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A multicenter study of venetoclax-based treatment for patients with Richter transformation of chronic lymphocytic leukemia.

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Abstract:
Patients with chronic lymphocytic leukemia (CLL) who develop Richter transformation (RT) have a poor prognosis when treated with chemoimmunotherapy regimens used for de novo diffuse large B-cell lymphoma. Venetoclax, a BCL2 inhibitor, has single agent efficacy in patients with RT and is potentially synergistic with chemoimmunotherapy. In this multicenter, retrospective study, we evaluated 62 patients with RT who received venetoclax-based treatment outside of a clinical trial, in combination with a Bruton tyrosine kinase inhibitor (BTKi; n=28), R-CHOP (n=13), or intensive chemoimmunotherapy other than R-CHOP (n=21). The best overall and complete response rates were 36%/25%, 54%/46%, and 52%/38%, respectively. The median progression-free and overall survival estimates for the same treatment groups were 4.9/14.3 months, 14.9 months/not reached, and 3.3/9 months, respectively. CLL with del(17p) was associated with a lower complete response rate in the total cohort (odds ratio [OR] 0.15; 95% confidence interval [CI] 0.04-0.6; p=0.01) and venetoclax-naïve subgroup (OR 0.13; 95%CI 0.02-0.66; p=0.01). TP53 mutated CLL was associated with a lower complete response rate (OR 0.15; 95%CI 0.03-0.74; p=0.02) and shorter progression-free survival (hazard ratio 3.1; 95%CI 1.21-7.95; p=0.02) only in venetoclax-naïve subgroup. No other clinical or baseline characteristics, including prior venetoclax treatment for CLL, showed statistically significant association with outcomes. Grade 3-4 neutropenia and thrombocytopenia events were most frequent with intensive chemoimmunotherapy + venetoclax; grade 3-4 infection rates were similar across treatment groups. In this difficult-to-treat RT patient population, venetoclax-based combination regimens achieved high response rates, with durable remission and survival observed in a subset of patients.

Conflict of interest: COI declared - see note

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A multicenter study of venetoclax-based treatment for patients with Richter transformation of chronic lymphocytic leukemia

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KEY POINT 1: In this retrospective study, venetoclax-based combination regimens led to higher complete remission rates (25 - 38%) than historical studies

KEY POINT 2: The pretreatment characteristic of CLL with del(17p) was associated with a lower CR rate to venetoclax-based treatments for RT.

ABSTRACT:

Patients with chronic lymphocytic leukemia (CLL) who develop Richter transformation (RT) have a poor prognosis when treated with chemoimmunotherapy regimens used for *de novo* diffuse large B-cell lymphoma. Venetoclax, a BCL2 inhibitor, has single agent efficacy in patients with RT and is potentially synergistic with chemoimmunotherapy. In this multicenter, retrospective study, we evaluated 62 patients with RT who received venetoclax-based treatment outside of a clinical trial, in combination with a Bruton tyrosine kinase inhibitor (BTKi; n=28), R-CHOP (n=13), or intensive chemoimmunotherapy other than R-CHOP (n=21). The best overall and complete response rates were 36%/25%, 54%/46%, and 52%/38%, respectively. The median progression-free and overall survival estimates for the same treatment groups were 4.9/14.3 months, 14.9 months/not reached, and 3.3/9 months, respectively. CLL with del(17p) was associated with a lower complete response rate in the total cohort (odds ratio [OR] 0.15; 95% confidence interval [CI] 0.04-0.6; p=0.01) and venetoclax-naïve subgroup (OR 0.13; 95%CI 0.02-0.66; p=0.01). *TP53* mutated CLL was associated with a lower complete response rate (OR 0.15; 95%CI 0.03-0.74; p=0.02) and shorter progression-free survival (hazard ratio 3.1; 95%CI 1.21-7.95; p=0.02) only in venetoclax-naïve subgroup. No other clinical or baseline characteristics, including prior venetoclax treatment for CLL, showed statistically significant

association with outcomes. Grade 3-4 neutropenia and thrombocytopenia events were most frequent with intensive chemoimmunotherapy + venetoclax; grade 3-4 infection rates were similar across treatment groups. In this difficult-to-treat RT patient population, venetoclax-based combination regimens achieved high response rates, with durable remission and survival observed in a subset of patients.

INTRODUCTION

Richter transformation (RT) is the histologic transformation of chronic lymphocytic leukemia (CLL) into an aggressive lymphoma. Diffuse large B-cell lymphoma (DLBCL) is the most common presentation (90% of cases) with an incidence of 0.5-1% per year.[1] Unlike *de novo* DLBCL, this diagnosis carries a poor prognosis, with anthracycline-based chemotherapy regimens delivering a median overall survival (OS) <12 months and few long term survivors.[2,3] Novel treatment approaches are needed. Venetoclax, an oral BCL2 inhibitor and key agent in the current CLL treatment paradigm, demonstrated single-agent activity in a small cohort (n=7) of patients with RT with 43% overall response rate (ORR).[4] Venetoclax combined with DA-EPOCH-R (dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab) achieved a median OS of 19.6 months.[5] The accompanying complete response (CR) rate of 50% is the highest reported in patients with RT and suggests an at least additive, if not synergistic, effect when considering the CR rates of 20% and 0% with EPOCH-R and venetoclax monotherapy, respectively.[2,4] The efficacy and tolerability of other venetoclax containing combinations in the treatment of RT is unknown. In this study, we evaluated the outcomes of patients with RT treated with venetoclax-based regimens, outside clinical trials, including novel-novel combinations and chemotherapy combinations.

