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Fixed-duration obinutuzumab-ibrutinib-venetoclax for Richter's transformation: results from the phase II GIVeRS trial

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Richter's transformation (RT) is a life-threatening complication of chronic lymphocytic leukemia (CLL), associated with aggressive clinical behavior and poor survival, and remains an area of high unmet clinical need(1). Despite therapeutic advances in CLL, RT continues to be characterized by poor outcomes, with limited efficacy and short response duration following standard chemoimmunotherapy(2). Moreover, most patients are elderly and frequently have significant comorbidities, limiting eligibility for potentially curative allogeneic hematopoietic stem-cell transplantation(3). Given the reported activity of BTK inhibitors and venetoclax in RT, together with the established efficacy of the obinutuzumab–ibrutinib–venetoclax triplet in high-risk CLL, we conducted a prospective phase II study evaluating this chemotherapy-free combination in patients with RT(4, 5). Early metabolic responses were observed; however, durability was limited, with a median progression-free survival (PFS) of 4.4 months and a median overall survival (OS) of 7.8 months, suggesting that while this regimen is feasible and preserves quality of life, it may be better suited as an induction platform rather than definitive therapy.

Molecular studies have identified recurrent genetic alterations in RT, particularly TP53 inactivation (50–60%) and aberrations involving NOTCH1 or MYC (~30%); however, these biological insights have translated into limited therapeutic advances, and clinical outcomes remain poor(6). Chemoimmunotherapy regimens for DLBCL-type RT continue to represent the most commonly used treatment approach and yield overall response rates of 40–60%, although responses are typically transient, with median PFS ranging from approximately 3–10 months and median OS from 6–21 months(2).

Outside clinical trials, frontline treatment generally mirrors strategies used for de novo DLBCL, most commonly R-CHOP or dose-adjusted R- EPOCH. Attempts to improve outcomes by adding targeted agents to chemotherapy backbones have provided limited additional benefit (7, 8). Most patients with RT are older and have significant comorbidities, limiting eligibility for allogeneic hematopoietic stem-cell transplantation, which remains the only potentially curative therapeutic option but is feasible in only a minority of patients.

The combination of an anti-CD20 monoclonal antibody with a BTK inhibitor and a BCL2 inhibitor has demonstrated substantial efficacy in CLL, and both ibrutinib and venetoclax have demonstrated activity in RT(4, 5).

Based on this rationale, we designed a phase II, open-label, non-randomized, single-arm, multicenter study to evaluate the safety and efficacy of ibrutinib, venetoclax, and obinutuzumab in patients with RT (NCT04939363). The study was investigator-initiated on behalf of the Israeli CLL Study Group and conducted across four centers in Israel. The study was performed in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki, with approval from institutional review boards at each participating center. All patients provided written informed consent prior to enrollment.

Eligible patients were aged ≥18 years with histologically confirmed DLBCL-type RT based on local pathology assessment. Prior therapy for RT was permitted, and patients could also have received previous treatment for CLL.

The GIVe-RS regimen consisted of 12 cycles, each 28 days. Obinutuzumab was administered intravenously for six cycles: 100 mg on day 1 and 900 mg on day 2, followed by 1000 mg on days 8 and 15 of cycle 1, and 1000 mg on day 1 of cycles 2–6. Ibrutinib 560 mg was administered orally once daily on days 1–28 of cycles 1–12. Venetoclax was initiated on cycle 1 day 15 and escalated from 20 mg to 400 mg using an accelerated 7–14-day ramp-up schedule at the investigator's discretion based on tolerability and tumor lysis syndrome (TLS) risk, with close inpatient monitoring. Venetoclax 400 mg daily was then continued through cycle 12. (Figure 1 supplements)

The primary endpoint was the investigator-assessed 6-month overall metabolic response (OMR) rate according to Lugano 2014 criteria(9). Secondary endpoints included complete metabolic response (CMR), PFS, OS, and duration of response. Radiologic assessments were performed centrally after cycles 3, 6, and 12. Safety assessments included treatment-emergent adverse events graded according to CTCAE v5.0. Patients also completed monthly patient-reported outcome assessments using EuroQol EQ-5D and FACT-Lym instruments(10, 11).

