%)	0	1 (1%)	0	0	0	0	0	0
Metabolism and nutrition disorders	101 (39%)	73 (38%)	28 (42%)	24 (9%)	16 (8%)	8 (12%)	7 (3%)	3 (2%)	4 (6%)	0	0	0
Decreased appetite	22 (9%)	12 (6%)	10 (15%)	2 (1%)	1 (1%)	1 (1%)	0	0	0	0	0	0
Musculoskeletal and connective tissue disorders	87 (34%)	62 (32%)	25 (37%)	9 (3%)	6 (3%)	3 (4%)	0	0	0	0	0	0
Arthralgia	37 (14%)	24 (13%)	13 (19%)	0	0	0	0	0	0	0	0	0
Back pain	33 (13%)	20 (10%)	13 (19%)	2 (1%)	2 (1%)	0	0	0	0	0	0	0
Benign, malignant, and unspecified neoplasms (including cysts and polyps)	38 (15%)	28 (15%)	10 (15%)	16 (6%)	14 (7%)	2 (3%)	7 (3%)	4 (2%)	3 (4%)	1 (<1%)	0	1 (1%)

(Table 3 continues on next page)

	Grade 1 or 2			Grade 3			Grade 4			Grade 5		
	All patients (N=258)	BCRi-naive group (n=191)	BCRi-pretreated group (n=67)	All patients (N=258)	BCRi-naive group (n=191)	BCRi-pretreated group (n=67)	All patients (N=258)	BCRi-naive group (n=191)	BCRi-pretreated group (n=67)	All patients (N=258)	BCRi-naive group (n=191)	BCRi-pretreated group (n=67)
(Continued from previous page)												
Nervous system disorders	63 (24%)	41 (21%)	22 (33%)	9 (3%)	7 (4%)	2 (3%)	3 (1%)	1 (1%)	2 (3%)	2 (1%)	1 (1%)	1 (1%)
Headache	25 (10%)	15 (8%)	10 (15%)	2 (1%)	0	2 (3%)	0	0	0	0	0	0
Psychiatric disorders	34 (13%)	19 (10%)	15 (22%)	4 (2%)	1 (1%)	3 (4%)	0	0	0	0	0	0
Renal and urinary disorders	30 (12%)	22 (12%)	8 (12%)	2 (1%)	2 (1%)	0	0	0	0	0	0	0
Respiratory, thoracic, and mediastinal disorders	111 (43%)	78 (41%)	33 (49%)	20 (8%)	12 (6%)	8 (12%)	4 (2%)	2 (1%)	2 (3%)	2 (1%)	2 (1%)	0
Cough	51 (20%)	36 (19%)	15 (22%)	4 (2%)	2 (1%)	2 (3%)	0	0	0	0	0	0
Dyspnoea	20 (8%)	11 (6%)	9 (13%)	8 (3%)	6 (3%)	2 (3%)	0	0	0	0	0	0
Skin and subcutaneous tissue disorders	99 (38%)	69 (36%)	30 (45%)	7 (3%)	5 (3%)	2 (3%)	0	0	0	0	0	0
Vascular disorders	39 (15%)	30 (16%)	9 (13%)	17 (7%)	11 (6%)	6 (9%)	2 (1%)	2 (1%)	0	0	0	0

Adverse events for categories in which ≥10% of patients within a group had grade 1 or 2, grade 3, grade 4, or grade 5 adverse events.

Table 3: **Summary of treatment-emergent adverse events**

treatment-emergent adverse events were reported in 203 (79%) patients, most common being neutropenia (96 [37%]), anaemia (34 [13%]), and thrombocytopenia (33 [13%]); and serious treatment-emergent adverse events were reported in 136 (53%) patients, most commonly being pneumonia (21 [8%]) and febrile neutropenia (15 [6%]). For the overall cohort (n=248), there were 70 (27%) deaths during the study, of which 21 (8%) occurred within 30 days of the last dose of venetoclax, and 13 (5%) were attributable to adverse events (appendix p 11); 33 (13%) deaths were due to disease progression. Six symptomatic COVID-19 infections (2%), including two serious adverse events, were reported among BCRi-naive patients. No patients discontinued venetoclax or died due to COVID-19 infection.

Generally, patients in the BCRi-naive group had lower rates of treatment-emergent adverse events than patients in the BCRi-pretreated group, especially for grade 4 treatment-emergent adverse events (30% *vs* 57%), serious adverse events (50% *vs* 60%), and deaths (24% *vs* 37%). However, grade 5 treatment-emergent adverse events and adverse events leading to death were observed in 11 (6%) BCRi-naive patients versus two (3%) BCRi-pretreated patients. Both treatment groups had treatment-emergent adverse events leading to venetoclax dose interruption, reduction, or discontinuation at similar rates. Full reasons for discontinuation are provided in the appendix (p 21).

