Efficacy of venetoclax monotherapy in patients with relapsed chronic lymphocytic leukaemia in the post BCR inhibitor setting: a UK wide analysis

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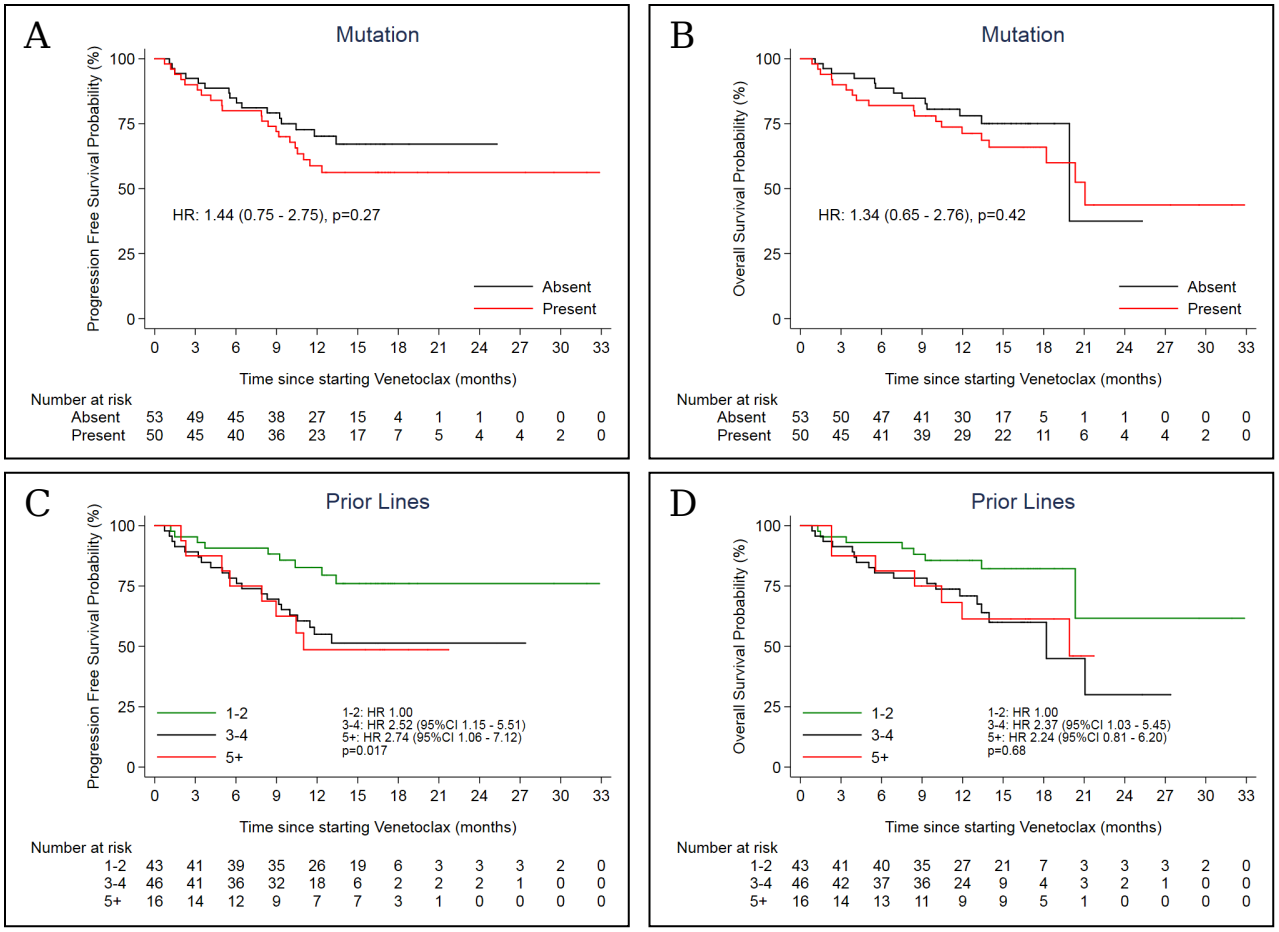
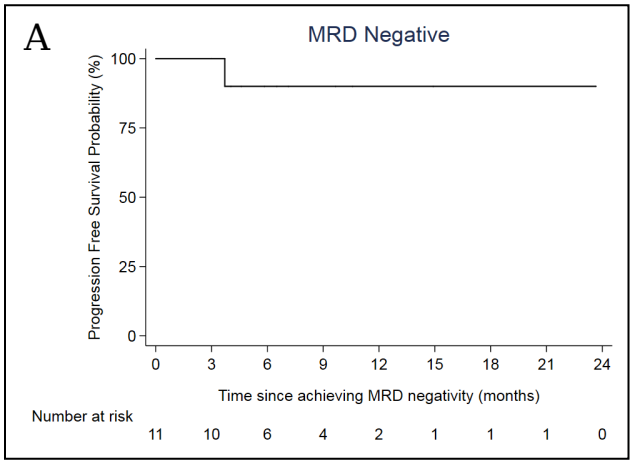
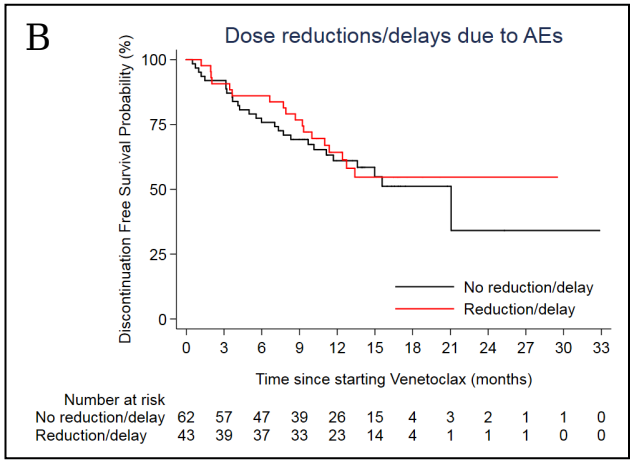
Key Words:	CHRONIC LYMPHOCYTIC LEUKAEMIA, B cell receptor inhibitor, ibrutinib, venetoclax, idelalisib

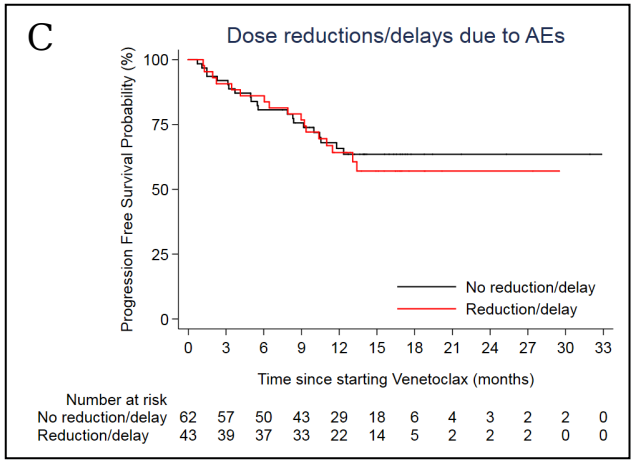
Supplementary Fig 1A-D



Supplementary Figure 2A-C







Supplementary Table I: Univariate Analysis for PFS and OS by baseline factors

Factor	PFS Events/N	PFS HR (95% CI)	PFS p-value*	OS Events/N	OS HR (95% CI)	OS p-value*
All Patients						
Age (for an increase of 10 years)	38/105	1.21 (0.87 – 1.69)	0.26	33/105	1.49 (1.02 – 2.17)	0.037
Sex						
Male	29/77	1.00	0.61	28/77	1.00	0.11
Female	9/28	0.82 (0.39 – 1.74)		5/28	0.47 (0.18 – 1.22)	
ECOG						
0	4/32	1.00	0.0005	2/32	1.00	0.0001
1	18/46	4.02 (1.36 – 11.93)		13/46	3.02 (0.98 – 9.34)	
2	14/23	7.42 (2.43 – 22.64)		14/23	7.45 (2.44 – 22.75)	
3	2/4	4.29 (0.79 – 23.42)		2/4	5.54 (1.00 – 30.70)	
17P or TP53 mutation						
Absent	16/53	1.00	0.27	13/53	1.00	0.42
Present	21/50	1.44 (0.75 – 2.75)		19/50	1.34 (0.65 – 2.76)	
Number of prior lines (for an increase of 1 line)	38/105	1.20 (1.06 – 1.36)	0.005	33/105	1.05 (0.92 – 1.21)	0.45
Number prior lines (tertiles)						
1-2	9/43	1.00	0.017	8/43	1.00	0.068
3-4	21/46	2.52 (1.15 – 5.51)		18/46	2.37 (1.03 – 5.45)	
5+	8/16	2.74 (1.06 – 7.12)		7/16	2.24 (0.81 – 6.20)	
Previous BTKi						
No	8/32	1.00	0.15	8/32	1.00	0.62
Yes	30/73	1.76 (0.81 – 3.84)		25/73	1.22 (0.55 – 2.73)	
Previous Pi3Ki						
No	25/68	1.00	0.79	21/68	1.00	0.91
Yes	12/36	0.91 (0.46 – 1.81)		11/36	1.4 (0.50 – 2.17)	
Patients treated with a BTKi						
Duration of BTK (for an increase of 1 month)	30/73	1.00 (0.97 – 1.02)	0.74	25/73	0.99 (0.96 – 1.03)	0.71
Duration of BTK						
<6 months	6/15	1.00	0.85	5/10	1.00	0.75
6 months - 1 year	5/12	1.12 (0.34 – 3.66)		5/12	1.41 (0.40 – 4.92)	
1-2 years	7/17	1.12 (0.38 – 3.34)		4/17	0.47 (0.12 – 1.81)	
2-3 years	9/21	1.01 (0.36 – 2.85)		8/21	1.00 (0.33 – 3.08)	
≤4 years	3/8	0.86 (0.21 – 3.44)		3/8	0.90 (0.21 – 3.81)	
Patients treated with a Pi3Ki						
Duration of Pi3Ki (for an increase of 1 month)	12/36	1.03 (0.96 – 1.11)	0.43	11/36	1.04 (0.96 – 1.13)	0.30
Duration of Pi3Ki						
<6 months	3/13	1.00	0.56	3/13	1.00	0.41
6 months-1 year	6/13	2.58 (0.64 – 10.35)		5/13	2.15 (0.51 – 9.06)	
1-3 years	3/10	1.51 (0.30 – 7.47)		3/10	1.85 (0.36 – 9.53)	

*Log rank test for trend used for ordinal variables.

Supplementary Table II: Multivariate Analysis for PFS and OS by baseline factors

Factor		PFS		OS	
		HR (95% CI)	p-value	HR (95% CI)	p-value
All Patients**					
Age (for an increase of 10 years)		1.18 (0.80 – 1.73)	0.40	1.57 (1.03 – 2.38)	0.035
Sex					
	Male	1.00	0.15	1.00	0.018
	Female	0.54 (0.96 – 1.41)		0.29 (0.10 – 0.81)	
ECOG					
	0	1.00	0.0026	1.00	0.009
	1	3.83 (1.27 – 11.54)		3.12 (0.98 – 9.91)	
	2	7.51 (2.32 – 24.27)		9.09 (2.80 – 29.42)	
	3	2.20 (0.24 – 20.61)		2.90 (0.30 – 28.04)	
17P or TP53 mutation					
	Absent	1.00	0.34	1.00	0.26
	Present	1.43 (0.68 – 2.99)		1.62 (0.70 – 3.72)	
Number prior lines (for an increase in one line)		**1.16 (0.96 – 1.41)**	**0.12**	**1.03 (0.81 – 1.31)**	**0.80**
Previous of BTK					
	No	1.00	0.51	1.00	0.56
	Yes	1.50 (0.46 – 4.91)		1.49 (0.39 – 5.70)	
Previous Pi3Ki					
	No	1.00	0.73	1.00	0.60
	Yes	1.21 (0.42 – 2.49)		1.37 (0.43 – 4.39)	
Patients with previous BTK					
Age (for an increase of 10 years)		**0.98 (0.63 – 1.53)**	**0.94**	**1.35 (0.81 – 2.25)**	**0.26**
Sex					
	Male	1.00	0.37	1.00	0.043
	Female	0.67 (0.28 – 1.60)		0.31 (0.10 – 0.96)	
ECOG					
	0	1.00	0.0021	1.00	0.0004
	1	4.05 (1.16 – 14.2)		3.69 (0.94 – 14.39)	
	2	8.52 (2.18 – 33.34)		14.92 (3.38 – 65.89)	
	3	-**		-**	
17P or TP53 mutation					
	Absent	1.00	0.23	1.00	0.20
	Present	1.79 (0.70 – 4.59)		2.09 (0.68 – 6.45)	
Number prior lines (for an increase in one line)		**1.03 (0.78 – 1.34)**	**0.85**	**0.72 (0.45 – 1.15)**	**0.17**
Previous Pi3Ki					
	No	1.00	0.80	1.00	0.42
	Yes	1.20 (0.31 – 4.68)		1.83 90.42 – 8.05)	
Duration of BTK (for an increase of 1 month)		**0.99 (0.95 – 1.02)**	**0.80**	**0.99 (0.95 – 1.03)**	**0.61**

Patients with Previous Pi3Ki					
Age (for an increase of 10 years)		**1.71 (0.80 – 3.67)**	**0.17**	**1.78 (0.83 – 3.79)**	**0.14**
Sex					
	Male	1.00	0.58	1.00	0.38
	Female	0.50 (0.04 – 5.72)		0.28 (0.02 – 4.68)	
ECOG					
	0	1.00	0.038	1.00	0.026
	1	6.61 (0.67 – 65.1)		5.42 (0.59 – 49.93)	
	2	21.97 (1.44 – 336.1)		19.59 (1.49 – 256.86)	
	3	46.85 (1.57 – 1394.37)		56.11 (1.99 – 1585.597)	
17P or TP53 mutation					
	Absent	1.00	0.31	1.00	0.83
	Present	2.36 (0.44 – 12.56)		1.22 (0.20 - 7.27)	
Number prior lines (for an increase in one line)		**1.37 (1.04 – 1.82)**	**0.026**	**1.12 (0.83 – 1.52)**	**0.46**
Previous BTK					
	No	1.00	0.86	1.00	0.91
	Yes	0.84 (0.12 – 5.71)		0.90 (0.13 – 6.15)	
Duration of Pi3ki (for an increase of 1 month)		**1.04 (0.94 – 1.17)**	**0.44**	**1.06 (0.95 – 1.18)**	**0.32**

*102 patients with complete data. The patient with the unknown Pi3Ki exposure has been excluded. **No events in 2 patients. N.B. No significant interactions with age/number prior lines or mutation/number prior lines.