From August 2021 to October 2024, 12 patients with RT were enrolled. Eight patients (67%) were male. Median age at initial CLL diagnosis was 73 years (range, 52–85). Three patients (25%) had received prior therapy for CLL (median, one prior line), all with chemoimmunotherapy; none had received targeted agents. Median interval from CLL diagnosis to transformation was 66 months (range, 0–211). IGHV status was available for seven patients, of whom five (71%) had unmutated disease. TP53 or del(17p) status was available for five patients, all of whom were negative.(Table 1)(Figure 2 supplements)

At the time of RT diagnosis, median age was 78 years (range, 62–87). Eight patients (67%) were treatment-naïve for RT, while four (33%) had relapsed or refractory disease following progression on prior R-CHOP–based regimens. Extranodal involvement was present in five patients (42%), including gastrointestinal tract, testis, bone marrow, and one case with muscular involvement. Elevated LDH was observed in eight patients (67%). Additional baseline characteristics are summarized in supplement Table 1.

Cell-of-origin analysis showed that five patients had germinal center B-cell (GCB) subtype and six had non-GCB subtype (one missing). A double-/triple-expressor phenotype was present in nine patients (75%). Bone marrow involvement was identified in one patient, and bulky disease (>5 cm) was present in three patients. At RT diagnosis, median hemoglobin was 11.8 g/dL, median white blood cell count was 11.8×10^9/L, and median absolute lymphocyte count was 3×10^9/L.

Two patients were excluded from response evaluation because they did not undergo scheduled interim PET imaging. One patient died due to metastatic carcinoma within 30 days post-screening (A retrospective review of baseline PET-CT imaging did not reveal findings suggestive GI malignancy at study entry), and one patient died due to cerebrovascular accident. (Neuroimaging performed at the time of the event did not demonstrate intracranial hemorrhage.)At 3 months, OMR and CMR rates among 10 response-evaluable patients were 70% and 40%, respectively. Following interim PET assessment, one patient with stable disease proceeded to allogeneic stem-cell transplantation, and one patient who developed severe diarrhea discontinued treatment and subsequently died. A

At 6 months, response evaluation was available for 8 patients, among whom OMR and CMR rates were 37.5% and 25%, respectively. During a median follow-up of 23 months, six patients (50%) experienced disease progression, and 10 patients (83.3%) died. Median PFS was 4.4 months and median OS was 7.8 months. (figure 1).

Causes of death included RT progression, intractable diarrhea, infections (including sepsis and COVID-19 during subsequent bendamustine–rituximab therapy), neurologic deterioration, and acute myeloid leukemia.

The most common treatment-emergent adverse events were neutropenia (40%), thrombocytopenia (50%), diarrhea (40%), and skin rash (50%). Two patients developed COVID-19 but recovered while on treatment. One case of grade 1 laboratory tumor lysis syndrome was observed, with no cases of clinical TLS or atrial fibrillation.(Supplement Table 1)

Quality-of-life analyses demonstrated no significant decline in global health status or lymphoma-specific functional measures during treatment. Patients who remained on therapy reported preserved quality of life, consistent with the predominantly oral administration of ibrutinib and venetoclax. (figure 2)

In recent years, the treatment landscape of CLL has shifted from chemoimmunotherapy toward targeted therapies, resulting in improved survival and quality of life(12). Nevertheless, RT remains a highly aggressive complication with no universally accepted standard therapy. Outside clinical trials, most centers continue to use regimens designed for de novo DLBCL, yet median survival remains below one year.