At study entry, 214 (83%) of 258 patients were categorised as at high risk of tumour lysis syndrome and 252 (98%) of 258 patients received prophylaxis for tumour lysis syndrome, including hydration (252 [98%]), allopurinol (231 [90%]), and rasburicase (71 [28%]). 118 (46%) of 258 patients were admitted to hospital during ramp-up to receive tumour lysis syndrome prophylaxis; 87 (46%) of 191 patients in the BCRi-naive group and 31 (46%) of 67 patients in the BCRi-experienced group. No patients had clinical tumour lysis syndrome, or grade 4 or 5 adverse events of tumour lysis syndrome. 13 (5%) of 258 patients met Howard criteria for laboratory tumour lysis syndrome, of which treatment-emergent adverse events of tumour lysis syndrome were reported for six (2%) patients (two patients with grade 1 events and four with grade 3 events). Two patients had serious tumour lysis syndrome events, and venetoclax dose interruptions and reductions due to tumour lysis syndrome occurred in three and one patients, respectively; no patients discontinued due to tumour lysis syndrome.

145 (56%) of 258 patients had neutropenia-related adverse events of special interest. Granulocyte colony-stimulating factor was administered to 119 (46%) patients for blood count recovery. BCRi-naive patients had lower rates of febrile neutropenia than BCRi-pretreated patients (eight [4%] of 191 patients *vs* ten [15%] of 67 patients, respectively). Neutropenia adverse events

were most commonly managed using dose interruptions (36 [14%] of 258 patients) and reductions (ten [4%] of 258 patients). One patient discontinued venetoclax due to neutropenia. 50 (19%) of 258 patients had serious infections, including opportunistic infections, and of these, 43 (17%) patients had grade 3 or worse infections (grade 4, n=6; grade 5, n=2). The most common serious infections were pneumonia (21 [8%]), lower respiratory tract infection (four [2%]), and influenza (three [1%]). 50 (19%) of 258 patients developed neoplasms (benign, malignant, or unspecified); 39 (20%) of 191 patients in the BCRi-naive group and 11 (16%) of 67 patients in the BCRi-experienced group. A full listing of subsequent anticancer treatments is provided in the appendix (p 22).

Discussion

This study demonstrated a complete remission or complete remission with incomplete marrow recovery rate of 35% in BCRi-naive patients with relapsed or refractory chronic lymphocytic leukaemia. 26% of the study population were BCRi-pretreated patients. The complete remission or complete remission with incomplete marrow recovery rate of 27% and overall response rate of 64% suggest encouraging efficacy of venetoclax monotherapy in this BCRi-pretreated population. Venetoclax monotherapy was previously investigated in phase 2 trials with relapsed or refractory BCRi-pretreated chronic lymphocytic leukaemia; complete remission or complete remission with incomplete marrow recovery rates were lower than in the current study, although overall response rates and median progression-free survival were not notably different.[3,13] The results of this study are consistent with a real-world retrospective analysis of heavily pretreated patients with relapsed or refractory BCRi-pretreated chronic lymphocytic leukaemia receiving venetoclax monotherapy, where 85% responded and 23% had complete remission or complete remission with incomplete marrow recovery.[19]

Previous exposure to BCRis and number of previous therapies have been associated with reduced response rates in previous clinical trials and real-world studies[14,15,19] and suggest that early use of venetoclax should be the preferred choice; however, the current overall response rate was 64% in the BCRi-pretreated group, suggesting that patients still benefit after BCRi discontinuation.

Post-hoc progression-free survival analyses were performed to stratify patients' risk using *IGHV* status, del(17p) status, and genomic complexity.[20,21] Interestingly, patients with mutated *IGHV* had longer progression-free survival than those with unmutated *IGHV*. Unlike BCRi-naive patients, in BCRi-pretreated patients, *IGHV* status, *TP53* status, and genomic complexity was not associated with differential outcomes. Patients also had undetectable minimal residual disease activity less frequently with mutated *IGHV* versus unmutated *IGHV*; these findings contrast with previously published studies of venetoclax in relapsed or refractory chronic lymphocytic leukaemia[22] and should be evaluated in larger cohorts and cautiously interpreted. In the BCRi-naive group, there appeared to be differences in each stratified analysis, an observation that does not hold true for BCRi-pretreated patients. However, fewer lines of therapy and fewer negative prognostic factors present in the BCRi-naive group might have contributed to this result. These findings warrant additional analysis and will be explored in future publications.