METHODS

This study was approved by the Institutional Review Boards at each participating institution. We analyzed patients with RT treated with a venetoclax-based regimen at The University of Texas M.D. Anderson Cancer Center (n=34), Mayo Clinic (n=17), The Ohio State University (n=7), and Dana-Farber Cancer Institute (n=4) between 3/2012 and 3/2021. Patient and disease characteristics from the time of venetoclax-based treatment start were ascertained. CLL characteristics were captured at the time of start of any novel therapy for CLL or the latest time-period in case of patients with no prior treatment with novel agents. Chemotherapy regimens considered more intensive than standard R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) in this study included DA-EPOCH-R, R-Hyper-CVAD (rituximab, cyclophosphamide, vincristine, doxorubicin, dexamethasone), high-dose methotrexate and cytarabine, and OFAR (oxaliplatin, fludarabine, cytarabine, rituximab). Collectively these regimens are referred to as intensive chemoimmunotherapy + venetoclax in the rest of the manuscript. Most patients treated with intensive chemotherapy or R-CHOP, received venetoclax from cycle 2 with daily ramp up of venetoclax (20/50/100/200/400 mg daily) and continued 400mg daily for 10 days thereafter. There was heterogeneity in the venetoclax ramp up among patients treated with BTKi+ venetoclax +/- anti-CD-20 antibody, with most patients undergoing accelerated ramp up aiming to reach a 400 mg daily target dose within 2 weeks. Patients who were on venetoclax prior to RT did not have dose ramp up. Retrospective response assessment was as per Lugano 2014 guidelines.[6] Toxicity was graded per iwCLL 2018 guidelines (hematologic toxicity) or CTCAE v5.0 (non-hematologic toxicity).[7] OS was defined as the time from the start of treatment to death and progression-free survival (PFS) was defined as time between the start of treatment and disease progression or death. Survival outcomes were analyzed using the Kaplan-Meier method, with and without censoring for allogeneic hematopoietic stem cell transplantation (alloHSCT). Median follow-up was calculated

using the reverse Kaplan-Meier method.[8] No formal statistical comparisons were made between the different treatment groups given the non-randomized nature and potential selection biases in treatment allocation. Associations between dichotomized pre-treatment patient and disease characteristics and response rates were evaluated using the Chi-square method; associations between dichotomized pre-treatment characteristics and time-to-event outcomes were evaluated using the log rank test.

This study was approved by the Institutional Review Boards at each participating institution.

RESULTS

Sixty-two patients were identified with a median age of 67 years (range, 43-83 years). High-risk CLL disease characteristics were frequently identified: 52/59 (88%) patients with available data had unmutated *IGHV*; 31/59 (53%) had del(17p); 16/37 (43%) had *TP53* mutation, and 25/54 (46%) had complex karyotype (defined as ≥ 3 abnormalities on CpG-stimulated karyotype). Twelve patients with available data (12/14, 86%) had clonally related RT. Among all patients, the median number of prior CLL-directed therapies was 2 (range, 0-7), including prior chemoimmunotherapy (55%), prior Bruton tyrosine kinase inhibitor (BTKi, 68%), and prior venetoclax (24%). Of note, in the BTKi + venetoclax group, reason for prior BTKi discontinuation was progressive CLL in 9 patients, RT in 11 and adverse effects in 1 patient. In the overall cohort, 18% of patients had received no prior treatment for CLL and 56% of patients had received no prior RT treatment; 11% of patients were previously untreated for both CLL and RT. Venetoclax-based RT treatment subgroups consisted of BTKi + venetoclax +/- anti-CD20 antibody (n=28), R-CHOP + venetoclax (n=13); and intensive chemoimmunotherapy + venetoclax (n=21); baseline characteristics for each treatment group are shown in **Table 1**. Median follow-up from the start of venetoclax-based RT treatment was 34 months (95% CI, 27-50 months).

The best objective response rate (ORR) in all patients was 44% and CR rate was 34%. Based on the type of treatments received, the ORR/CR rates were 36%/25% with BTKi + venetoclax +/- anti-CD20 antibody, 54%/46% with R-CHOP + venetoclax, and 52%/38% with intensive chemoimmunotherapy + venetoclax. Among patients with available results, the undetectable measurable residual disease (U-MRD) rates for co-existing CLL (assessed by flow cytometry at some point during treatment, with a sensitivity of 0.01%, in blood or bone marrow) were 45% for BTKi + venetoclax +/- anti-CD20 antibody, 55% for R-CHOP + venetoclax, and 67% for intensive chemoimmunotherapy + venetoclax. Considering baseline clinical findings (e.g., bulky