Targeted agents have demonstrated clinical activity in RT. BTK inhibitors and venetoclax have shown responses as monotherapy or in combination with chemotherapy. Next-generation BTK inhibitors, including zanubrutinib and acalabrutinib, have reported response rates of approximately 50–60% in small series, (13, 14). while pirtobrutinib has demonstrated activity in the BRUIN study (15). Immune checkpoint inhibitor combinations and T-cell–directed therapies, including bispecific antibodies such as epcoritamab and glofitamab, as well as anti-CD19 CAR T-cell therapies, have also shown promising activity(16).

Building on prior data supporting the triplet combination in high-risk CLL, we evaluated a chemotherapy-free regimen in RT. Early metabolic responses were observed; however, durability was limited, with median PFS of 4.4 months and OS of 7.8 months. These results were inferior to some contemporary targeted or immunotherapy-based combinations, likely reflecting the advanced age and frailty of our cohort. Despite these limitations, this study provides prospective evidence on a fully targeted, chemotherapy-free combination of a BTK inhibitor, a BCL2 inhibitor, and an anti-CD20 antibody in Richter transformation, a rare clinical entity for which prospective data remains scarce.

The accelerated venetoclax ramp-up strategy was feasible, with only one laboratory TLS event and no clinical TLS. Hematologic toxicity was common, and severe diarrhea in two elderly patients led to treatment discontinuation, underscoring tolerability challenges.

Patient-reported outcomes were encouraging, demonstrating preservation of quality of life and functional status during therapy. Overall, these findings suggest that this fully targeted combination induces early responses with manageable safety but lacks sufficient durability as definitive therapy. The regimen may therefore serve best as an induction backbone, potentially bridging eligible patients to consolidative strategies such as allogeneic transplantation.

This study is limited by its small sample size, very elderly population, and incomplete genomic characterization. Nevertheless, it provides prospective data supporting feasibility of a chemotherapy-free triplet regimen in RT and contributes to ongoing efforts to improve targeted therapeutic strategies.

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Table 1. Patient demographics clinical and laboratory characteristics

parameters	n=12 (%)
Age (years) at diagnosis of CLL	73 (45-80)
Age (years) at diagnosis of RT: Median	78 (62-87)
Age >65 yr - no. (%) at diagnosis of RT	11 (92%)
Male sex - no. (%)	8 (67%)
Ethnicity: Jews	11 (92%)
Arabs	1 (8%)
IGHV mutation status - no. (%)	
Mutated	2/7 (29%)
Unmutated	5/7 (71%)
Dohner Scale (13q-,11q- 12+,17p-)	
13qdel	1/7 (14%)
11qdel	0/7 (0%)
17pdel	0/7 (0%)
Trisomy 12	5/7 (71%)
TP53mut	0/5 (0%)
Median time from diagnosis of CLL to RT	66 months. (0-211)
ECOG performance status:	
0	7 (58%)
1	2 (17%)
2	3 (25%)
Ann Arbor stage at diagnosis of DLBCL-RT	
I+IE	3 (25%)
II	3 (25%)
III	3 (25%)
IV	3 (25%)

MYC, BCL2, or BCL6 expression by immunohistochemistry	
Double expressor	6 (50%)
Triple expressor	2 (17%)
None	2 (17%)
Bone marrow involvement by DLBCL	
Yes	1 (8%)
No	11(92%)
Site of DLBCL- RS	
Nodal	6 (50%)
Extra-nodal	6 (50%): • Gastric 2 • Testis 1 • Bone marrow, 1 • Muscles 1
Bulky disease RT	
(lymph node diameter >5cm)	3 (25 %)
Beta2-microglobulin RT: Median (range)	2.8 (1.9-6.1 mg/liter)
Tumor lysis syndrome risk category - no. (%)	
Intermediate and High risk:	5 (42%)
Elevated LDH -RT (above the upper normal limit)	8 (67%)
<u>Number of prior lines of therapy for CLL</u>	
0	3 (25%)
≥1	9 (75%)
<u>Lines of prior therapy for RT</u>	
0	8 (67%)
≥1	4 (33%) (R+CHOP)