The safety profile reported here was consistent with previously published venetoclax data in relapsed or refractory chronic lymphocytic leukaemia.[3,4,10,13] No clinical tumour lysis syndrome adverse events were observed, and no patients discontinued venetoclax due to tumour lysis syndrome. Although common, neutropenia was managed with brief interruptions or reductions in venetoclax dosing.

Limitations of this study include the single-arm study design without a comparator, and low statistical power for subgroup analyses.

This phase 3b trial VENICE-1 indicates venetoclax monotherapy can have deep and durable responses in patients with relapsed or refractory chronic lymphocytic leukaemia, including BCRi-pretreated patients; high rates of complete remission or complete remission with incomplete marrow recovery were observed over long-term follow-up, with no new safety signals identified. To our knowledge, this is the largest study of venetoclax monotherapy to be carried out in this setting and is consistent with the data previously reported, supporting early use of venetoclax within chronic lymphocytic leukaemia.

Contributors

Study concept and Design: APK, BJC, VK, GEP, FF. Clinical data collection: APK, ÖA, FD, YH, BF, MGD, BL, MM, PP, DR, AS, AT, MT, and FF. Exploratory data and patient-reported outcome data collection, and statistical analyses: CHM, A-MvdK-K, SL, BS, LDR, RP, BJC, TB, XW, KS, and TV. All authors participated in the analysis and interpretation of results, and manuscript preparation. At least two authors (BJC, TB, and TV) have accessed and verified the raw data. All authors had access to relevant data and participated in the drafting, review, and approval of this manuscript. No honoraria or payments were made for authorship. Venetoclax is being developed in a collaboration between AbbVie and Genentech.

Declaration of interests

APK is an advisory board member of and received research funding from Astra Zeneca, Janssen, Roche (Genentech), AbbVie, Bristol Myers Squibb, and LAVA. ÖA is an AbbVie speaker and advisory board member. YH declares honoraria from AbbVie, Janssen, AstraZeneca, Roche, and Medison; is an advisory board member for AbbVie, Jansen, AstraZeneca, Medison, and Eli Lilly; and declares a research grant from Janssen. BF is an advisory board member for Takeda Pharmaceuticals, Janssen, and Pfizer and declares speaker fees from AbbVie. MGD declares speaker fees from AbbVie. BL declares speakers bureau or honoraria from AbbVie, Alexion, AMGEN, Astellas, Astex, Bristol Myers Squibb (Celgene), Jazz, Janssen Novartis, Otsuka, Paladin, Pfizer, Roche, and Treadwell, and consulting fees from AbbVie, Novartis, and Pfizer. MM declares speaker bureau from AbbVie and honoraria from Janssen. PP declares a research support grant from AbbVie and honoraria or speaker's bureau from AbbVie, AstraZeneca, and Roche. AS declares consultancy or speaker fees from Alexion, AbbVie,

AstraZeneca, ADC Therapeutics, Beigene, Bristol Myers Squibb, Celgene, Epizyme, Genentech, Janssen, Jazz Therapeutics, Kite Pharma, Eli Lilly, MorphoSys, Novartis, Pharmacyclics, SeaGen, GenMab, and TG Therapeutics; payments for presentations or lectures from AstraZeneca, ADC Therapeutics, AbbVie, Beigene, Genentech, GenMab, Jazz Therapeutics, Janssen, Kite Pharma, Eli Lilly, Pharmacyclics, SeaGen, and TG Therapeutics; and participation on the data safety monitoring board for Alexion. CM declares funding from AbbVie for microarray analysis. A-MvdK-K declares funding from AbbVie for funded microarray analysis. RP, BJC, XW, TB, KS, GEP, and TV are AbbVie employees and may hold stock or options. VK was an AbbVie employee at time of study and may hold stock or options. Francesco Forconi is an advisory board member for BeiGene; declares honoraria from AbbVie, Janssen-Cilag, Beigene, and AstraZeneca; speakers bureau from AbbVie, Janssen-Cilag, and AstraZeneca; and travel and accommodation from AbbVie, Janssen-Cilag, and Beigene. FD, DR, AT, MT, SL, BS, and LDR declare no competing interests.

Data sharing

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymised, individual, and trial-level data (analysis datasets), as well as other information (eg protocols, clinical study reports, or analysis plans), 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. These 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, statistical analysis plan, and execution of a data sharing agreement. Data requests can be submitted at any time after approval in the US and Europe and after acceptance of this manuscript for publication. 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://vivli.org/ourmember/abbvie/ then select 'Home'.

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