adenopathy, lactate dehydrogenase elevation) and CLL molecular features (e.g., complex karyotype, *TP53* aberrations), only the presence of del(17p) in CLL was associated with a lower odds ratio (OR 0.15, 95% CI 0.04-0.60; p=0.010) of achieving a CR (**Table 2**). Only 2/15 (13%) CR were observed in patients who previously received venetoclax for CLL compared to 19/47 (40%) in venetoclax-naïve patients, although this was not statistically significant due to the small sample size (OR 0.40, 95% CI 0.10-1.63; p=0.33). Among venetoclax-naïve patients, CR rate was significantly lower in patients with del(17p) (OR 0.13, 95% CI 0.02-0.66; p=0.01) and *TP53* mutated CLL (OR 0.15, 95% CI 0.03-0.74; p=0.02, Supplemental Table S1). Interestingly, similar CR rates were seen amongst patients treated with BTKi + venetoclax +/- anti-CD20 antibody for RT regardless of prior BTKi exposure for CLL treatment (29% with no prior BTKi versus 24% with prior BTKi; OR 0.78, 95% CI 0.11-5.34, p=0.58). Of note, 14 patients (14/34) treated with chemotherapy-based regimen (R-CHOP or intensive chemotherapy) achieved a CR. Of them, 9 patients received venetoclax maintenance following the completion of chemotherapy. Five patients did not receive venetoclax maintenance due to disease progression (n=3) and subsequent alloHSCT (n=2). No formal comparison was performed between the two groups due to low patient numbers.

A total of 10 patients (16%) proceeded to alloHSCT after venetoclax-based treatments. Of these patients, best response to venetoclax-based treatment was CR (6/10), PR (n=1), PD (n=1), and missing response evaluation (n=2). The median time from commencing venetoclax to alloHSCT in patients who had CR or PR to venetoclax based treatments was 5 months (range, 4-19 months).

The median PFS for the total cohort was similar whether censored at alloHSCT or without censoring at alloHSCT (4.9 months, **Supplemental Figure S1**). The median PFS estimates according to therapy received (**Figure 1A**) were 5 months with BTKi + venetoclax + anti-CD20 antibody, 14.9 months with R-CHOP + venetoclax, and 3.3 months with intensive

chemoimmunotherapy + venetoclax. No significant differences were seen in median PFS estimates of individual treatment groups whether censoring was performed at alloHSCT or not (**Figure 1B**). We performed a landmark analysis (at 18-week from the start of chemotherapy-based regimen time point) in responders, which showed a numerically longer median PFS in patients who had subsequent alloHSCT (42.1 vs. 36.4 months, p=0.290, Supplemental Figure S2). Similarly, numerically shorter PFS estimates were seen with a number of clinical and baseline CLL characteristics, such as prior receipt of venetoclax, BTKi, del(17p), and *TP53* mutation; however, these differences were not statistically significant (**Table 2**). Among venetoclax-naïve patients, presence of *TP53* mutation in CLL cells was associated with significantly shorter median PFS (HR 3.1, 95% CI 1.21-7.95; p=0.02, Supplemental Table S1 and Figure S3). The median OS for the total cohort was 13.5 months (**Supplementary Figure S1**). The estimated median OS according to therapy received (**Figure 2**) was 14.3 months with BTKi + venetoclax +/- anti-CD20 antibody, not reached with R-CHOP + venetoclax, and 9 months with intensive chemoimmunotherapy + venetoclax. At last follow-up, 26 patients (42%) remained alive. Among the 36 patients who died, the most common cause of death was disease progression (n=26). Five patients died from infection/sepsis: 3 in the BTKi + venetoclax +/- anti-CD20 antibody group and 2 in the intensive chemoimmunotherapy + venetoclax group. Among the 5 patients with an infectious cause of death, 2 were receiving the venetoclax-based treatment (both BTKi + venetoclax +/- anti-CD20 antibody) at time of the infection: 1 patient died in CR and 1 patient died before initial response assessment. One patient treated with R-CHOP + venetoclax died from a subdural hematoma. One patient who received intensive chemoimmunotherapy + venetoclax died from subsequent chimeric antigen receptor T-cell therapy associated immune effector cell-associated neurotoxicity syndrome. Three patients with no known evidence of disease progression died while on a subsequent line of therapy (1-on an unclear clinical trial, 1-polatuzumab + rituximab + venetoclax, 1-transitioned care to local

oncology) without a known cause of death (one each lost to follow up, transitioned care to local physician, and had sudden death, respectively).

Grade 3-4 neutropenia and thrombocytopenia were more common with intensive chemoimmunotherapy + venetoclax (89%; 95%, **Table 3**) and R-CHOP + venetoclax (78%; 56%) compared to BTKi + venetoclax +/- anti-CD20 antibody (46%; 39%). Febrile neutropenia was most frequently observed in patients receiving intensive chemoimmunotherapy + venetoclax (48%) and was similar between those treated with R-CHOP + venetoclax (23%) and BTKi + venetoclax +/- anti-CD20 antibody (29%). The rates of grade 3-4 infection were similar across these three treatment groups: 43%, 31%, and 36%, respectively. Patients receiving R-CHOP + venetoclax were more likely to be able to complete 6 cycles of combination therapy compared to those receiving intensive chemoimmunotherapy + venetoclax (OR 0.07, 95% CI 0.01-0.88; p=0.02, **Supplemental Table S2**). The total duration of venetoclax in patients responding in each combination subgroup is shown in **Supplemental Table S3**.