Supplementary Table III: Reasons for unplanned admissions

Reason	N (%)
Infection	22 (48.9)
Perforated sigmoid tumour	1 (2.2)
RT	1 (2.2)
TLS	1 (2.2)
Biochemical TLS	1 (2.2)
Worsening SOB	1 (2.2)
Bleeding	2 (4.4)
High calcium	1 (2.2)
Isolated hyperphosphatemia	1 (2.2)
PD	2 (4.4)
Neutropenic fever	1 (2.2)
Abnormal LFTs	1 (2.2)
Other*	7 (15.6)
Missing**	2 (4.4)

*Only one gave details ("Admission was for volvulus, a problem patient had since idelalisib")
**Two patients have unplanned admissions reported but no reasons (patients 5 and 10)

Efficacy of venetoclax monotherapy in patients with relapsed chronic lymphocytic leukaemia in the post-BCR inhibitor setting: a UK wide analysis

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Running title: Venetoclax efficacy in relapsed, refractory CLL

Key Words: chronic lymphocytic leukaemia; B cell receptor inhibitor, ibrutinib, idelalisib, p53 venetoclax; BCL2.

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Abstract

Venetoclax is a BCL2 inhibitor with activity in relapsed/refractory (R/R) chronic lymphocytic leukaemia (CLL). We conducted a multi-centre retrospective analysis of 105 R/R CLL patients who received venetoclax pre-National Health Service commissioning. The median age was 67 years and median prior lines was 3 (range: 1-15). 48% had *TP53* disruption. At ≥2 lines, 60% received a Bruton Tyrosine Kinase inhibitor (BTKi) and no prior phosphoinositide 3-kinase inhibitor (Pi3Ki), 25% received a Pi3Ki and no prior BTKi, and 10% received both. Patients discontinued B cell receptor inhibitor (BCRi) because of toxicity in 44% and progression in 54%. Tumour lysis syndrome risk was low, intermediate or high in 27%, 25%, and 48% respectively. Overall response was 88% (30% complete response [CR]). The overall response rate was 85% (CR 23%) in BTKi-exposed patients, 92% (CR 38%) in Pi3Ki-exposed patients and 80% (CR 20%) in both (p=0.59). With a median follow-up of 15.6 months, 1-year progression-free survival was 65.0% and 1-year overall survival was 75.1%. Dose reduction or temporary interruption did not result in an inferior progression-free or discontinuation-free survival. Risk of progression or death after stopping a prior BCRi for progression was double compared to those stopping for other reasons (predominantly toxicity) (Hazard Ratio 2.01 p=0.05). Venetoclax is active and well tolerated in R/R CLL post ≥1 BCRi. Reason(s) for stopping BCRi influences venetoclax outcomes.

Introduction

The therapeutic landscape for patients with chronic lymphocytic leukaemia (CLL) has undergone transformative changes over recent years, particularly with the advent of novel kinase inhibitors targeting Bruton tyrosine kinase (BTK) and phosphoinositide 3-kinase (PI3K), disrupting signalling downstream of the B cell receptor (BCR) pathway. Ibrutinib monotherapy and Idelalisib alongside rituximab represent modern standard of care options in patients with relapsed CLL following respective phase III trials displaying an overall survival benefit versus anti-CD20 monoclonal antibody monotherapy (Byrd *et al*, 2013; Furman *et al*, 2014).

Although many patients achieve durable remissions on either agent, there are no plateaus noted on progression-free survival (PFS) analyses and, as such, patients receiving either agent will continue to relapse on therapy. Relapse may occur earlier in patients with *TP53* disruption (*TP53* deletion and / or *TP53* mutation) and / or complex karyotype (Byrd *et al*, 2015). Accumulating evidence suggests that many BCR inhibitor (BCRi)-treated patients outside of the clinical trial setting discontinue BTK and Pi3K inhibitors due to intolerable toxicity. For example, a recently published retrospective series reported that of 621 patients treated with ibrutinib (536 relapsed-refractory [R/R] and 80 treatment-naïve), 42% had discontinued ibrutinib at a median of 7 months. Toxicity was the dominant cause of discontinuation in both previously treatment-naïve patients (63.1%) and R/R patients (50.2%) (Mato *et al*, 2018a). Idelalisib has a well described toxicity prolife including a considerable burden of intolerable adverse events (AEs) and treatment discontinuation (Mato *et al*, 2017a).

In light of these data, effective, non-toxic therapy in the post-BCRi setting has become a focus of clinical need. Venetoclax is a potent, selective and orally bioavailable small-molecule inhibitor of the anti-apoptotic protein BCL2, with demonstrable activity in patients with R/R CLL, including *TP53*-disrupted disease. Two phase II trials

demonstrate impressive activity in these settings with an overall response rate (ORR) of approximately 80% in the BCRi-naïve setting (Roberts *et al*, 2015; Stilgenbauer *et al*, 2016). As a result, venetoclax was approved in the European Union for adults with *TP53*-disrupted CLL who are either unsuitable for, or have failed a BCRi and for those without *TP53* disruption who have failed both chemo-immunotherapy and a BCRi. (http://www.ema.europa. eu/docs/en_GB/document_library/EPAR_-_Product_Information/ human/004106/WC500218800.pdf).

Recent data have established the clear activity of venetoclax post-BCRi. Jones *et al* (2017) demonstrated an ORR of 65% following ibrutinib (n=91) with a median PFS of 24·7 months (95% confidence interval [CI] 19·2–not reached [NR]), and estimated 12-month PFS of 75% (95% CI 64–83%). A separate cohort in the same trial recently reported an ORR of 67% in 36 patients who received idelalisib as their last BCRi pre-enrolment. For these patients, the median PFS had not yet been reached and estimated 12-month PFS was 79% (Coutre *et al*, 2018). Results from a small cohort within the trial of heavily pre-treated, dual BCRi exposed patients (n=28) were recently reported, with a lower ORR of 39% (Wierda *et al*, 2017a).

In a recent published series, Mato *et al* (2018b) presented data from a separate US cohort outlining venetoclax monotherapy efficacy in 141 patients, win which 89% had been exposed to a BCRi. Patients had received 3 prior lines and 45% had 17p deletion. The ORR was 72% (complete response [CR] 19.4%) and with a short median follow-up of 7 months, the median PFS and overall survival (OS) was not reached. The projected 12-month PFS and OS was 68% and 88%, respectively.

Mato *et al* (2017b) provided the largest real world data (RWD) sets of venetoclax monotherapy in relapsed CLL. Most of the 204 patients across US and international community and academic centres successfully completed the dose ramp-up and maintained a maximum dose of 400 mg o.d. Toxicity was manageable, and it was CLL progressive disease (PD) (47%), not toxicity (11%) that lead to most venetoclax discontinuation. The ORR was 77% (28% CR) and the median PFS and OS were not reached. In this series, only 63% were exposed to BCRi and no minimal residual disease (MRD) data were presented. Venetoclax was active in patients resistant to ibrutinib although patients with prior ibrutinib exposure and poor risk cytogenetics were associated with an inferior PFS.

It is clear that venetoclax is an effective agent in high-risk R/R CLL, including patients previously exposed to BCRi therapy. However, for the published RWD data, the median follow-up is short, there is a lack of MRD response data on venetoclax and a lack of information on the impact of patient performance status (PS) on outcome.

In light of the high incidence of BCRi discontinuation in the non-trial setting (Mato *et al*, 2018a), and the demonstrable efficacy of venetoclax in the post-BCRi setting, we wished to analyse the early experience of venetoclax monotherapy in routine practice. Venetoclax was available free-of-charge to named UK and Irish

patients from 2015, initially prior to European Medicines Agency (EMA) approval via a named-patient scheme and subsequently through the early access to medicine scheme prior to National Health Service (NHS) commissioning. Thus, a defined consecutive cohort of patients was available for evaluation, representing early experience of venetoclax monotherapy in routine clinical practice.

Material and Methods

The UK CLL Forum invited UK clinicians to contribute data on patients with R/R CLL, treated with venetoclax within the named-patient schemes from August 2015 to November 2017. Patient data from 44 participating centres were collected using a pre-specified extraction sheet including details on: baseline characteristics; duration of first remission; number of prior lines of therapy; *TP53* status prior to venetoclax; duration of prior BCRi and reasons for BCRi discontinuation; histological transformation events; objective response per International Workshop on CLL (iwCLL) criteria (Hallek *et al*, 2018); and use of rasburicase. For AE data, given the nature of the study, we focused on elective and unplanned hospitalisations, infection episodes, tumour lysis syndrome (TLS) events, dose interruptions and permanent discontinuation. TLS events were defined according to the Howard criteria, which specify criteria for laboratory and clinical TLS (Howard *et al*, 2011). Follow-up was censored at the most recent hospital visit or death. The database was locked in August 2018 for analysis.

PFS was defined as the time from the start of venetoclax until PD or death from any cause, discontinuation-free survival (DFS) was defined as the time from the start of venetoclax until discontinuation or death, and OS was defined as the time from start of venetoclax to time of death from any cause. Duration of response (DOR) was measured from the date of best response until PD date. Patients who died of unrelated causes were censored at death. Survival analyses were calculated in standard fashion by Kaplan-Meier analysis (Kaplan & Meier, 1958). Univariable and multivariable Cox regression was used to examine the associations between baseline factors, PFS and OS (Cox, 1972). Chi squared or Fisher's exact tests were used to compare ORR rates between different baseline groups. Statistical analyses were performed in STATA 15.1 (StataCorp, College Station, TX, USA).

Patients were treated with venetoclax in line with the EMA label, employing the now established weekly ramp-up phase from 20 mg o.d. to 400 mg o.d., and typically received monotherapy until PD, toxicity or death. Data on any additional therapies given alongside venetoclax (indicated, for example, for autoimmune phenomena), including anti-CD20 monoclonal antibody therapy, were also collected.

Patients were assessed by their treating clinician according to the iwCLL criteria (Hallek *et al*, 2018), although bone marrow biopsies and computed tomography imaging was not uniformly undertaken given the nature of this RWD collection. Data on MRD evaluation by flow cytometry of peripheral blood (as per the European Research Initiative on CLL consensus recommendations) (Rawstron *et al*, 2018) were collected where available.

Results

We present data on 105 patients who commenced venetoclax between August 2015 and November 2017. The median age was 67 years (range 39-87) with a predominance of males (73% male, 27% female) (Table I). Patients had received a median of 3 prior lines of therapy (range 1-15 lines). Prior to venetoclax, the Eastern Cooperative Oncology Group performance status (ECOG PS) was 0-1 in 74% (78/105) and 2-3 in 26% (27/105). Forty-eight percent of patients had evidence of *TP53* disruption defined by either a *TP53* deletion by fluorescence *in situ* hybridisation (FISH) analysis or *TP53* abnormality by mutational analysis. *TP53* status was unknown in 2 patients.

At second or subsequent line of therapy, 60% (62/104) of patients had received ibrutinib or another BTK inhibitor (BTKi) and no prior Pi3K inhibitor (Pi3Ki), 25% (26/104) of patients had received idelalisib or another Pi3Ki (duvelisib; n=1) and no prior BTKi, 10% (10/105) had received both a prior BTKi and Pi3Ki (Table I). Tirabrutinib was the only other BTKi used (n=2). One patient may have previously been exposed to idelalisib within a blinded randomised trial (excluded from all BCRi analyses). Only 6% (6/105) patients were BCRi-naive.