Figure legend

Figure 1:

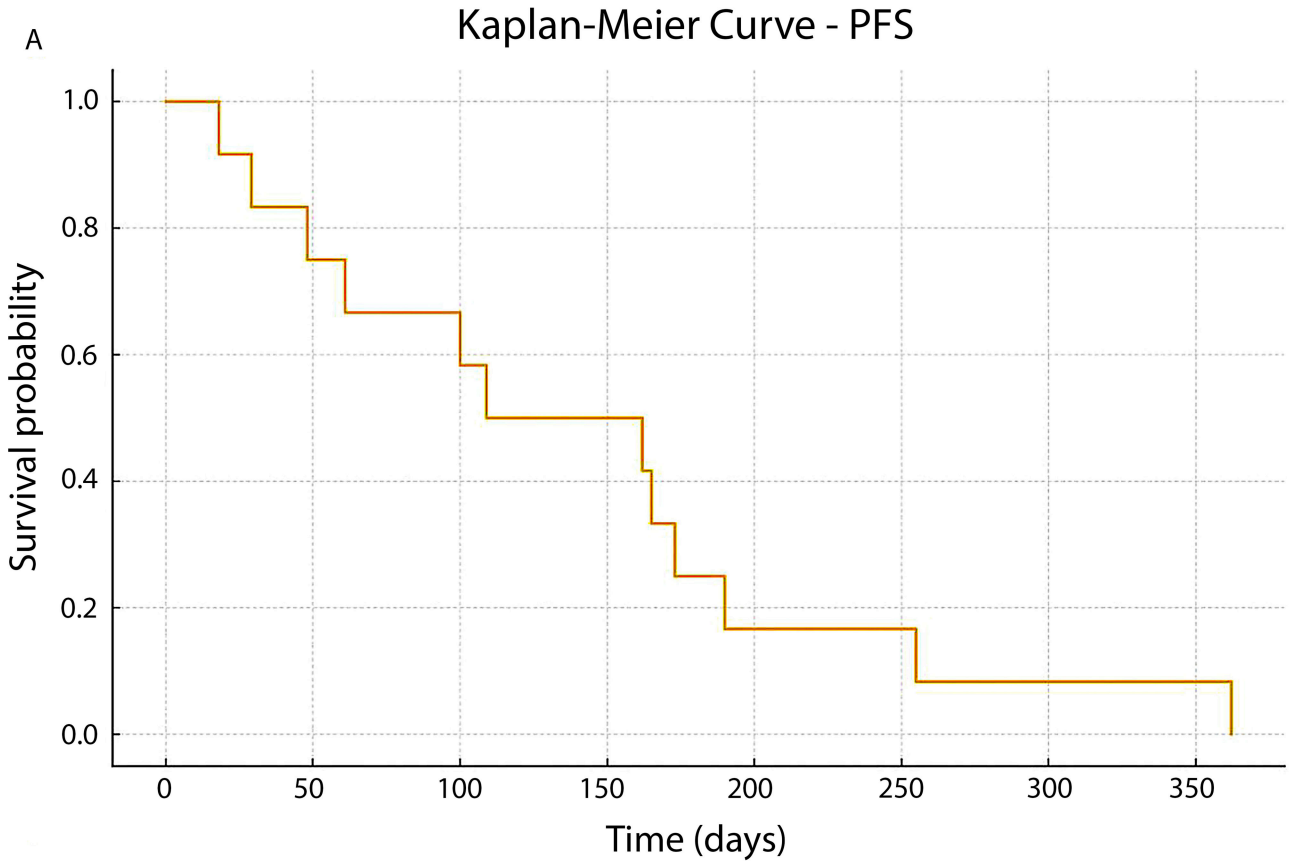
Kaplan-Meier curves illustrating survival outcomes in the study cohort.