DISCUSSION

Low CR rates and short survival with standard DLBCL treatment regimens demand investigation of novel approaches and a separate treatment paradigm for RT.[9] This multicenter, retrospective study provides the largest assessment to date of the efficacy and tolerability of venetoclax-based treatment in patients with RT. Here, in a contemporary cohort with many novel agent-exposed patients, we observed CR in 1-out-of-4 patients treated without cytotoxic chemotherapy (BTKi + venetoclax +/- anti-CD20 antibody) and nearly half of patients receiving R-CHOP + venetoclax. The median PFS appeared poor overall, at less than 6 months; however, estimates ranged up to 15 months in the R-CHOP + venetoclax subgroup, and some long-term survivors, even without allogeneic stem cell transplant consolidation, were observed across all treatments. Although a subset of patients experienced durable remissions with these

venetoclax-based approaches, subsequent alloHSCT should be considered in eligible patients, until sufficient experience is accrued with larger non-transplanted cohorts of venetoclax-treated patients demonstrating a cure fraction approaching that which would be expected after alloSCT.

Limited prospective data for R-CHOP in patients with RT come from a phase II trial conducted in the 2000's by the German CLL Study group including 15 patients with RT. The ORR was 67% with 1 (7%) CR (by 1999, CT-based response assessment) and median PFS and OS were 10 months and 21 months, respectively.[10,11] In the current study, the highest CR rate and longest survival estimates were in the 13 patient subgroup treated with R-CHOP + venetoclax. However, among this study's overall cohort, the R-CHOP + venetoclax subgroup had a lower rate of *TP53* aberrations and a higher percentage of previously untreated patients, both of which have been previously associated with improved outcomes.[12,13]

Intensification of chemotherapy to address inadequate results with R-CHOP has had limited success. Historically, intensive anthracycline-containing (e.g., Hyper-CVAD and DA-EPOCH-R) and platinum-containing (e.g., OFAR) regimens have mostly achieved low CR rates (≤ 20%) and short median OS (< 12 months).[2,14-16] A phase II study of DA-EPOCH-R + venetoclax including 26 patients with RT appeared to improve upon these outcomes with a 50% CR rate and a 19.6-month median OS,[5] but at a cost of a high incidence of grade 3-4 hematologic toxicity and risk of infection. Similarly, intensive chemoimmunotherapy + venetoclax achieved responses in over half of patients and a 38% CR rate in the current study. Yet, the survival outcomes for this subgroup did not replicate the DA-EPOCH-R + venetoclax trial outcomes but rather remain in line with prior intensive chemoimmunotherapy data. We acknowledge that direct comparison to the phase II study of DA-EPOCH-R + venetoclax is problematic since 1) this regimen was grouped with other intensive chemoimmunotherapy regimens in the current study, and 2) the current cohort was more heavily pre-treated both in regard to prior CLL

treatment (2 versus 1 median prior lines; more novel agent-exposed) and more patients had had prior RT-directed treatment (56% versus 93% with no prior RT treatment).

Venetoclax has been studied as an adjunct to chemotherapy regimens in DLBCL and double-hit lymphoma (high grade B-cell lymphoma with rearrangements of *MYC* and *BCL2* and/or *BCL6*). DA-EPOCH-R + venetoclax showed promising results (97% ORR, 93% CR rate, 83% 2-year PFS) in a phase I study with a high risk cohort including 50% patients with double-hit lymphoma.[17] However, the subsequent Alliance A051701 study, which randomized patients to DA-EPOCH-R +/- venetoclax, demonstrated excess treatment-related mortality in the venetoclax arm, which led to early discontinuation of the study.[18] R-CHOP + venetoclax, evaluated in the phase Ib/II CAVALLI study, appeared to strike a better balance between aggressiveness of therapy and acceptable toxicity, particularly in patients with BCL2 overexpression by immunohistochemistry.[19] When evaluating the potential risk:benefit ratio of adding venetoclax to chemoimmunotherapy, one must consider that the outcomes of chemoimmunotherapy in RT are far inferior to those of chemoimmunotherapy in double-hit lymphoma, so the benefit of improving remission rates is more likely to outweigh the risks of increased infection-related morbidity and mortality in RT than in double-hit lymphoma. Infection-related mortality present in this retrospective series warrants consideration (5 deaths total; 2 during therapy) and likely reflects both the challenging nature of this patient population and cumulative therapy-related myelosuppression. Thus, while venetoclax appears to have activity in combination with other agents in RT, new approaches are needed to improve tolerability in patients with RT, who are often older, frail, and heavily pre-treated. In the current study, with the caveats that this was a non-randomized comparison and numbers were small, R-CHOP + venetoclax and BTKi + venetoclax +/- anti-CD20 antibody appeared more deliverable than intensive chemoimmunotherapy + venetoclax, with lower rates of febrile neutropenia compared to intensive chemoimmunotherapy + venetoclax, which recapitulates data from *de novo* DLBCL.