Patients had discontinued BCRi therapy because of toxicity in 44% (48/109 total BCRi treatment lines) and PD in 54% (59/109 treatment lines). According to BCRi subgroup, 36% (27/73) stopped BTKi due to toxicity and 64% (46/73) due to PD whilst 58% (21/36) stopped PI3Ki due to toxicity and 36% (13/36) due to PD. Two (2%) patients stopped PI3Ki with responsive disease with the clinician's intention of achieving a deeper response prior to allogenic stem cell transplantation (alloSCT). The median duration of BTKi and PI3Ki therapy was 15 (range 0.25-48) months and 8.5 (range 1-27) months, respectively. The median interval from BTKi and PI3Ki discontinuation to starting venetoclax was 50 (range -2 to 976) days and 125 (range 0-837) days respectively.

Additional therapy received alongside venetoclax was noted in 15% (16/105) patients and included rituximab (n=7), steroids (n=5), obinutuzumab (n=1), ibrutinib (n=1), both rituximab and steroids (n=1) and unknown (n=1).

By pre-defined criteria (https://www.venclextahcp.com/venclexta-dosing-regimen/tumor-lysis-syndrome-risk-assessment.html), the TLS risk was low, intermediate or high in 27% (28/105), 25% (26/105) and 48% (50/105) patients respectively (Table I). TLS risk was not classified in 1 patient. Seventy-two percent (73/102) of patients received ≥1 dose of rasburicase as TLS prophylaxis. Overall, patients received a median of 2 doses of rasburicase (range 0-17) and were electively admitted to an inpatient bed for a median of 1 (range 0-6) occasion(s). Sixty-two percent (65/105) of the cohort were elective admitted during dose escalation at least on 1 occasion.

Response rates and survival outcomes

The ORR of venetoclax monotherapy in the 105 patients was 88% (30% CR [31/105] and 58% [61/105] partial response [PR]). With a median follow-up of 15.6 months (range 26 days-32.9 months), 33 patients had died, 12

patients were alive having stopped venetoclax (reasons: PD [n=3], alloSCT [n=7], toxicity [n=2]) and 60 patients remain on venetoclax. Seven other patients had stopped venetoclax for toxicity but had subsequently died.

The ORR in patients who received a prior BTKi was 85% (CR 23%, PR 62%), a prior Pi3Ki was 92% (CR 38%, PR 54%) and 80% (CR 20%, PR 60%) for the 10 patients who were previously exposed to both BCRi classes. All 6 BCRi-naïve patients responded (ORR 100%) with 5 (83%) documented CRs (Table II, Fisher's exact p=0.59 for ORR comparing the four groups). The ORR in patients without *TP53*-disruption was 89% (CR 28%, PR 61%), and 86% (CR 32%, PR 54%) for those with *TP53* disruption (Chi-squared, p=0.68).

The median PFS was not reached, with a 1-year PFS of 65.0% (95% CI 54.7-73.6) and 60.9% (95% CI 50.1-70.0) at the median follow-up of 15.6 months. The median OS was 21.1 months, a 1-year OS 75.1% (95% CI 65.4-82.5) and 69.5% (95% CI 58.9-77.9) at the median follow-up of 15.6 months (Fig 1A-B).

Duration of response

The time to best ORR in the 92 responsive patients was 3.7 months (range 0.7-18.1 months) with a median DOR not reached and 75.4% (range 62.0-84.7) of patients achieving a DOR of 1 year or greater. The median time to PR as best response was 3.4 months (range 0.2-14.8) and CR as best response was 4.5 months (range 0.7-18.1). Of those patients obtaining a PR, 64.8% (95% CI 44.9-79.0) had a DOR of 1 year compared to 91.8% (95% CI 70.9-97.9%) at 1 year for those reaching CR. (Fig 2A). Patients responding to venetoclax experienced a longer survival than non-responders. Notably, the depth of response influenced OS; patients achieving CR experienced a superior OS compared to patients achieving PR. OS at 6 months for patients achieving CR was 100%, PR 83.8 % (95% CI 71.1-78.5), SD 25% (95% CI 8.9-66.5) and PD 22% (95% CI 3.4-51.3). The PFS rate at 12 months for complete responders was 95.7% (95% CI 72.9-99.4) and 66.4% (95% CI 50.0-78.5) for partial responders (Fig 2B).

Outcome according to BCRi discontinuation

We evaluated by reason for BCRi discontinuation in the 86 patients exposed to a *single* BCRi (i.e. analysis excluding the dual BCRi exposed [n=10], BCRi-naïve patients [n=6], the single patient on a blinded trial [n=1] and those stopped to obtain a deeper response [n=2]). The ORR to venetoclax in patients stopping a BCRi for toxicity was 92% (33/36; CR 22%; PR 69%) and for those with CLL progression on a BCRi was 84% (42/50; CR 28%;PR 56%; p=0.67). The PFS and OS were not statistically significantly different according to whether a patient had been exposed to a BTKi only, a PI3Ki only, or both. None of the BCRi-naïve patients treated with venetoclax has experienced progression to date (Fig 3A-B). For the whole cohort, those patients stopping BCRis for progression appeared to have an inferior PFS compared to patients stopping for reasons other than PD (toxicity n=46; deeper response required n=2), although this reached borderline statistical significance. In the 99 patients who were previously BCRi exposed, the risk of progression or death for patients stopping a prior BCRi for PD was double compared to those stopping for other reasons (predominantly toxicity) (hazard ratio [HR] 2.01 [0.99-4.05], p=0.05) (Fig 3C).

Nine patients who received venetoclax as a therapeutic bridge to alloSCT all responded to venetoclax. All patients stopped venetoclax prior to alloSCT and did not restart venetoclax following engraftment. Two patients have died following alloSCT, both from infection at 7.1 and 4.7 months after stopping venetoclax. The remaining 7 patients all remain in remission at a median of 14.6 (range 4.4 - 17.5) months following cessation of venetoclax.

Univariable and Multivariable Analyses

We wished to explore whether factors such as *TP53* disruption, number of prior lines of therapy and ECOG PS were associated with survival outcomes following venetoclax. These factors were included alongside a series of additional baseline factors within a univariable and multivariable analysis of PFS and OS (Supplementary Table I and II). Poorer baseline ECOG PS was associated with inferior PFS (HR compared to ECOG 0: 4.02 [1.36-11.93] for ECOG 1; 7.42 [2.43-22.64] ECOG 2; 4.29 [0.79-23.42] ECOG 3, p=0.0014) and OS (ECOG 1: 3.02 [0.98-9.34]; ECOG 2: 7.45 [2.44-22.75]; ECOG 3: 5.54 [1.00-30.70], p=0.0006) on univariable analysis. ECOG PS was the only factor that retained its significance for PFS on multivariable analysis (p=0.0026), however the number of events was still low.

There was no significant difference in PFS (p=0.27) or OS (p=0.42) when patients with *TP53*-disrupted CLL were compared to *TP53*-intact CLL (Supplementary Fig 1A-B). The number of prior treatment lines was significantly associated with PFS (HR compared to 1-2 lines: 2.52 [1.15-5.51] for 3-4 lines, 2.74 [1.06-7.12] for 5+ lines, p=0.017) within the univariable analysis (Supplementary Fig 1C-D). A similar effect was seen for OS (HR: 2.37 [1.03-5.45] for 3-4 lines, 2.24 [0.81-6.20] for 5+ lines, p=0.068) although this did not reach statistical significance. However, the number of prior treatment lines did not retain its significance for PFS on multivariable analysis (p=0.12). Age and male gender were significantly associated with inferior OS on multivariable analysis. Inferior OS was not observed in *TP53*- disrupted patients (HR disrupted *vs* non-disrupted: 1.62 [0.70-3.72], p=0.34).

Minimal residual disease

MRD was assessed by multi-colour flow cytometry on peripheral blood in 27% (28/105) after commencing venetoclax treatment. Of those assessed, 39% (11/28) had undetectable MRD ($<10^{-4}$) (7 patients in CR; 4 in PR) and 61% (17/28) were positive (2 CR; 15 PR). Eleven patients achieved undetectable MRD at a median of 8.3 months (range 4.5-10.4) with 1 patient subsequently experiencing a clinical relapse 3.7 months later. The other 10 MRD-negative patients have been followed for a median of 6.8 months (range 3-23.7) since achieving MRD negativity with no further clinical relapses at the time of database lock (Supplementary Fig 2A).

AEs, venetoclax dose reductions and discontinuations

Venetoclax was generally well tolerated. During the course of venetoclax, 41% (43/105) patients had either a dose reduction or treatment interruption due to an AE. However, these patients were *not* more likely to

discontinue venetoclax permanently due to an AE. In total, 8% (8/105) stopped venetoclax permanently due to toxicity (6.5% [4/58] in no prior dose reduction group versus 9.3% [4/43] temporary prior dose reduction group [p=0.71]). Dose reduction or temporary interruption of venetoclax did not appear to result in an inferior PFS or DFS (Supplementary Fig 2B-C). There were no treatment-related deaths.

Overall, 43% (45/105) have stopped venetoclax. Discontinuation was most commonly due to PD (CLL; n=14, Richter transformation (RT); n=9). Nine patients stopped prior to alloSCT, 7 patients stopped due to toxicity, 5 due to death from unrelated causes (1 congestive cardiac failure [CCF], 1 cerebrovascular accident [CVA], 1 intracranial haemorrhage and 1 metastatic squamous cell carcinoma, 1 acute myeloid leukaemia [AML]) and 1 due to frailty.

Unplanned hospital admissions whilst on venetoclax occurred in 42% (44/103) of cases (median 0 (range 0-6)). Reasons for the unplanned admissions are outlined in Supplementary Table III. The dominant reason for admission was infection (22 episodes of infection non-otherwise specified, and 1 episode of neutropenic fever). There was 1 case of clinical TLS, 1 separate case of biochemical TLS and 1 case of isolated hyperphosphataemia. All 3 patients reached full dose and recovered with no clinical sequalae within the ramp-up phase.

To date, 33 patients have died in this cohort; 13 from PD of CLL, 10 from RT (1 B-PLL, 6 DLBCL, 1 unknown histology and 2 clinically suspected but not confirmed by histology), 3 from infection, and 7 from other causes (1 CVA, 1 CCF, 1 intracranial haemorrhage, 1 general frailty/poor nutrition, 1 metastatic squamous cell carcinoma, 2 AML).

Survival outcomes post progression

In total, 27 patients experienced PD due to CLL or RT on venetoclax. Five patients continued venetoclax beyond CLL PD with 2 patients still on venetoclax and 3 patients having subsequently died (1 CLL, 1 RT, 1 infection). Of the remaining 22 patients, 13 progressed with CLL and 9 with RT (1 patient also stopped venetoclax for toxicity and later developed RT). All patients with RT have died and 10/13 patients with CLL progression have died. Of all 27 patients with PD events on venetoclax, 5 remain alive with a median OS of 1.5 months (95% CI 0.4-8.0 months) (Fig 4A-B).

Of those that progressed with RT, 2 patients are known to have received further therapy. One patient received 2 cycles of RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone) then 2 cycles of RGDP (rituximab, gemcitabine, dexamethasone, cisplatin) but failed to respond. The second patient received 3 cycles of RCHOP then 3 cycles of RGDP but failed to respond. Seven other RT patients received supportive palliative care and subsequent therapy was unknown in 1 patient. Of the 13 patients that progressed with CLL, 1 patient received palliative radiotherapy, 7 patients received best supportive care and subsequent therapy was unknown in 4 patients.

Discussion

We report on a large UK series of the earliest venetoclax-treated R/R CLL patients outside of the clinical trial setting. Our cohort represents the majority of the patients treated within the early access schemes prior to formal venetoclax approval (105 patients of approximately 130). As is typical for early access schemes, patients were heavily pre-treated and had high-risk clinical features. The vast majority were BCRi exposed and almost half had evidence of *TP53*-disruption. Our dataset clearly demonstrates the efficacy of venetoclax monotherapy in routine practice for patients across a large and representative range of academic and non-academic centres with R/R, high-risk CLL with ORR, DOR and PFS comparable to clinical trial cohorts (Jones *et al*, 2017; Stilgenbauer *et al*, 2016; Coutre *et al*, 2018) and recently published US RWD (for example, 1-year PFS 65% compared to 1-year PFS 68% in US RWD)(Mato *et al*, 2018b). Our data provide the first evidence in the non-trial setting of equivalent efficacy and survival in patients exposed to BTKi, PI3Ki or both classes of BCRi. Notably, and by contrast to recently published US RWD (Mato *et al*, 2018b), we did not find significant differences in response or survival outcomes according to *TP53* status. Consistent with a pooled analysis of 3 clinical trials of venetoclax monotherapy (Wierda *et al*, 2017b), we demonstrate that more heavily pre-treated patients had an inferior PFS, although significance was not retained as an independent predictive factor in a multivariable analysis. In fact, the only characteristic that was significantly associated with inferior PFS in a multivariable model was ECOG PS. Twenty-eight percent had an ECOG PS >1 and thus would not have been eligible for the venetoclax clinical studies (Jones *et al*, 2017; Coutre *et al*, 2018; Stilgenbauer *et al*, 2016). Clearly, ECOG PS is influenced by a range of patient and disease characteristics (for example, prior therapeutic lines and disease biology) although we could not find a clear statistical interaction between ECOG and *TP53* status or prior lines of therapy (data not shown). However, the number of patients and events in the subgroups are relatively small so no strong conclusions can be drawn.