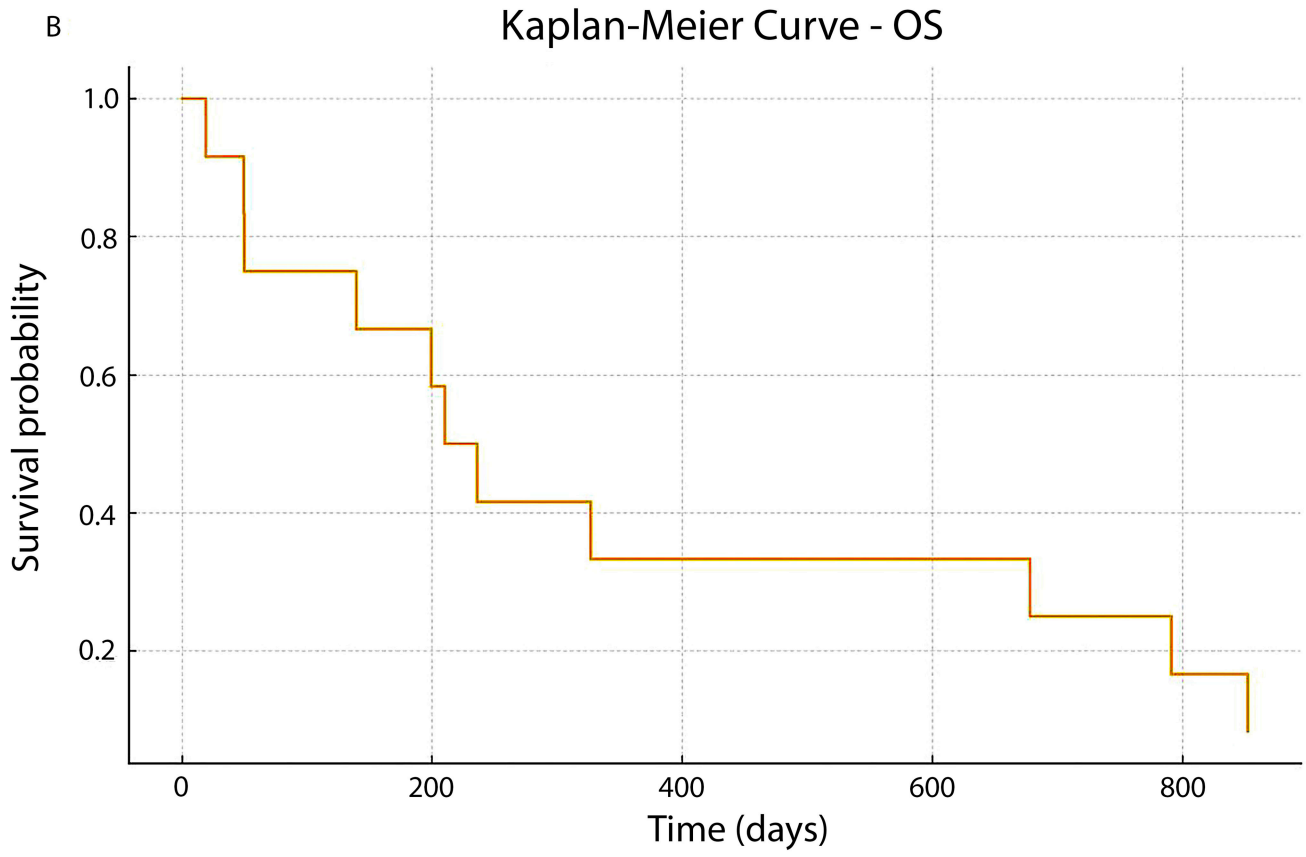
(A) Progression-free survival (PFS).