Considering delivery of chemotherapy cycles in responding patients only, proportionally more patients treated with R-CHOP + venetoclax were able to receive 6 cycles of chemotherapy than those treated with intensive chemoimmunotherapy + venetoclax (6/7 vs 3/10). Additionally, there were no infection-related deaths in the 13 patients treated with R-CHOP + venetoclax. A prospective, multi-center study evaluating R-CHOP + venetoclax (NCT03054896) is ongoing with initial results also suggesting less toxicity compared to intensive chemotherapy + venetoclax and similar efficacy.[20] In a patient fit for a chemotherapy + venetoclax approach, R-CHOP + venetoclax is likely preferred over intensive chemotherapy + venetoclax; however, greater clarity around this will be provided by the full results from the trial by Davids and colleagues.

BTK inhibitors also have activity in RT with responses demonstrated but PFS still short. Acalabrutinib, a covalent BTKi, achieved a 40% ORR (8% CR) and median PFS of 3.2 months in the RT cohort (n=25) of the phase I/II ACE-CL-001 study.[21] Patients with RT (n=50) receiving the non-covalent BTKi, pirtobrutinib, on the phase I/II BRUIN study had a 54% ORR (10% CR), but median PFS was 3.7 months.[22] Extensive study of venetoclax + BTKi in CLL patient populations support the safe combination of these agents. Our results, including a CR rate of 24% even in the setting of prior BTKi for CLL, support further evaluation of venetoclax + BTKi combinations for treatment of RT. This approach may have added appeal in patients with comorbidities or frailty precluding chemoimmunotherapy-based approaches or patients already treated with prior chemoimmunotherapy for either CLL or RT. We await data from prospective trials (NCT05388006 [acalabrutinib + venetoclax + durvalumab]; NCT05536349 [pirtobrutinib + venetoclax + obinutuzumab]) to see whether non-chemotherapy-based approaches yield high response rates in patients with RT, especially those with *TP53* abnormalities who had inferior outcomes in our study. The tolerability of these regimens relative to chemotherapy + venetoclax regimens will also be important to evaluate.

Non-uniform prognostic and follow-up data are limitations inherent to the retrospective nature of this study. The heterogenous patient populations amongst the treatment subgroups precludes a fair direct comparison. Nevertheless, the findings from the overall cohort and standalone subgroup analyses provide important insights into the evolving landscape of RT management emphasizing incorporation of a novel agent. The majority of our cohort had received CLL-directed treatment but had not received venetoclax for CLL. As venetoclax is now a standard of care option for patients with CLL in either the first line or relapsed setting, this is a limitation of the study. Certainly, from the limited data available in our study, patients with prior venetoclax exposure for CLL had lower likelihood of achieving CR than those who were venetoclax-naïve (13% *vs* 40%), suggesting that alternative treatment approaches may be preferred in such patients. However, given the small numbers in our study, further data are needed to confirm this.

In summary, in a difficult-to-treat RT patient population, venetoclax-based combination regimens achieved higher CR rates than historical studies using chemotherapy, including a nearly 50% CR rate in the subgroup treated with R-CHOP + venetoclax, but at the cost of considerable myelosuppression and high rates of infection. Survival outcomes remained poor overall; however, durable PFS and OS was observed in a small subset of patients irrespective of alloHSCT. Prospective studies evaluating venetoclax-based chemotherapy or novel agent combinations actively accruing and in development are expected to further inform the RT treatment paradigm.

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BeiGene, AstraZeneca, AbbVie, DTRM, Octapharma. Honoraria (institution): Merck, BeiGene, MEI pharma, Alexion, Octapharma. Consultancy: Merck, BeiGene, MEI pharma, Alexion, Octapharma. **SSK**: Research funding (institution): Kite/Gilead, Humanigen, Lentigen, Tolero/Sumtomo, Morphosys, LEAHLabs. Honoraria (institution): Kite/Gilead. Consultancy, Speakers Bureau, or membership on advisory committees: Novartis, Kite/Gilead, Humanigen, LEAHLabs, CapstanBio, Torque, Luminary Therapeutics. Patents and Royalties: MustangBio, Sendero, Mettaforge. Current equity holder in private company: LEAHLabs. **YW**: Research funding (to institution): Incyte, InnoCare, LOXO Oncology, Eli Lilly, MorphoSys, Novartis, Genentech, Genmab; Advisory board (compensation to institution): Eli Lilly, LOXO Oncology, TG Therapeutics, Incyte, InnoCare, Kite, Jansen, BeiGene, AstraZeneca; Consultancy (compensation to institution): Innocare, AbbVie; Honorarium (to institution): Kite. **WGW**: Research Funding*:* AbbVie, Inc; Acerta Pharma; Bristol-Myers Squibb; Cyclacel Pharmaceuticals; Genentech, A member of the Roche Group; Gilead Sciences Inc.; Janssen Biotech Inc.; Juno Therapeutics; Kite Pharma; Loxo Oncology Inc.; Oncternal Therapeutics; Pharmacyclics LLC; Sunesis Pharmaceuticals Inc.; Xencor. **JAW:** Advisor: AbbVie, Arqule, AstraZeneca, BeiGene, Janssen, Loxo, Newave, Pharmacyclics. Consultant: AbbVie, Arqule, AstraZeneca, BeiGene, Genentech, Janssen, Loxo, Newave, Pharmacyclics. Researcher: Karyopharm, MingSight, Pharmaceuticals MorphoSys, Schrodinger, Verastem. Speaker: AbbVie, Arqule, AstraZeneca, BeiGene, Janssen, Loxo, Newave, Pharmacyclics. **SAP**: Research funding (institution): Janssen, AstraZeneca, Merck, and Genentech. Honoraria (institution): Pharmacyclics, Merck, AstraZeneca, Janssen, BeiGene, Genentech, Amgen, MingSight Pharmaceuticals, TG Therapeutics, Novalgen Limited, Kite Pharma, and AbbVie; **PT**: Research funding: AbbVie, Adaptive Biotechnologies, Genentech, Lilly, Pharmacyclics; consultancy/honoraria: AbbVie, Adaptive Biotechnologies, Ascentage, AstraZeneca, BeiGene, Genentech, Genmab, Janssen, Lilly, Merck, Pharmacyclics.