We provide further evidence of the safety and tolerability of venetoclax in the non-trial setting across a range of hospitals and demonstrate that dose attenuation and temporary treatment interruptions did not impact on PFS or OS. However, we cannot exclude survival bias within this specific analysis i.e. patients with superior survival may be more likely to have dose attenuation over time. Our reported rate of clinical and biochemical TLS is that which resulted in unplanned admission and, as such, the rate may differ compared to series reporting all cases of biochemical TLS. Notwithstanding this caveat, the TLS rate of 1% is consistent with that reported in clinical trials (Stilgenbauer *et al*, 2016; Davids *et al*, 2018) following the modifications to the dosing schedule to mitigate against TLS risk. The rate of TLS in our series is lower than the US RWD set. The reasons for this are not fully clear but may be related to risk assessment and prophylaxis strategies. We recognise the potential bias for under-reporting those cases without unplanned admission and misclassification according to the Howard criteria (Howard *et al*, 2011). However, there was no demonstrable evidence concerning toxicities associated with TLS in our series.

By contrast to published non-clinical trial BCRi data, where toxicity was the most common reason for BCRi discontinuation (followed by CLL PD (Mato *et al*, 2018a)), PD was the commonest reason for venetoclax discontinuation. These data are strikingly similar to results reported by Mato *et al*, (2018b) (22/45 PD [CLL and RT] and 7/45 toxicity in the present UK series; 22/41 PD [CLL and RT] and 9/41 toxicity in the US series).

We provide the first evidence of a superior PFS for venetoclax-treated patients who discontinued BCRi for toxicity as compared to those who experienced progression on BCRi; the latter group of patients were twice as likely to progress or die following venetoclax compared to those failing BCRi for an alternative cause (predominantly toxicity) (HR 2.01 [0.99-4.05] p=0.05). Consistent with data from clinical trials, we observed durable responses in patients obtaining CR and those achieving undetectable MRD in peripheral blood (including patients in PR). Although follow-up durations for both trial and non-trial cohorts are still relatively short, it seems likely that depth of response to venetoclax will translate into prolongation of PFS. Data such as these may be of particularly use when considering the role of consolidation therapy, for example alloSCT, in a selected, fit subgroup of R/R CLL patients obtaining responses on venetoclax. We also clearly demonstrate that patients who fail to respond to, or progress following, venetoclax have a dismal outcome with very limited survival. The unmet clinical need has therefore shifted to patients who fail both BCRi and venetoclax. Developing effective novel agents for such patients will prove challenging, not least because of the disease kinetics and short survival times but also because of the relatively high proportion of RT.

Our study has a number of limitations. Although our data were collected from representative UK centres, retrospective data collection is subject to the inherent biases of patient level data collection, AE reporting and response assessment. Recognising this, we attempted, where possible, to mitigate against such biases by applying established criteria and focusing on the most objective parameters. For example, we assigned reported 'clinical complete responses' (without bone marrow biopsy confirmation) as partial responses in line with iwCLL criteria. Similarly, we sought TLS data in line with established criteria. Moreover, we pragmatically limited our data collection to focus on routinely available clinical factors and simple venetoclax dosing information and thus did not request information on *IGHV* mutational status, cytogenetic information beyond *TP53* status, or detailed information on maximum venetoclax dose reached and relative dose intensity. Consequently, we were able to achieve a near complete study database.

These limitations notwithstanding, our study details a large, multi-centre early experience of venetoclax in R/R CLL, demonstrating responses and survival outcomes consistent with published trials and US RWD. Importantly, we observed responses in patients exposed to either or both BTK and Pi3K inhibitor(s) and demonstrate, for the first time outside clinical trials, favourable clinical outcomes of patients obtaining CR and/or those achieving undetectable peripheral blood MRD. Patients with progression post-BCRi and venetoclax as sequential monotherapies remain a major challenge, but we look forward to emerging data from prospective trials investigating venetoclax in combination with BCRi and monoclonal antibody therapies

(Seymour *et al*, 2018; Hillmen *et al*, 2017). Combinatorial targeted approaches aimed at eradicating detectable MRD earlier in therapy are likely to impact favourably on how we approach CLL therapy in future.

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Table I: Patient Demographics, Baseline Clinical Characteristics, Prior BCR inhibitor and Venetoclax dosing

Baseline Characteristics	Post-BTKi alone (n = 62)	Post-Pi3Ki alone (n = 26)	Post-BTKi and -Pi3K (n = 10*)	BCRi-naïve (n = 6)	All patients (n = 105)
Age prior to Venetoclax use (n = 105) (median and range in years)	68 (46-86)	65 (39-87)	66 (59-77)	72 (61-79)	67 (39-87)
Gender					
Male	42 (69%)	22 (85%)	9 (90%)	3 (50%)	77 (73%)
Female	20 (31%)	4 (15%)	1 (9%)	3 (50%)	28 (27%)
Prior lines of therapy pre-Venetoclax (median and range)	3 (1-5)	2.5 (1-7)	5 (3-15)	1 (1-3)	3 (1-15)
ECOG PS at start of Venetoclax					
ECOG PS 0	17 (27%)	11 (42%)	3 (30%)	1 (17%)	32 (30%)
ECOG PS 1	28 (45%)	8 (31%)	6 (60%)	4 (67%)	46 (44%)
ECOG PS 2	14 (23%)	6 (23%)	1 (10%)	1 (17%)	23 (22%)
ECOG PS 3	3 (5%)	1 (4%)	0 (0%)	0 (0%)	4 (4%)
Relapsed or Refractory within 3 years of purine analogue					
Yes	22 (35%)	7 (27%)	3 (30%)	0 (0%)	32 (30%)
No	40 (65%)	19 (73%)	7 (70%)	6 (100%)	73 (70%)
***TP53*-disrupted**					
Yes	36 (58%)	10 (38%)	4 (36%)	0 (0%)	50 (48%)
No	24 (39%)	16 (62%)	6 (64%)	6 (100%)	53 (50%)
Not known	2 (3%)	0 (0%)	0 (0%)	0 (0%)	2 (2%)
Prior BTKi					
Duration of prior BTKi (**n = 73**) (median and range in months)	16 (1-48)	N/A	9 (0.25-35)*	N/A	15 (0.25-48)
Reasons for stopping BTKi					
PD	42 (68%)	N/A	4 (36%)	N/A	46 (64%)
Toxicity	20 (32%)	N/A	7 (64%)*	N/A	27 (36%)
Deeper response required	0 (0%)	N/A	0 (0%)	N/A	0 (0%)
Prior Pi3Ki					
Duration of prior Pi3Ki (**n = 36**)* (median and range in months)	N/A	8 (1-27)	9.5 (1-26)*	N/A	8.5 (1-27)
Reasons for stopping Pi3Ki					

PD	N/A	8 (31%)	5 (50%)	N/A	13 (36%)
Toxicity	N/A	16 (62%)	5 (50%)	N/A	21 (58%)
Deeper response required	N/A	2 (8%)	0 (0%)	N/A	2 (6%)
Prior BCRi					
Duration of prior BCRi (**n = 109**)* (median and range in months)	N/A	N/A	N/A	N/A	12 (0.25-48)
Reasons for stopping BCRi					
PD	N/A	N/A	N/A	N/A	59 (54%)
Toxicity	N/A	N/A	N/A	N/A	48 (44%)
Deeper response required	N/A	N/A	N/A	N/A	2 (2%)
TLS group					
High	28 (45%)	12 (46%)	4 (40%)*	5 (83%)	50 (48%)
Intermediate	16 (26%)	6 (23%)	4 (40%)	0 (0%)	26 (25%)
Low	18 (29%)	7 (27%)	2 (20%)	1 (17%)	28 (27%)
Not known	0 (0%)	1 (4%)	0 (0%)	0 (0%)	1 (1%)
Doses of rasburicase* **	2 (0-17)	2 (0-7)	2 (0-7)	1 (0-3)	2 (0-17)
Number of elective admissions (median and range)	1 (0-6)	2 (0-6)	2 (0-4)	0.5 (0-3)	1 (0-6)
Number of unplanned admissions (median and range)	0 (0-6)	0 (0-6)	0 (0-5)	0 (0-1)	0 (0-6)
Additional therapy alongside Venetoclax					
Bridging Steroids	3	1	1	0	5
Rituximab	5	1	1	0	7
Other**	3	0	1	0	4
Venetoclax dose attenuation					
Yes	28 (45%)	8 (31%)	4 (36%)	3 (50%)	43 (41%)
No	34 (55%)	18 (69%)	7 (64%)	3 (50%)	62 (59%)
Venetoclax stopped permanently due to related AE					
es	6 (10%)	2 (8%)	0 (0%)	0 (0%)	8 (8%)
o	56 (90%)	24 (92%)	11 !100%)	6 (100%)	97 (92%)

*=1 patient in blinded trial of idelalisib therefore uncertain whether received

Abbreviations: AE: adverse event; BCRi: B cell receptor inhibitor; BTKi: Bruton tyrosine kinase inhibitor; ECOG PS: Eastern Cooperative Oncology Group performance status; N/A: not applicable; PD: progressive disease; Pi3Ki: phosphoinositide 3-kinase inhibitor; TLS: tumour lysis syndrome

Table II: Best Objective Response and outcomes With Venetoclax

	Post-BTKi alone (n = 62)	Post-Pi3Ki alone (n = 26)	Post-BTKi and -Pi3K (n = 10)*	BCRi-naïve (n = 6)	All patients (n = 105)
Overall response rate					
CR	14 (23%)	10 (38%)	2 (20%)	5 (83%)	31 (30%)
Clinical PR / PR	39 (62%)	14 (54%)	6 (60%)	1 (17%)	61 (58%)
Clinical SD / SD	2 (3%)	1 (4%)	1 (10%)	0 (0%)	4 (4%)
Clinical PD / PD	7 (11%)	1 (4%)	1 (10%)	0 (0%)	9 (9%)
ORR	53 (85%)	24 (92%)	8 (80%)	6 (100%)	92 (88%)
Ongoing patients on venetoclax	33 (53%)	14 (54%)	7 (70%)	6 (100%)	60 (58%)
Reasons for permanent discontinuation of venetoclax					
CLL PD	9 (15%)	1 (4%)	3 (27%)	0 (0%)	13 (12%)
AlloSCT	4 (6%)	4 (15%)	1 (9%)	0 (0%)	9 (9%)
Richter transformation (biopsy confirmed or suspected)	7 (11%)	2 (8%)	0 (0%)	0 (0%)	9 (9%)
toxicity**	6 (10%)	2 (8%)	0 (0%)	0 (0%)	8 (8%)
other	1 (2%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)
unrelated deaths	2 (3%)	3 (12%)	0 (0%)	0 (0%)	5 (5%)
Death					
Yes	21 (34%)	8 (31%)	3 (30%)	0 (0%)	33 (31%)
No	41 (66%)	18 (69%)	7 (64%)	6 (100%)	72 (69%)

*=1 patient in blinded trial of idelalisib therefore uncertain if received

** = 1 patient that stopped due to toxicity subsequently developed Richter Transformation

Abbreviations: AE: adverse event; AlloSCT: allogeneic stem cell transplantation; BCRi: B-cell receptor inhibitor; BTKi: Bruton tyrosine kinase inhibitor; CLL: chronic lymphocytic leukaemia; CR: complete response; ORR: overall response rate; PD: progressive disease; Pi3Ki: phosphoinositide 3-kinase inhibitor; PR: partial response; SD: stable disease; TLS: tumour lysis syndrome.

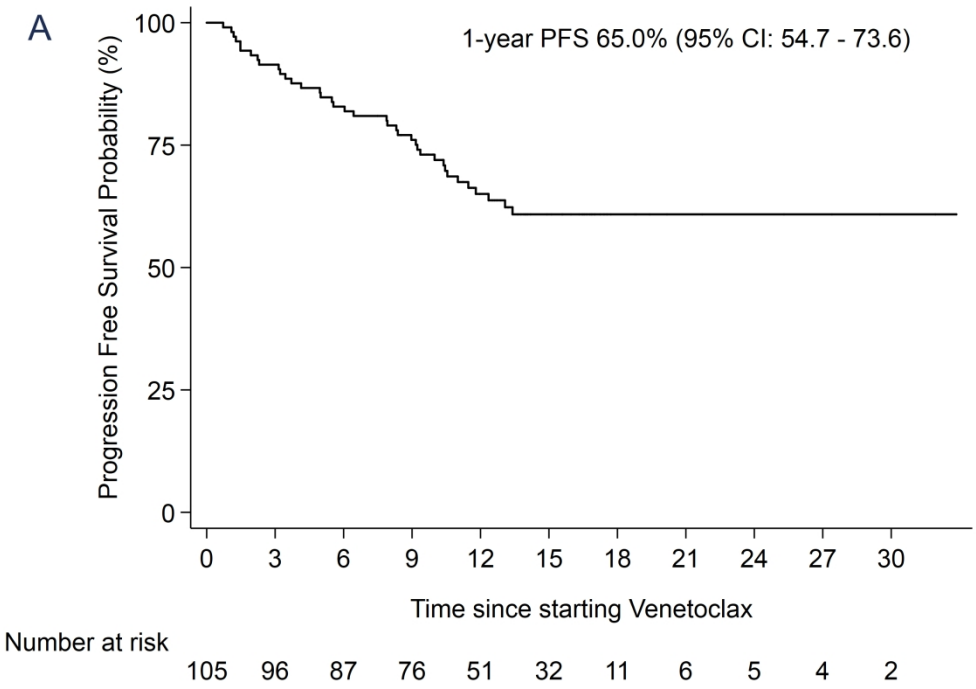
Figure legends

Figure 1. Survival curves for all patients.
A: Progression-free survival of all patients
B: Overall survival of all patients
CI: confidence interval; OS: overall survival; PFS: progression-free survival.