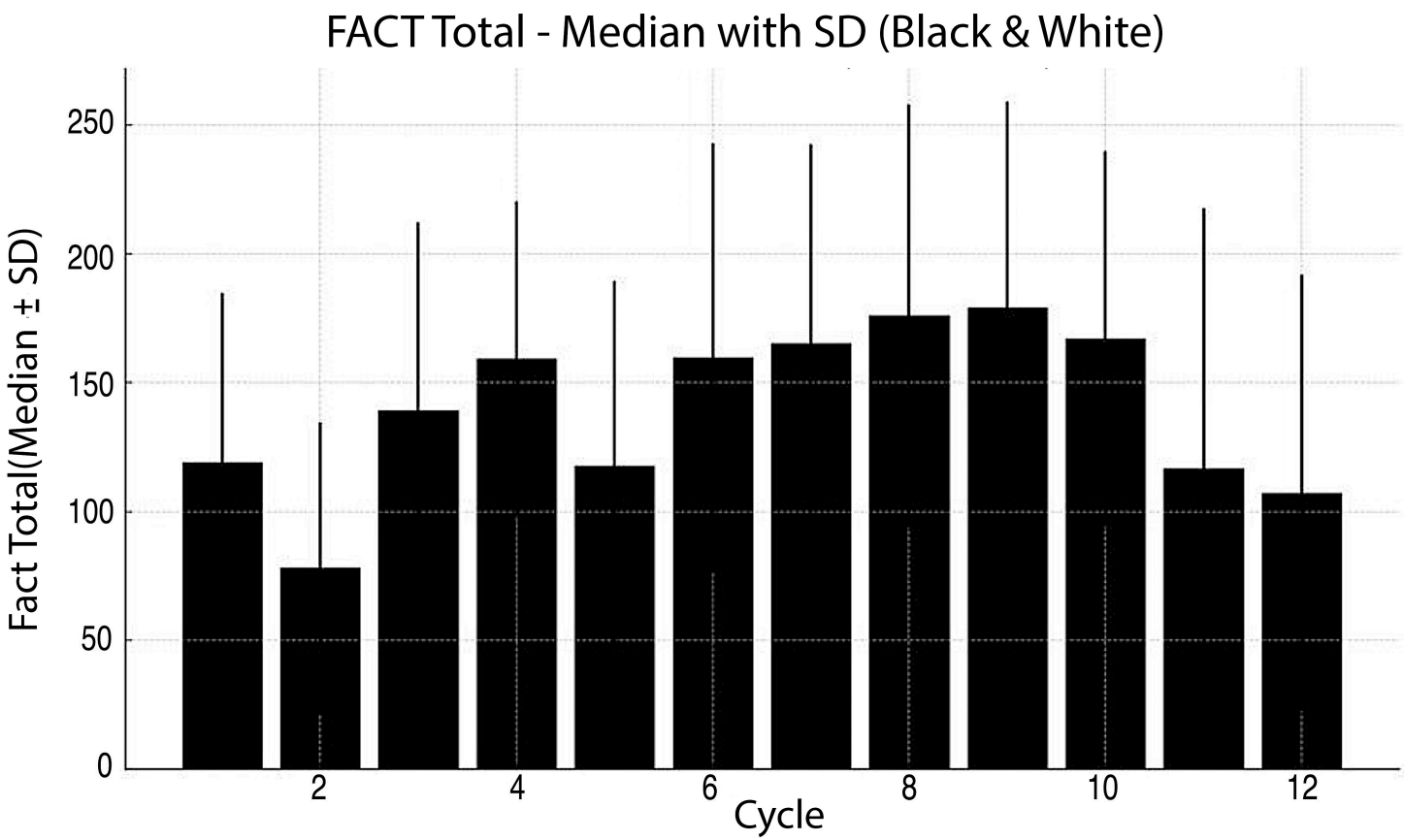
(B) Overall survival (OS).