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Figure Legends:

Figure 1: (A) Progression-free survival estimates according to therapy received for Richter transformation, censored for hematopoietic stem cell transplantation; (B) Progression-free survival estimates according to therapy received for Richter transformation, uncensored for hematopoietic stem cell transplantation.

Figure 2: Overall survival estimates according to therapy received for Richter transformation.

442 **Table 1: Summary of Baseline Characteristics**

Baseline Characteristics, N=62 except where stated	All Patients N=62	BTKi[‡] + VEN ± CD20 mAb n=28	R-CHOP + VEN n=13	IC[¶] + VEN n=21
	n (%), or [range]			
Age, median	67 [43-83]	65 [45-83]	69 [43-77]	65 [48-73]
ECOG PS 2 or 3[†]	8/56 (14)	4/25 (16)	2/12 (17)	2/19 (11)
CLL				
Median no. of prior treatments	2 [0-7]	2 [0-7]	1 [0-5]	2 [0-5]
Prior therapies received				
Untreated	11 (18)	3 (11)	4 (31)	4 (19)
BTKi[1]	42 (68)	22 (79)	6 (46)	14 (67)
VEN[2]	15 (24)	7 (25)	5 (39)	3 (14)
Chemoimmunotherapy	34 (55)	17 (61)	6 (46)	11 (52)
Allo-HSCT	3 (5)	3 (11)	0	0
Disease characteristics				
Unmutated *IGHV*, n=59	52/59 (88)	23/27 (85)	10/11 (91)	19/21 (91)
Deletion (17p), n=59	31/59 (53)	16/27 (59)	4/13 (31)	11/19 (58)
TP53 mutation, n=37	16/37 (43)	8/15 (53)	2/9 (22)	6/13 (46)
NOTCH1 mutation, n=34	11/34 (32)	3/11 (27)	3/8 (38)	5/15 (33)
Complex karyotype, n=54	25/54 (46)	13/27 (48)	3/11 (27)	9/16 (56)

443

Richter Transformation				
Median time to RT from the diagnosis of CLL, years	7 [0-28]	8 [0-28]	6 [0-15]	7 [0-18]
Median no. of prior treatments for RT	0 [0-10]	2 [0-4]	0 [0-4]	0 [0-10]
Received chemotherapy for RT	20 (32)	12 (43)	3 (23)	5 (24)
Disease characteristics				
Clonally related, n=14	12/14 (86)	9/9 (100)	2/3 (67)	1/2 (50)
Complex karyotype, n=18	16/18 (89)	10/12 (83)	2/2 (100)	4/4 (100)
TP53 mutated, n=19	11/19 (58)	6/10 (60)	0	5/9 (56)
TP53 deletion, n=21	13/21 (62)	7/12 (58)	1/3 (33)	5/6 (83)
NOTCH1 mutated, n=14	6/14 (43)	3/8 (38)	1/2 (50)	2/4 (50)
LDH, n=58				
>ULN	44/58 (76)	22/28 (79)	6/11 (55)	16/19 (84)
>2x ULN	23/58 (40)	9/28 (32)	2/11 (18)	12/19 (63)
Largest lymph node, n=55				
≥5 cm	25/55 (45)	10/27 (37)	5/10 (50)	10/18 (56)
≥10 cm	8/55 (15)	2/27 (7)	1/10 (10)	5/18 (28)
PET-CT (prior to VEN), n=49				
SUV >5	46/49 (94)	20/22 (91)	8/8 (100)	18/19 (95)
SUV >10	33/49 (67)	15/22 (68)	6/8 (75)	12/19 (63)
N/A	13/62 (21)	6/28 (21)	5/13 (38)	2/21 (10)

Abbreviations: BTKi, bruton tyrosine kinase inhibitors; VEN, venetoclax; mAb, monoclonal antibody; R-CHOP, rituximab-cyclophosphamide, doxorubicin, vincristine, and prednisone; IC, intensive chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; no., number; CLL, chronic lymphocytic lymphoma; Allo-HSCT, allogeneic-hematopoietic stem cell transplant; RT, Richter transformation; LDH, lactate dehydrogenase; ULN, upper limit of normal; N/A, not available.