Figure 2. Duration of response and overall survival.
A: duration of response according to remissions status
B: overall survival according to response
*clinical complete responses (without bone marrow biopsy confirmation) were assigned as partial responses in line with iwCLL criteria (Hallek *et al* 2018)
CI: confidence interval; CR: complete response; OS: overall survival; PD: progressive disease; PR: partial response; SD: stable disease.

Figure 3. Survival according to B cell receptor inhibitor.
A: Progression-free survival according to prior B cell receptor inhibitor exposure
B: Overall survival according to prior B cell receptor inhibitor exposure
C: Progression-free survival according to reason for stopping prior B cell receptor inhibitor
BCRi: B-cell receptor inhibitor; BTKi: Bruton tyrosine kinase inhibitor; CI: confidence interval; HR: hazard ratio; PD: progressive disease; Pi3Ki: phosphoinositide 3-kinase.

Figure 4. Overall survival following progression on venetoclax.
A: Overall survival following progression on venetoclax
B: Overall survival following progression on venetoclax according to cause of progression
CI: confidence interval; CLL: chronic lymphocytic leukaemia; OS: overall survival;



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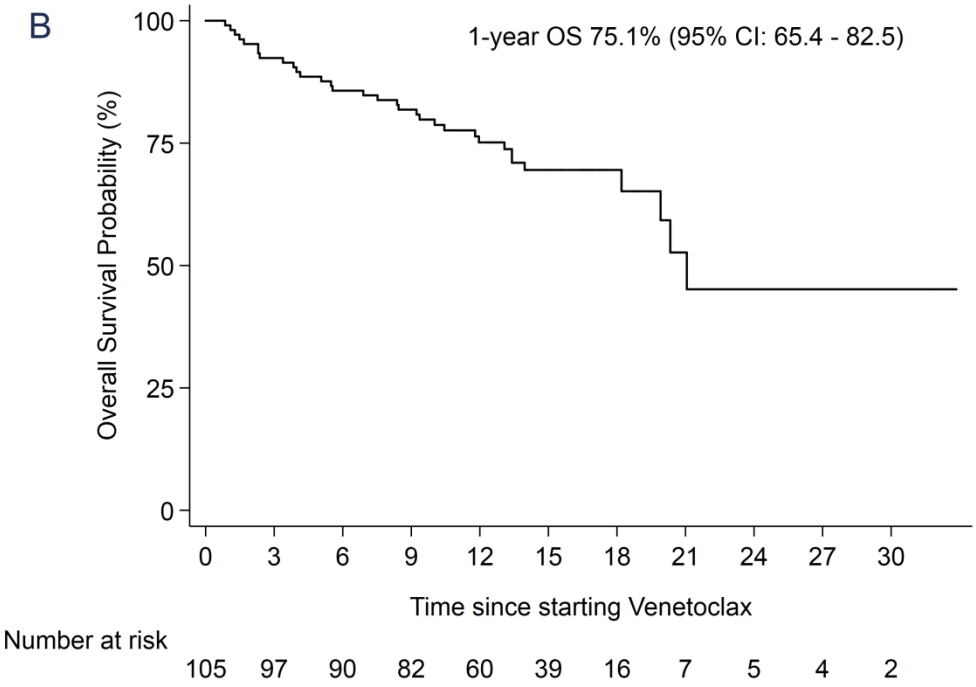

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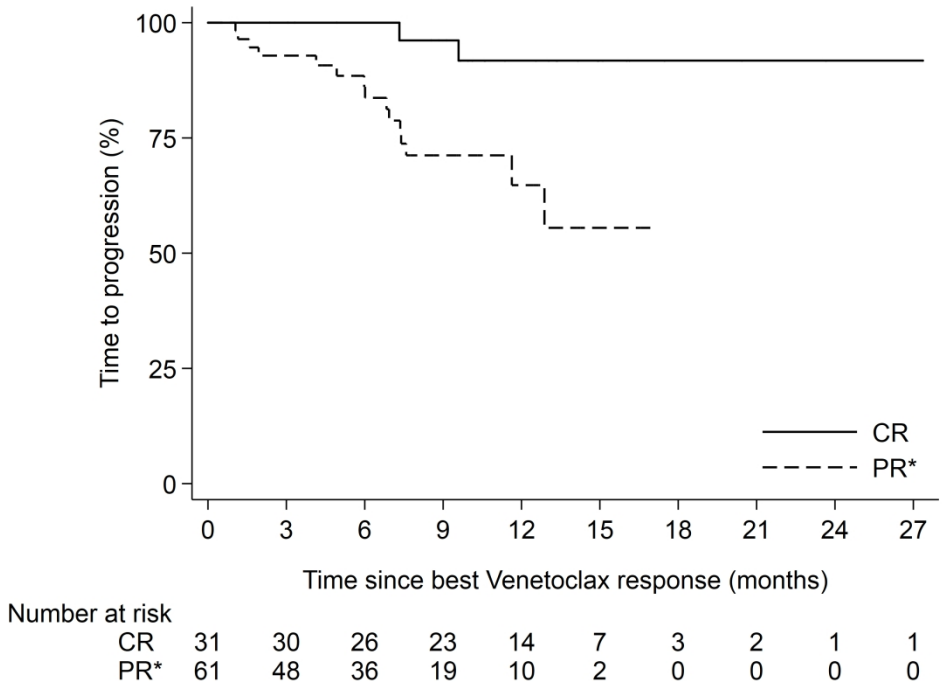

Number at risk

CR	31	30	26	23	14	7	3	2	1	1
PR*	61	48	36	19	10	2	0	0	0	0

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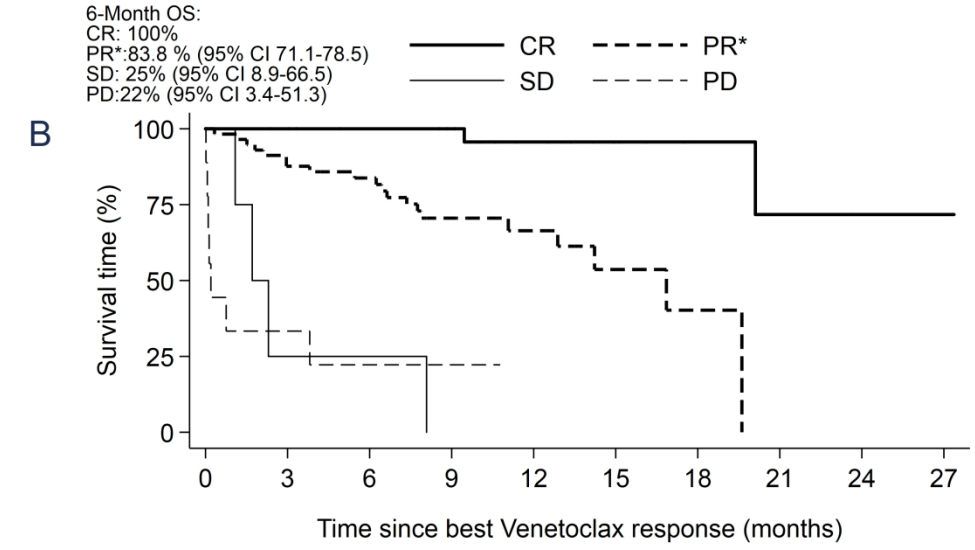

Number at risk

CR	31	30	26	24	15	8	4	2	1	1
PR*	61	49	39	25	16	5	1	0	0	0
SD	4	1	1	0	0	0	0	0	0	0
PD	9	3	2	1	0	0	0	0	0	0

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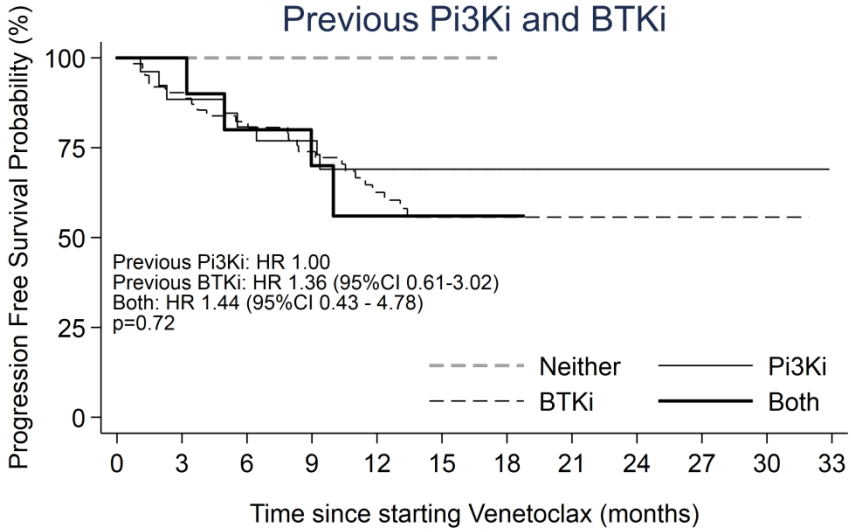

Number at risk

Neither	6	6	6	5	4	2	0	0	0	0	0	0
Pi3Ki	26	23	21	20	14	9	3	1	1	1	1	0
BTKi	62	56	51	44	30	18	7	5	4	3	1	0
Both	10	10	8	6	3	3	1	0	0	0	0	0

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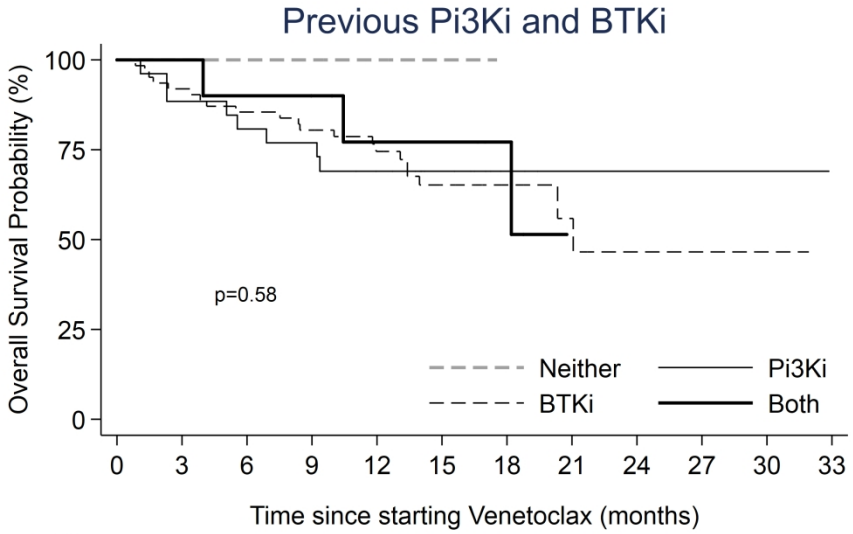
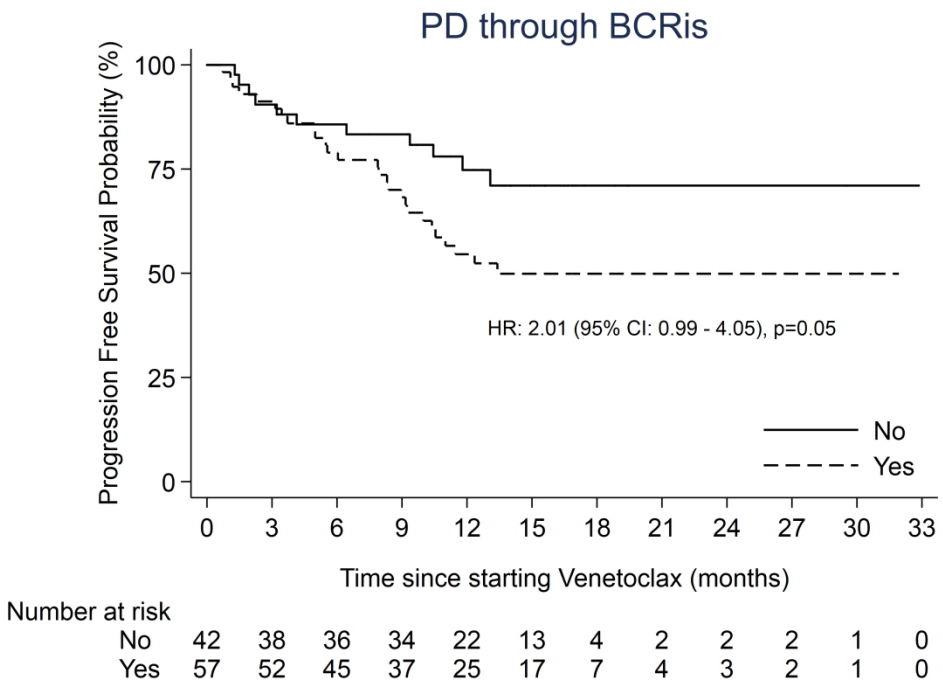