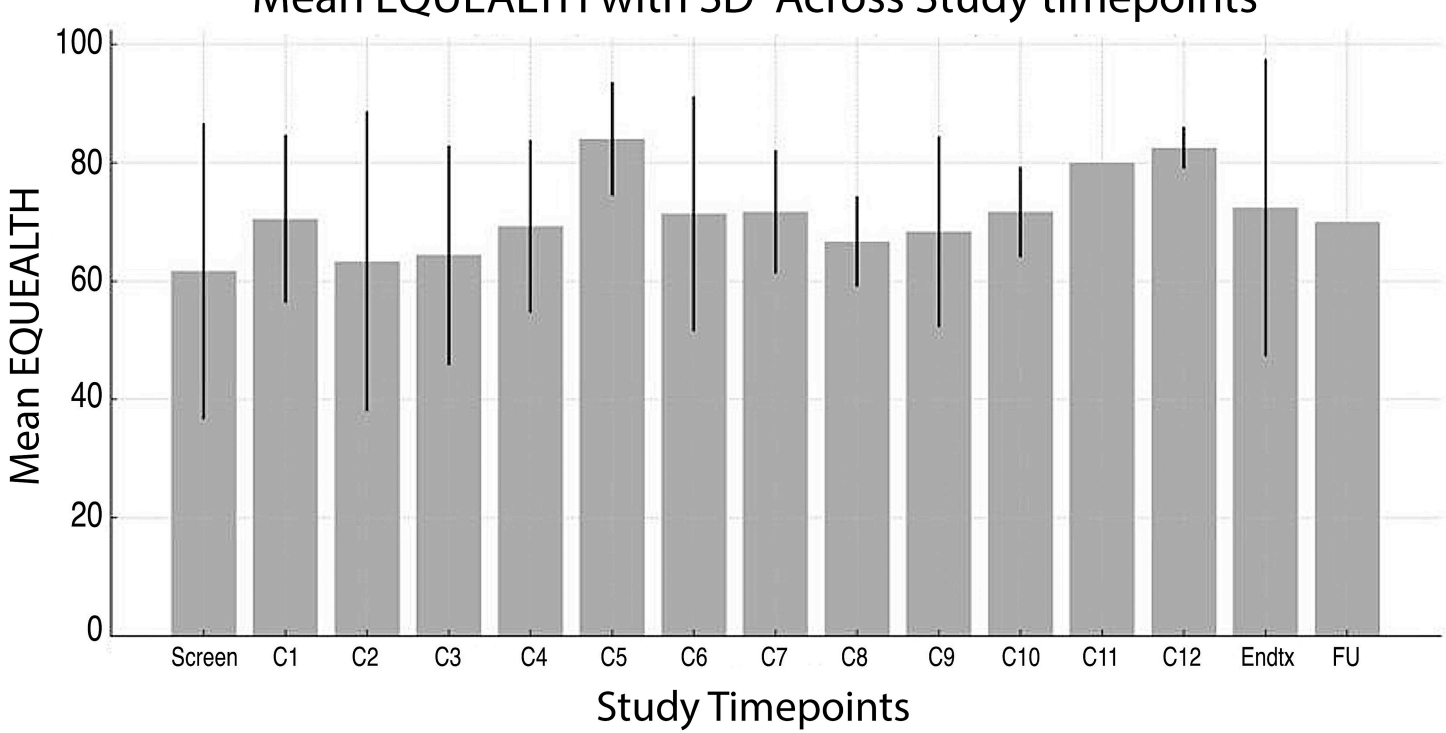
Figure 2:

Monthly patient-reported outcome assessments, including the EuroQol (EQ-5D) quality-of-life questionnaire and the FACT-Lym (Functional Assessment of Cancer Therapy–Lymphoma) instrument presentation with standard deviation.