‡ 26 patients received ibrutinib and 2 patients received acalabrutinib

¶ 12 patients received R-EPOCH; 3 – ibrutinib + R-EPOCH; 1 – acalabrutinib + R-EPOCH; 1 – ibrutinib + R-hyperCVAD; 1 – R-hyperCVAD; 1 – ibrutinib + OFAR; 1 – OFAR; 1 – methotrexate + cytarabine

† No patients had ECOG PS of 4

[1] In the BTKi + venetoclax group, reason for BTKi discontinuation was progressive CLL in 9 patients, Richter transformation in 11 patients and adverse effects in 1

[2] In the patients who received venetoclax for CLL, 12 developed Richter transformation during venetoclax therapy and their Richter therapy consisted of adding on the remainder of the regimen. In the BTKi + venetoclax group, 2 patients received allogeneic- stem cell transplant for CLL after achieving remission with venetoclax and another stopped venetoclax due to CLL progression.

Table 2: Complete Response and Progression-Free Survival Stratified by Baseline Characteristics

Variable	CR	OR [95% CI], p value	Median PFS	HR [95% CI], p value
	N (%)		Months [range]	
Previously received VEN for CLL				
Yes, n=15	2 (13)	0.40 [0.10-1.63], 0.33	3.3 [2.8-3.7]	1.19 [0.6-2.36], 0.61
No, n=47	19 (40)		6.8 [0-15.5]	
Previously received BTKi for CLL				
No, n=7	2 (29)	0.49 [0.16-1.48-], 0.33	11 [0-22.2]	0.99 [0.52-1.88], 0.98
Yes, n=21	5 (24)		4.6 [3.6-5.7]	
Del(17p) in CLL (n=59)*				
Yes, n=23	3 (13)	0.15 [0.04-0.6], **0.01**	4.4 [2.2-6.6]	1.75 [0.95-3.22], 0.07
No, n=36	18 (50)		11 [0-23.7]	
TP53 mutation in CLL (n=41)*				
Yes, n=20	6 (30)	0.39 [0.11-1.41], 0.26	2.3 [0-7.1]	0.56 [0.27-1.19], 0.13
No, n=21	11 (52)		16.6 [0-44]	
Complex karyotype in CLL (n=54)*				
Yes, n=25	7 (28)	0.55 [0.18-1.73], 0.46	8 [0-23.5]	0.93 [0.49-1.76], 0.82
No, n=29	12 (41)		4.4 [2.5-6.3]	
LDH >ULN (n=58)*				
Yes, n=44	14 (32)	0.47 [0.14-1.59], 0.37	4.6 [0.82-8.5]	1.12 [0.55-2.30], 0.75
No, n=14	7 (50)		6.8 [0-20.3]	

LDH >2xULN				
Yes, n=23	7 (30)	0.66 [0.22-2], 0.65	4 [3.2-4.8]	1.33 [0.71-2.47], 0.37
No, n=35	14 (40)		7.1 [0-21.5]	
Adenopathy ≥5cm (n=55) *				
Yes, n=25	7 (28)	0.58 [0.19-1.82], 0.52	4 [2.8-5.2]	1.45 [0.77-2.74], 0.25
No, n=30	12 (40)		8 [0-20.5]	
Adenopathy ≥10cm				
Yes, n=8	1 (13)	0.23 [0.03-2.03], 0.31	2.3 [0-4.9]	1.77 [0.73-4.3], 0.20
No, n=47	18 (38)		8 [0-18.6]	
Highest SUV >10 (n=49) *				
Yes, n=33	12 (36)	0.74 [0.22-2.48], 0.86	4 [3-6]	1.19 [0.58-2.44], 0.64
No, n=16	7 (44)		8 [0-32.9]	

Abbreviations: CR, complete response; OR, Odds ratio; PFS, progression-free survival; VEN, venetoclax; BTKi, Bruton tyrosine kinase inhibitors; CLL, chronic lymphocytic leukemia; LDH, lactate dehydrogenase; ULN, upper limit of normal; SUV, standardized uptake values.

*Information not available in all patients

Table 3: Summary of selected high-grade adverse effects observed in patients.

Adverse Effect	BTKi + VEN	R-CHOP + VEN	IC + VEN
Grade 5	2*/28 (7%)	1†/13 (8%)	2‡/21 (10%)
Grade ≥3 neutropenia	13/28 (46%)	8/11 (73%)	17/19 (89%)
Grade ≥3 thrombocytopenia	11/28 (39%)	5/11 (45%)	18/19 (95%)
Febrile neutropenia	8/28 (29%)	3/13 (23%)	10/21 (48%)
Grade ≥3 infections¶	10/28 (36%)	4/13 (31%)	9/21 (43%)

Abbreviations: BTKi, bruton tyrosine kinase inhibitors; VEN, venetoclax; mAb, monoclonal antibody; R-CHOP, rituximab-cyclophosphamide, doxorubicin, vincristine, and prednisone; IC, intensive chemotherapy.