Number at risk

Neither	6	6	6	5	4	2	0	0	0	0	0	0
Pi3Ki	26	23	21	20	14	9	3	1	1	1	1	0
BTKi	62	57	53	48	36	22	9	6	4	3	1	0
Both	10	10	9	8	5	5	3	0	0	0	0	0

1058x769mm (72 x 72 DPI)



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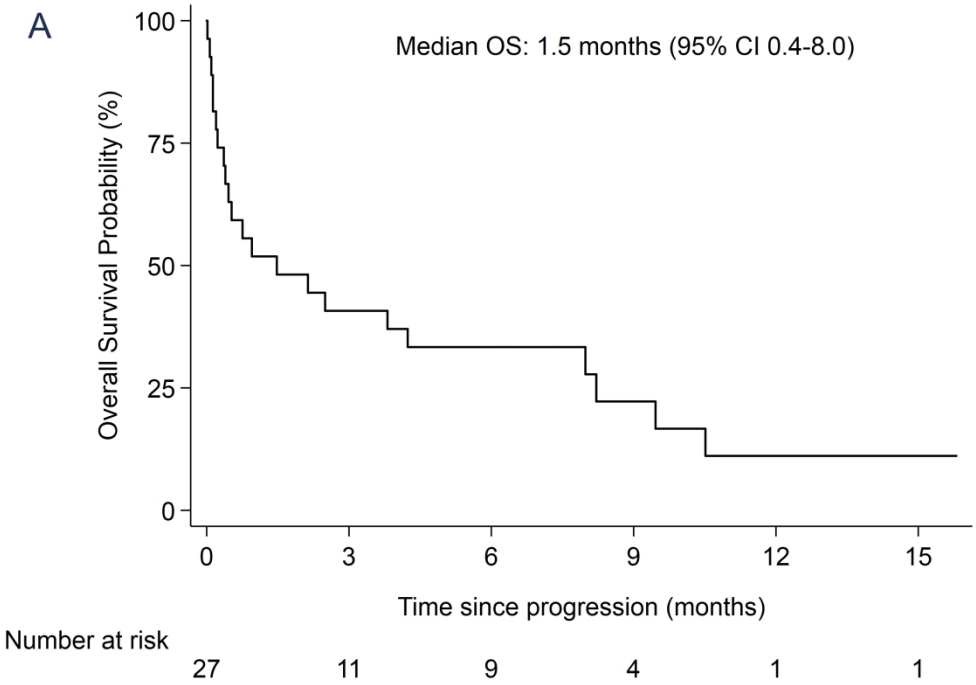

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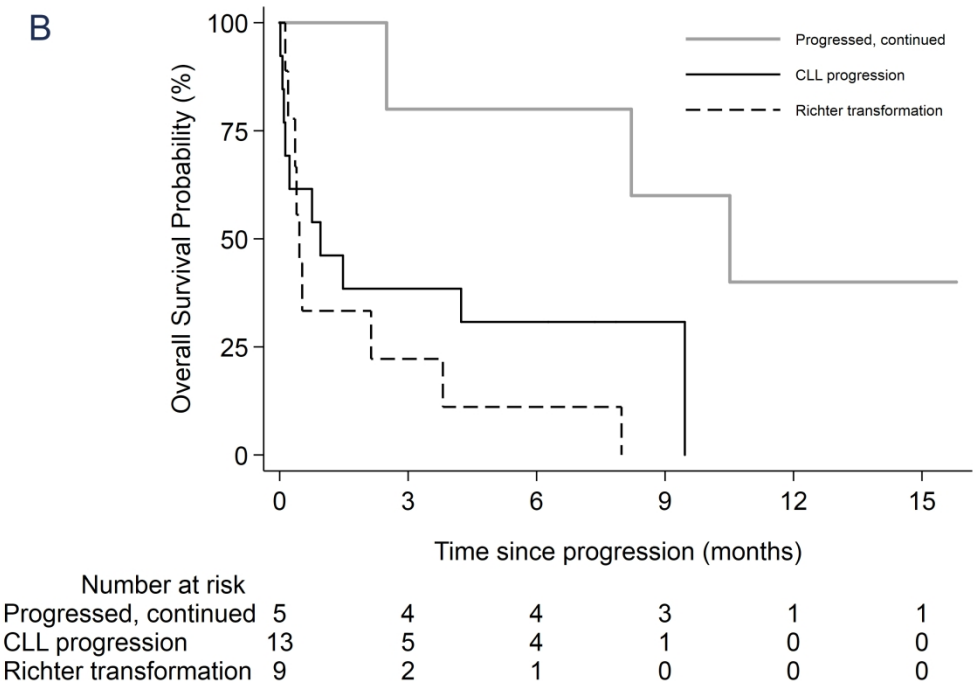

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~~Title Page~~

Efficacy of venetoclax monotherapy in patients with relapsed chronic lymphocytic leukaemia in the ~~post~~ post-BCR inhibitor setting: a UK wide analysis

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Running title: Venetoclax efficacy in relapsed, refractory CLL

Key Words: chronic lymphocytic leukaemia; B cell receptor inhibitor, ibrutinib, idelalisib, p53 venetoclax; BCL2.

~~Conflicts of Interest – TAE: Roche: Honorarium, Gilead: Honorarium; Research support; Travel to scientific conferences, Janssen: Honorarium, Abbvie: Honorarium; Travel to scientific conferences. AS receives honoraria from Abbvie, Gilead, Janssen, Roche and unrestricted educational grants from Janssen and Gilead. CPF: Janssen: Speaker and Consultancy honoraria, AbbVie: Research grant, speaker and consultancy honoraria, Gilead: Research grant, travel support and consultancy honoraria, Roche: Research grant, speaker and consultancy honoraria, Celgene: speaker and consultancy honoraria. AB: speakers fees, consultancy fees, honoraria and travel grants from Abbvie and Gilead, and consultancy fees from Roche and Janssen. NS: consultancy fees from Abbvie. PEMP: Honoraria: Gilead, Roche, Abbvie, Janssen. Research funding: Roche and Gilead. Abbvie – speaker, conference funding, consultancy, consultancy honoraria. Janssen – speaker, conference funding, consultancy honoraria. RW: Takeda, Gilead, Chugai, Abbvie, Janssen: sponsoring conferences, Abbvie: preparing educational material, Gilead: speaker, Gilead – speaker, conference funding, consultancy honoraria. FF: Roche, Abbvie: consultancy honoraria. None of the other authors have any conflicts of interest to declare.~~

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~~Supplemental Files: 2~~

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Abstract

Venetoclax is a BCL2 inhibitor with activity in relapsed/refractory (R/R) chronic lymphocytic leukaemia (CLL). We conducted a multi-centre retrospective analysis of 105 R/R CLL patients who received venetoclax pre-National Health Service commissioning. The median age was 67 years and median prior lines was 3 (range: 1-15). 48% had *TP53* disruption. At ≥2 lines, 60% received a Bruton Tyrosine Kinase inhibitor (BTKi) and no prior phosphoinositide 3-kinase ~~Pi3K~~ inhibitor (Pi3Ki), 25% received a Pi3Ki and no prior BTKi, and 10% received both. Patients discontinued B cell receptor inhibitor (BCRi) because of toxicity in 44% and progression in 54%. ~~TLS~~ Tumour lysis syndrome risk was low, intermediate or high in 27%, 25%, and 48% respectively. Overall response was 88% (30% complete response [CR]). ~~ORR~~ The overall response rate was 85% (CR 23%) in BTKi-exposed patients ~~was 85% (CR 23%)~~, 92% (CR 38%) in Pi3Ki-exposed patients ~~was 92% (CR 38%)~~ and 80% (CR 20%) in both ~~80% (CR 20%)~~ (p=0.59). With a median follow-up of 15.6 months, 1-year ~~PFS~~ progression-free survival was 65.0% and 1-year ~~OS~~ overall survival was 75.1%. Dose reduction or temporary interruption did not result in an inferior progression-free or discontinuation-free survival. Risk of progression or death after stopping a prior ~~B-cell receptor inhibitor (~~BCRi~~)~~ for progression was double compared to those stopping for other reasons (predominantly toxicity) (Hazard Ratio 2.01 p=0.05). Venetoclax is active and well tolerated in R/R CLL post ≥1 BCRi. Reason(s) for stopping BCRi influences venetoclax outcomes.

~~**Main Manuscript**~~

Introduction

The therapeutic landscape for patients ~~treated~~ with chronic lymphocytic leukaemia (CLL) has undergone transformative changes over recent years, particularly with the advent of novel kinase inhibitors targeting Bruton tyrosine kinase (BTK) and phosphoinositide 3-kinase (PI3K), disrupting signalling downstream of the B cell receptor (BCR) pathway. ~~(BCR).~~ Ibrutinib monotherapy and Idelalisib alongside rituximab represent modern standard of care options in patients with relapsed CLL following respective phase III trials displaying an overall survival benefit versus anti-CD20 monoclonal antibody monotherapy (Byrd *et al*, 2013; Furman *et al*, 2014).

Although many patients ~~enjoy~~ achieve durable remissions on either agent, there are no plateaus noted on progression-free survival (PFS) analyses and, as such, patients ~~with~~ receiving either agent will continue to relapse on therapy. Relapse may occur earlier in patients with *TP53* disruption (*TP53* deletion and / or *TP53* mutation) and / or complex karyotype (Byrd *et al*, 2015). Accumulating evidence suggests that many BCR inhibitor (BCRi)-treated patients outside of the clinical trial setting discontinue BTK and Pi3K inhibitors due to intolerable toxicity. For example, a recently published retrospective series reported that of 621 patients treated with ibrutinib (536 relapsed-refractory [R/R] and 80 treatment-naïve), 42% had discontinued ibrutinib at a median of 7 months. Toxicity was the dominant cause of discontinuation in both previously treatment-naïve patients (63.1%) and ~~relapse-refractory~~R/R patients (50.2%) (Mato *et al*, 2018a). Idelalisib has a well

described toxicity prolife including a considerable burden of intolerable adverse events (AEs) and treatment discontinuation (Mato *et al*, 2017a).

In light of these data, effective, non-toxic therapy in the post-BCRi setting has become a focus of clinical need. Venetoclax is a potent, selective and orally bioavailable small-molecule inhibitor of the anti-apoptotic protein BCL2, with demonstrable activity in patients with R/R CLL, including *TP53*-disrupted disease. Two phase II trials demonstrate impressive activity in these settings with an overall response rate (ORR) of approximately 80% in the ~~BCRi~~ BCRi-naïve setting (Roberts *et al*, 2015; Stilgenbauer *et al*, 2016). As a result, venetoclax was approved in the ~~EU~~ European Union for adults with *TP53*-disrupted CLL who are either unsuitable for, or have failed a BCRi and for those without *TP53* disruption who have failed both chemo-immunotherapy and a BCRi. (http://www.ema.europa. eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004106/WC500218800.pdf).

Recent data have established the clear activity of venetoclax post-BCRi. Jones ~~*and colleagues*~~*et al* (2017) demonstrated an ORR of 65% following ibrutinib ~~(Jones *et al*, 2017)~~ (n=91) with a median ~~progression-free survival (~~PFS~~)~~ of 24·7 months (95% confidence interval ~~([~~CI~~)~~] 19·2–not reached ~~([~~NR~~)),~~]), and estimated 12-month PFS of 75% (95% CI 64–83%). A separate cohort in the same trial recently reported an ORR of 67% in 36 patients who received idelalisib as their last BCRi pre-enrolment. For these patients, the median PFS had not yet been reached and estimated 12-month PFS was 79% (Coutre *et al*, 2018). Results from a small cohort within the trial of heavily pre-treated, dual BCRi exposed patients (n=28) ~~are~~ were recently reported, with a lower ORR of 39% (Wierda *et al*, 2017a).

In a recent published series, Mato ~~*and colleagues*~~*et al* (2018b) presented data from a separate US cohort outlining venetoclax monotherapy efficacy in 141 patients ~~(Mato *et al*, 2018b).~~, win which 89% had been exposed to a BCRi. Patients had received 3 prior lines and 45% had 17p deletion. The ORR was 72% (complete response [CR] 19.4%) and with a short median follow-up of 7 months, the median PFS and overall survival (OS) was not reached. The projected ~~12~~ 12-month PFS and OS ~~were~~ was 68% and 88%, respectively.