A
Kaplan-Meier Curve - PFS
Survival probability
1.0
0.8
0.6
0.4
0.2
0.0
0
50
100
150
200
250
300
350
Time (days)


B
Kaplan-Meier Curve - OS
Survival probability
1.0
0.8
0.6
0.4
0.2
0
200
400
600
800
Time (days)


FACT Total - Median with SD (Black & White)
Fact Total(Median ± SD)
250
200
150
100
50
0
2
4
6
8
10
12
Cycle

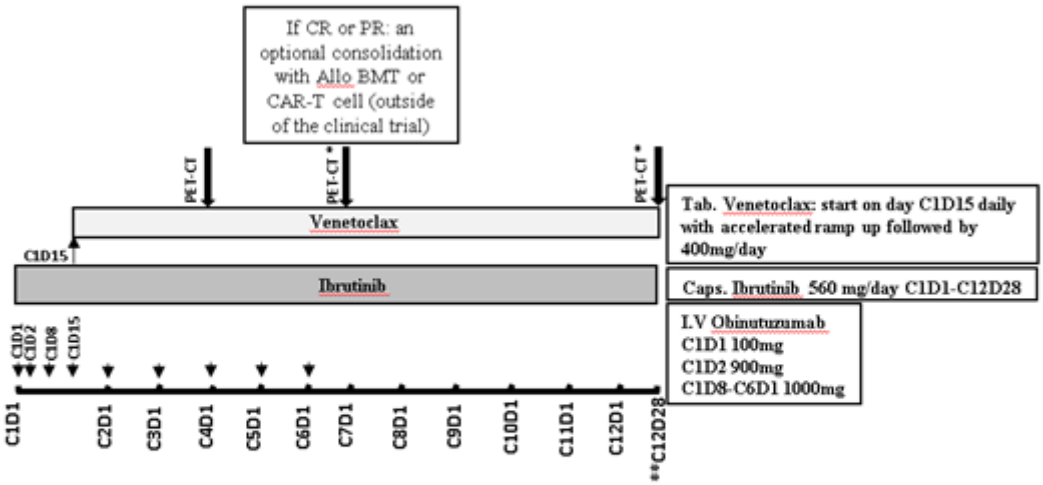

Mean EQUEALTH with SD Across Study timepoints
Mean EQUEALTH
100
80
60
40
20
0
Screen
C1
C2
C3
C4
C5
C6
C7
C8
C9
C10
C11
C12
Endtx
FU
Study Timepoints

Supplements:

Supp. Table 1: Treatment emergent adverse events at least possible related to study treatment (total events reported =93)

	Adverse Event	All Grades	Grade 3-4	Grade 5
No. of patients with events, N				
Hematologic disorders	Neutropenia	12 (100%)	12 (100%)	0
	Thrombocytopenia	12 (100%)	3 (25%)	0
	Anemia	2 (16.7%)	1 (8.3%)	0
	Neutropenic fever	3 (100%)	0	0
(8.3%)				
Gastrointestinal disorders	Abdominal pain	1 (8.3%)	0	0
	Colitis/diarrhea	7 (58%)	3 (100%)	0
	Constipation	2 (16.7%)	0	0
	Vomiting	1 (8.3%)	1 (8.3%)	0
General disorders	Severe general deterioration	2 (16.7%)	2 (16.7%)	2 ((16.7%)
Infusion related reaction	IRR	2 (16.7%)	0	0
Infections and infestations	Sepsis	1 (8.3%)	1 (8.3%)	0
	Urinary tract infection	1 (8.3%)	0	0
	Fungal infection	1 (8.3%)	0	0
	Neutropenic fever	3 (100%)	0	0
Nervous system disorders	Cerebral ischemia	1(8.3%)	1(8.3%)	1 (8.3%)
Skin	Rash	4 (33.3%)	1(8.3%)	0
Metabolism disorders	Hypomagnesemia	4 (33.3%)	3 (100%)	0
TLS	Tumor lysis syndrome	1 (8.3%)	0	0
Neoplasms	Metastatic squamous cell carcinoma	1(8.3%)	1(8.3%)	0

Supp Figure 1: study design



* In patients with bone marrow involvement by Richter's Syndrome Transformation at last examination: to confirm CR, repeat bone marrow biopsy.

** The study drugs will be given until one of the following occurs, whichever occurs first:

- 12 cycles completion
- Start of new anti-CLL or anti-lymphoma therapy
- Progression of RS
- Unacceptable toxicity

Supp Figure 2: patients flowchat