* Pneumonia due to unspecified organism and Nocardia pneumonia

478 † Subdural hematoma

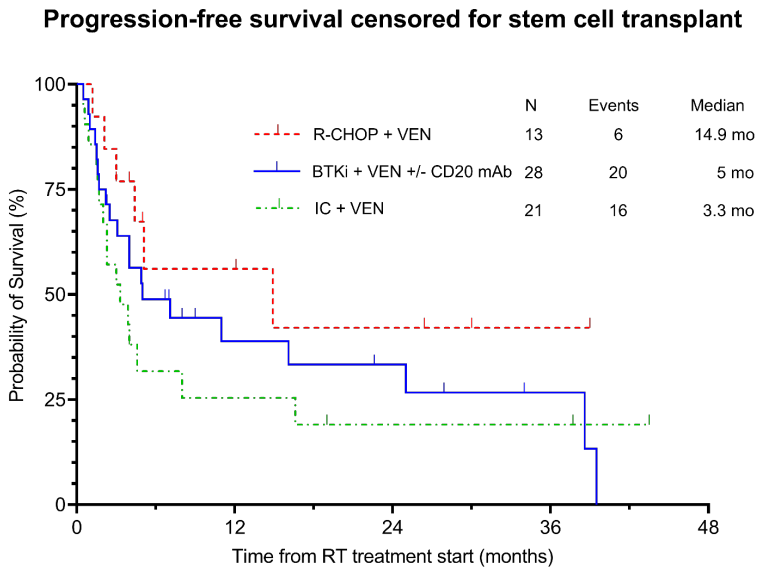
479 ‡ Vancomycin resistant Enterococci sp. Bacteremia and Human Herpes Virus-6 viremia

480 ¶ Information was only available for some patients. Nocardia pneumonia, pneumocystis jiroveci pneumonia, sepsis secondary to
481 Serratia organism, vancomycin resistant Enterococci sp. Bacteremia and Human Herpes Virus-6 viremia, cholecystitis, pneumonia
482 from an unspecified organism, pseudomonal pneumonia, pseudomonal urinary tract infection with bacteremia, coccidioides and
483 aspergillus brain abscess, clostridium difficile colitis, cytolomegalovirus infection, and cellulitis with an unspecified organism were
484 the infections observed in the cohort; some patients had more than one grade 3-4 infectious adverse effect.

485

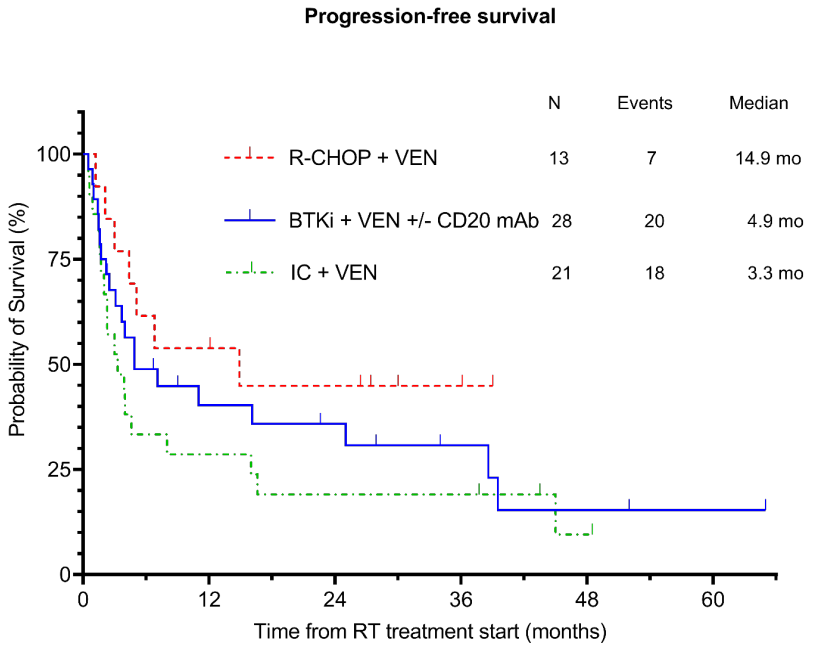
Figures:

Figure 1A: Progression-free survival estimates according to therapy received for Richter transformation, censored for allogeneic stem cell transplant.



Number at risk								
PFS, months	0	6	12	18	24	30	36	44
R-CHOP + VEN	13	6	5	4	4	2	2	0
BTKi + VEN	28	14	8	7	6	4	3	0
IC + VEN	21	6	5	4	3	3	3	1

Figure 1B: Progression-free survival estimates according to therapy received for Richter transformation, uncensored for allogeneic stem cell transplant.



Number at risk										
PFS, months	0	6	12	18	24	30	36	42	48	65
R-CHOP + VEN	13	9	7	6	6	3	2	0	0	0
BTKi + VEN	28	15	10	9	8	6	5	3	3	1
IC + VEN	21	8	7	5	5	5	5	4	2	0

Figure 2

Figure 2: Overall survival estimates according to therapy received for Richter transformation.