Mato ~~*and colleagues*~~*et al* (2017b) provided the largest real world data (RWD) sets of venetoclax monotherapy in relapsed CLL ~~currently in abstract form (Mato *et al*, 2017b)~~. Most of the 204 patients across US and international community and academic centres successfully completed the dose ramp-up and maintained a maximum dose of 400 mg o.d. Toxicity was manageable, and it was CLL progressive disease (PD) (47%), not toxicity (11%) that lead to most venetoclax discontinuation. The ORR was 77% (28% CR) and the median PFS and OS ~~was~~ were not reached. In this series, only 63% were exposed to BCRi ~~exposed~~ and no minimal residual disease (MRD) data were presented. Venetoclax was active in patients resistant to ibrutinib although patients with prior ibrutinib exposure and poor risk cytogenetics were associated with an inferior PFS.

It is clear that venetoclax is an effective agent in high-risk R/R CLL, including patients previously exposed to BCRi therapy. However, for the published RWD data, the median ~~follow~~ follow-up is short, there ~~are~~ is a lack of MRD response data on venetoclax and ~~there is~~ a lack of information on the impact of patient performance status (PS) on outcome.

In light of the high incidence of BCRi discontinuation in the non-trial setting (Mato *et al*, 2018a), and the demonstrable efficacy of venetoclax in the ~~post~~ post-BCRi setting, we wished to analyse the early experience of venetoclax monotherapy in routine practice. Venetoclax was available free-of-charge to named UK and Irish patients from 2015, initially prior to European Medicines Agency (EMA) approval via a named-patient scheme and subsequently through the early access to medicine ~~(EAMS)~~ scheme prior to National Health Service (NHS) commissioning. Thus, a defined consecutive cohort of patients was available for evaluation, representing early experience of venetoclax monotherapy in routine clinical practice.

Material and Methods

The UK CLL Forum invited UK clinicians to contribute data on patients with R/R CLL, treated with venetoclax within the named-patient schemes from ~~08/~~ August 2015 to ~~11/~~November 2017. Patient data from 44 participating centres were collected using a pre-specified extraction sheet including details on: baseline characteristics; duration of first remission; number of prior lines of therapy; *TP53* status prior to venetoclax; duration of prior BCRi and reasons for BCRi discontinuation; histological transformation events; objective response per International Workshop on CLL (iwCLL) criteria (Hallek *et al*, 2018); and use of rasburicase. For AE data, given the nature of the study, we focused on elective and unplanned hospitalisations, infection episodes, tumour lysis syndrome (TLS) events, dose interruptions and permanent discontinuation. TLS events were defined according to the Howard criteria, which specify criteria for laboratory and clinical TLS (Howard *et al*, 2011). Follow-up was censored at the most recent hospital visit or death. The database was locked in ~~07/~~August 2018 for analysis.

PFS was defined as the time from the start of venetoclax until PD or death from any cause, discontinuation-free survival (DFS) was defined as the time from the start of venetoclax until discontinuation or death, and OS was defined as the time from start of venetoclax to time of death from any cause. Duration of response (DOR) was measured from the date of best response until PD date. Patients who died of unrelated causes were censored at death. Survival analyses were calculated in standard fashion by Kaplan-Meier analysis (Kaplan & Meier, 1958). Univariable and multivariable Cox regression was used to examine the associations between baseline factors, PFS and OS (Cox, 1972). Chi squared or Fisher's exact tests were used to compare ORR rates between different baseline groups. Statistical analyses were performed in STATA 15.1 (StataCorp, College Station, TX, USA).

Patients were treated with venetoclax in line with the EMA label, employing the now established weekly ramp-up phase from 20 mg o.d. to 400 mg o.d., and typically received monotherapy until PD, toxicity or death. Data

on any additional therapies given alongside venetoclax (indicated, for example, for autoimmune phenomena), including anti-CD20 monoclonal antibody therapy, were also collected.

Patients were assessed by their treating clinician according to the ~~IWCLL~~iwCLL criteria (Hallek *et al*, 2018) ~~criteria~~, although bone marrow biopsies and ~~CT~~ computed tomography imaging was not uniformly undertaken given the nature of this RWD collection. Data on MRD evaluation by flow cytometry of peripheral blood (as per ~~ERIC~~ the European Research Initiative on CLL consensus recommendations) (Rawstron *et al*, 2018) were collected where available.

Results

We present data on 105 patients who commenced venetoclax between ~~08/~~August 2015~~-11/~~ and November 2017. The median age was 67 years (range 39-87) with a predominance of males (73% male, 27% female) (Table I). Patients had received a median of 3 prior lines of therapy (range 1-15 lines). Prior to venetoclax, the Eastern Cooperative Oncology Group performance status (ECOG PS) was 0-1 in 74% (78/105) and 2-3 in 26% (27/105). ~~48%~~Forty-eight percent of patients had evidence of *TP53* disruption defined by either a *TP53* deletion by ~~fluorescent~~ fluorescence *in situ* ~~hybridization~~ hybridisation (FISH) analysis or *TP53* abnormality by mutational analysis. *TP53* status was unknown in 2 patients.

At second or subsequent line of therapy, 60% (62/104) of patients had received ibrutinib or another BTK inhibitor (BTKi) and no prior Pi3K inhibitor (Pi3Ki), 25% (26/104) of patients had received idelalisib or another ~~Pi3K inhibitor (~~Pi3Ki~~)~~ (duvelisib; n=1) and no prior BTKi, 10% (10/105) had received both a prior BTKi and Pi3Ki (Table I). Tirabrutinib was the only other BTKi used (n=2). One patient may have previously been exposed to idelalisib within a blinded randomised trial (excluded from all BCRi analyses). Only 6% (6/105) patients were ~~BCRi~~ BCRi-naive.

Patients had discontinued BCRi therapy because of toxicity in 44% (48/109 total BCRi treatment lines) and PD in 54% (59/109 treatment lines). According to BCRi subgroup, 36% (27/73) stopped BTKi due to toxicity and 64% (46/73) due to PD whilst 58% (21/36) stopped PI3Ki due to toxicity and 36% (13/36) due to PD. Two (2%) patients stopped PI3Ki with responsive disease with the clinician's intention of achieving a deeper response prior to allogenic stem- cell transplantation (alloSCT). The median duration of BTKi and PI3Ki therapy was 15 (range 0.25-48) months and 8.5 (range 1-27) months, respectively. The median interval from BTKi and PI3Ki discontinuation to starting venetoclax was 50 (range -2 to 976) days and 125 (range 0-837) days respectively.

Additional therapy received alongside venetoclax was noted in 15% (16/105) patients and included rituximab (n=7), steroids (n=5), obinutuzumab (n=1), ibrutinib (n=1), both rituximab and steroids (n=1) and unknown (n=1).

By pre-defined criteria (https://www.venclextahcp.com/venclexta-dosing-regimen/tumor-lysis-syndrome-risk-assessment.html), the TLS risk was low, intermediate or high in 27% (28/105), 25% (26/105)~~,~~ and 48% (50/105) patients respectively (Table I). TLS risk was not classified in 1 patient. ~~72%~~Seventy-two percent (73/102) of patients received ≥1 dose of rasburicase as TLS prophylaxis. Overall, patients received a median of 2 doses of rasburicase (range 0-17) and were electively admitted to an inpatient bed for a median of 1 (range 0-6) occasion(s). ~~62%~~Sixty-two percent (65/105) of the cohort were elective admitted during dose escalation at least on 1 occasion.

Response rates and survival outcomes

The ORR of venetoclax monotherapy in the 105 patients was 88% (30% CR ~~([~~31/105~~)~~] and 58% ~~([~~61/105~~)~~] partial response [PR]). With a median follow-up of 15.6 months (range 26 days-32.9 months), 33 patients had died, 12 patients were alive having stopped venetoclax (reasons: PD ~~([~~n=3~~),~~], alloSCT ~~([~~n=7~~),~~], toxicity ~~([~~n=2~~))~~]) and 60 patients remain on venetoclax. ~~7~~ Seven other patients had stopped venetoclax for toxicity but had subsequently died.

The ORR in patients who received a prior BTKi was 85% (CR 23%, PR 62%), a prior Pi3Ki was 92% (CR 38%, PR 54%) and 80% (CR 20%, PR 60%) for the 10 patients who were previously exposed to both BCRi classes. All 6 BCRi-naïve patients responded (ORR 100%) with 5 (83%) documented CRs (Table II, Fisher's exact p=0.59 for ORR comparing the four groups). The ORR in patients without *TP53*-disruption was 89% (CR 28%, PR 61%), and 86% (CR 32%, PR 54%) for those with *TP53* disruption (Chi-squared, p=0.68).

The median PFS was not reached, with a 1-year PFS of 65.0% (95% CI 54.7-73.6) and 60.9% (95% CI 50.1-70.0) at the median follow-up of 15.6 months. The median OS was 21.1 months, a 1-year OS 75.1% (95% CI 65.4-82.5) and 69.5% (95% CI 58.9-77.9) at the median follow-up of 15.6 months (Fig 1A-B).

Duration of response

The time to best ORR in the 92 responsive patients was 3.7 months (range 0.7-18.1 months) with a median ~~duration of response (~~DOR~~)~~ not reached and 75.4% (range 62.0-84.7) of patients achieving a DOR of 1 year or greater. The median time to PR as best response was 3.4 months (range 0.2-14.8) and CR as best response was 4.5 months (range 0.7-18.1). Of those patients obtaining a PR, 64.8% (95% CI 44.9-79.0) ~~of patients obtaining a PR~~ had a DOR of 1 year compared to 91.8% (95% CI 70.9-97.9%) at 1 year for those reaching CR. (Fig 2A). Patients responding to venetoclax experienced a longer survival than non-responders. Notably, the depth of response influenced OS; patients achieving CR experienced a superior OS compared to patients achieving PR. OS at 6 months for patients achieving CR was 100%, PR 83.8 % (95% CI 71.1-78.5), SD 25% (95% CI 8.9-66.5) and PD 22% (95% CI 3.4-51.3). The ~~progression-free~~PFS rate at 12 months for complete responders was 95.7% (95% CI 72.9-99.4) and 66.4% (95% CI 50.0-78.5) for partial responders ~~was 66.4 (95% CI 50.0-78.5)~~ (Fig 2B).

Outcome according to BCRi discontinuation

We evaluated by reason for BCRi discontinuation in the 86 patients exposed to a *single* BCRi (i.e. analysis excluding the dual BCRi exposed ~~([~~n=10~~),~~], ~~BCRi~~ BCRi-naïve patients ~~([~~n=6~~),~~], the single patient on a blinded trial ~~([~~n=1~~)~~] and those stopped to obtain a deeper response ~~([~~n=2~~)).~~]). The ORR to venetoclax in patients stopping a BCRi for toxicity was 92% (33/36~~)~~ ~~(~~; CR 22~~%,~~ %; PR 69%) and for those with CLL progression on a BCRi was 84% (42/50~~)~~ ~~(~~; CR 28~~%,~~ %;PR 56%~~)~~ ~~(~~; p=0.67). The PFS and OS ~~was~~ were not statistically significantly different according to whether a patient had been exposed to a BTKi only, a PI3Ki only, or both. None of the BCRi-naïve patients treated with venetoclax has experienced progression to date (Fig 3A-B). For the whole cohort, those patients stopping BCRis for progression appeared to have an inferior PFS compared to patients stopping for reasons other than PD (toxicity n=46; deeper response required n=2), although this reached borderline statistical significance. In the 99 patients who were previously BCRi exposed, the risk of progression or death for patients stopping a prior BCRi for PD was double compared to those stopping for other reasons (predominantly toxicity) (hazard ratio [HR] 2.01 ~~([~~0.99-4.05~~)~~], p=0.05) (Fig 3C).

Nine patients who received venetoclax as a therapeutic bridge to alloSCT all responded to venetoclax. All patients stopped venetoclax prior to alloSCT and did not restart venetoclax following engraftment. Two patients have died following alloSCT, both from infection at 7.1 and 4.7 months after stopping venetoclax. The remaining 7 patients all remain in remission at a median of 14.6 (range 4.4 - 17.5) months following cessation of venetoclax.

Univariable and Multivariable Analyses

We wished to explore whether factors such as *TP53* disruption, number of prior lines of therapy and ECOG PS were associated with survival outcomes following venetoclax. These factors were included alongside a series of additional baseline factors within a univariable and multivariable analysis of PFS and OS (Supplementary Table I and II). Poorer baseline ECOG PS was associated with inferior PFS (~~hazard ratio (~~HR~~)~~ compared to ECOG 0: 4.02 ~~([~~1.36-11.93~~)~~] for ECOG 1; 7.42 ~~([~~2.43-22.64~~)~~] ECOG 2; 4.29 ~~([~~0.79-23.42~~)~~] ECOG 3, p=0.0014) and OS (ECOG 1: 3.02 ~~([~~0.98-9.34~~);~~]; ECOG 2: 7.45 ~~([~~2.44-22.75~~);~~]; ECOG 3: 5.54 ~~([~~1.00-30.70~~),~~], p=0.0006) on univariable analysis. ECOG PS was the only factor that retained its significance for PFS on multivariable analysis (p=0.0026), however the number of events ~~were~~ was still low.

There was no significant difference in PFS (p=0.27) or OS (p=0.42) when patients with *TP53*-disrupted CLL were compared to *TP53*-intact CLL (Supplementary Fig 1A-B). The number of prior treatment lines was significantly associated with PFS (HR compared to 1-2 lines: 2.52 ~~([~~1.15-5.51~~)~~] for 3-4 lines, 2.74 ~~([~~1.06-7.12~~)~~] for 5+ lines, p=0.017) within the univariable analysis (Supplementary Fig 1C-D). A similar effect was seen for OS (HR~~s~~: 2.37 ~~([~~1.03-5.45~~)~~] for 3-4 lines, 2.24 ~~([~~0.81-6.20~~)~~] for 5+ lines, p=0.068) although this did not reach statistical significance. However, the number of prior treatment lines did not retain its significance for PFS on multivariable analysis (p=0.12). Age and male gender were significantly associated with inferior OS on multivariable analysis. Inferior ~~overall survival~~OS was not observed in *TP53*- disrupted patients (HR disrupted *vs* non-disrupted: 1.62 ~~([~~0.70-3.72~~),~~], p=0.34).

Minimal residual disease

MRD was assessed by multi-colour flow cytometry on peripheral blood in 27% (28/105) after commencing venetoclax treatment. Of those assessed, 39% (11/28) had undetectable MRD ($<10^{-4}$) (7 patients in CR; 4 in PR) and 61% (17/28) were positive (2 CR; 15 PR). Eleven patients achieved undetectable MRD at a median of 8.3 months (range 4.5-10.4) with 1 patient subsequently experiencing a clinical relapse 3.7 months later. The other 10 ~~MRD~~ MRD-negative patients have been followed for a median of 6.8 months (range 3-23.7) since achieving MRD negativity with no further clinical relapses at the time of database lock (Supplementary Fig 2A).

AEs, venetoclax dose reductions and discontinuations

Venetoclax was generally well tolerated. During the course of venetoclax, 41% (43/105) patients had either a dose reduction or treatment interruption due to an AE. However, these patients were *not* more likely to discontinue venetoclax permanently due to an AE. In total, 8% (8/105) stopped venetoclax permanently due to toxicity (6.5% ~~([~~[4/58~~)~~] in no prior dose reduction group versus 9.3% ~~([~~[4/43~~)~~] temporary prior dose reduction group ~~([~~[p=0.71~~)).~~]). Dose reduction or temporary interruption of venetoclax did not appear to result in an inferior PFS or DFS (Supplementary Fig 2B-C). There were no ~~treatment~~ treatment-related deaths.

Overall, 43% (45/105) have stopped venetoclax. Discontinuation was most commonly due to PD (CLL; n=14, Richter~~'s~~ transformation (RT); n=9). Nine patients stopped prior to alloSCT, 7 patients stopped due to toxicity, 5 due to death from unrelated causes (1 congestive cardiac failure [CCF], 1 ~~CVA~~cerebrovascular accident [CVA], 1 intracranial haemorrhage and 1 metastatic squamous cell carcinoma, 1 ~~AML~~acute myeloid leukaemia [AML]) and 1 due to frailty.

Unplanned hospital admissions whilst on venetoclax occurred in 42% (44/103) of cases (median 0 (range 0-6)). Reasons for the unplanned admissions are outlined in Supplementary Table III. The dominant reason for admission was infection (22 episodes of infection non-otherwise specified, and 1 episode of neutropenic fever). There was 1 case of clinical TLS, 1 separate case of biochemical TLS and 1 case of isolated hyperphosphataemia. All 3 patients reached full dose and recovered with no clinical sequalae within the ~~ramp~~ ramp-up phase.

To date, 33 patients have died in this cohort; 13 from PD of CLL, 10 from RT (1 B-PLL, 6 DLBCL, 1 unknown histology and 2 clinically suspected but not confirmed by histology), 3 from infection, and 7 from other causes (1 CVA~~–~~, 1 CCF, 1 intracranial haemorrhage, 1 general frailty/poor nutrition, 1 metastatic squamous cell carcinoma, 2 AML).

Survival outcomes post progression

In total, 27 patients experienced PD due to CLL or RT on venetoclax. Five patients continued venetoclax beyond CLL PD with 2 patients still on venetoclax and 3 patients having subsequently died (1 CLL, 1 RT, 1

infection). Of the remaining 22 patients, 13 progressed with CLL and 9 with RT (1 patient also stopped venetoclax for toxicity and later developed RT). All patients with RT have died and 10/13 patients with CLL progression have died. Of all 27 patients with PD events on venetoclax, 5 remain alive with a median OS of 1.5 months (95% CI 0.4-8.0 months) (Fig 4A-B).

Of those that progressed with RT, 2 patients are known to have received further therapy. One patient received 2 cycles of RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone) then 2 cycles of RGDP (rituximab, gemcitabine, dexamethasone, cisplatin) but failed to respond. The second patient received 3 cycles of RCHOP then 3 cycles of RGDP but failed to ~~respons~~respond. ~~7~~ Seven other RT patients received supportive palliative care and subsequent therapy was unknown in 1 patient. Of the 13 patients that progressed with CLL, 1 patient received palliative radiotherapy, 7 patients received best supportive care and subsequent therapy was unknown in 4 patients.

Discussion

We report on a large UK series of the earliest venetoclax-treated R/R CLL patients outside of the clinical trial setting. Our cohort represents the majority of the patients treated within the early access schemes prior to formal venetoclax approval (105 patients of approximately 130). As is typical for early access schemes, patients were heavily pre-treated and had ~~high~~ high-risk clinical features. The vast majority were BCRi exposed and almost half had evidence of *TP53*-disruption. Our dataset clearly demonstrates the efficacy of venetoclax monotherapy in routine practice for patients across a large and representative range of academic and non-academic centres with R/R, high-risk CLL with ORR, DOR~~,~~ and PFS comparable to clinical trial cohorts (Jones *et al*, 2017; Stilgenbauer *et al*, 2016; Coutre *et al*, 2018) and recently published US RWD (for example, 1-year PFS 65% compared to 1-year PFS 68% in US RWD)(Mato *et al*, 2018b). Our data provide the first evidence in the non-trial setting of equivalent efficacy and survival in patients exposed to ~~either~~ BTKi, PI3Ki or both classes of BCRi. Notably, and by contrast to recently published US RWD (Mato *et al*, 2018b), we did not find significant differences in response or survival outcomes according to *TP53* status. Consistent with a pooled analysis of 3 clinical trials of venetoclax monotherapy (Wierda *et al*, 2017b), we demonstrate that more heavily pre-treated patients had an inferior PFS, although significance was not retained as an independent predictive factor in a multivariable analysis. In fact, the only characteristic that was significantly associated with inferior PFS in a multivariable model was ECOG PS. ~~28%~~Twenty-eight percent had an ECOG PS >1 and thus would not have ~~ineligible~~ been eligible for the venetoclax clinical studies (Jones *et al*, 2017; Coutre *et al*, 2018; Stilgenbauer *et al*, 2016). Clearly, ECOG PS is influenced by a range of patient and disease characteristics (for example, prior therapeutic lines and disease biology) although we could not find a clear statistical interaction between ECOG and *TP53* status or prior lines of therapy (data not shown). However, the number of patients and events in the subgroups are relatively small so no strong conclusions can be drawn.

We provide further evidence of the safety and tolerability of venetoclax in the non-trial setting across a range of hospitals~~. We~~ and demonstrate that dose attenuation and temporary treatment interruptions did not

impact on PFS or OS. However, we cannot exclude survival bias within this specific analysis i.e. patients with superior survival may be more likely to have dose attenuation over time. ~~The~~ Our reported rate of clinical and biochemical TLS ~~we report~~ is that which resulted in unplanned admission and, as such, the rate may differ compared to series reporting all cases of biochemical TLS. Notwithstanding this caveat, the TLS rate of 1% is consistent with that reported in clinical trials (Stilgenbauer *et al*, 2016; Davids *et al*, 2018) following the modifications to the dosing schedule to mitigate against TLS risk. The rate of TLS in our series is lower than the US RWD set. The reasons for this are not fully clear but may be related to risk assessment and prophylaxis strategies. We recognise the potential bias for under-reporting those cases without unplanned admission and misclassification according to the Howard criteria (Howard *et al*, 2011). However, there was no demonstrable evidence ~~of~~ concerning toxicities associated with TLS in our series.

By contrast to published ~~non~~ non-clinical trial BCRi data, where toxicity was the most common reason for BCRi discontinuation (followed by CLL PD (Mato *et al*, 2018a)), PD was the commonest reason for venetoclax discontinuation. These data are strikingly similar to results reported by ~~Mato and colleagues (~~Mato *et al*, (2018b) (22/45 PD ~~([~~CLL and RT~~)~~] and 7/45 toxicity in the present UK series; 22/41 PD ~~([~~CLL and RT~~)~~] and 9/41 toxicity in the US series).

We provide the first evidence ~~for~~ of a superior PFS for venetoclax-treated patients who discontinued BCRi for toxicity as compared to those who experienced progression on BCRi; the latter group of patients were twice as likely to progress or die following venetoclax compared to those failing BCRi for an alternative cause (predominantly toxicity) (HR 2.01 ~~([~~0.99-4.05~~)~~] p=0.05). Consistent with data from clinical trials, we observed durable responses in patients obtaining CR and those achieving undetectable MRD in peripheral blood (including patients in PR). Although follow-up durations for both trial and non-trial cohorts are still relatively short, it seems likely that depth of response to venetoclax will translate into prolongation of PFS. Data such as these may be of particularly use when considering the role of consolidation therapy, for example alloSCT, in a selected, fit subgroup of R/R CLL patients obtaining responses on venetoclax. We also clearly demonstrate that patients who fail to respond to, or progress following, venetoclax have a dismal outcome with very limited survival. The unmet clinical need has therefore shifted to patients who fail both BCRi and venetoclax. Developing effective novel agents for such patients will prove challenging, not least because of the disease kinetics and short survival times but also because of the relatively high proportion of RT.

Our study has a number of limitations. Although our data were collected from ~~a~~ representative UK centres, retrospective data collection is subject to the inherent biases of patient level data collection, AE reporting and response assessment. Recognising this, we attempted, where possible, to mitigate against such biases by applying established criteria and focusing on the most objective parameters. For example, we assigned ~~for~~ reported 'clinical complete responses' (without bone marrow biopsy confirmation) ~~we assigned~~ as partial responses in line with ~~IWCLL~~iwCLL criteria. Similarly, we sought TLS data in line with established criteria. Moreover, we pragmatically limited our data collection to focus on routinely available clinical factors and

simple venetoclax dosing information and thus did not request information on *IGHV* mutational status, cytogenetic information beyond *TP53* status, or detailed information on maximum venetoclax dose reached and relative dose intensity. Consequently, we were able to achieve a near complete study database.

These limitations notwithstanding, our study details a large, multi-centre early experience of venetoclax in R/R CLL, demonstrating responses and survival outcomes consistent with published trials and US RWD. Importantly, we observed responses in patients exposed to either or both BTK and Pi3K inhibitor(s) and demonstrate, for the first time outside clinical trials, favourable clinical outcomes of patients obtaining CR and/or those achieving undetectable peripheral blood MRD. Patients with progression post-BCRi and venetoclax as sequential monotherapies remain a major challenge, but we look forward to emerging data from prospective trials investigating venetoclax in combination with BCRi and monoclonal antibody therapies (Seymour *et al*, 2018; Hillmen *et al*, 2017). Combinatorial targeted approaches aimed at eradicating detectable MRD earlier in therapy are likely to impact favourably on how we approach CLL therapy in future.

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Table I: Patient Demographics, Baseline Clinical Characteristics, Prior BCR inhibitor and Venetoclax dosing

Baseline Characteristics	~~Post~~ Post-BTKi alone (n = 62)	Post-~~-~~Pi3Ki alone (n = 26)	Post-~~-~~BTKi and -Pi3K (n = 10*)	~~BCRi~~ BCRi-naïve (n = 6)	All patients (n = 105)
Age prior to Venetoclax use (n = 105) (median and range in years)	68 (46-86)	65 (39-87)	66 (59-77)	72 (61-79)	67 (39-87)
Gender					
Male	42 (69%)	22 (85%)	9 (90%)	3 (50%)	77 (73%)
Female	20 (31%)	4 (15%)	1 (9%)	3 (50%)	28 (27%)
Prior lines of therapy pre-Venetoclax (median and range)	3 (1-5)	2.5 (1-7)	5 (3-15)	1 (1-3)	3 (1-15)
ECOG ~~performance status (~~PS~~)~~ at start of Venetoclax					
ECOG PS 0	17 (27%)	11 (42%)	3 (30%)	1 (17%)	32 (30%)
ECOG PS 1	28 (45%)	8 (31%)	6 (60%)	4 (67%)	46 (44%)
ECOG PS 2	14 (23%)	6 (23%)	1 (10%)	1 (17%)	23 (22%)
ECOG PS 3	3 (5%)	1 (4%)	0 (0%)	0 (0%)	4 (4%)
Relapsed or Refractory within 3 years of purine analogue					
Yes	22 (35%)	7 (27%)	3 (30%)	0 (0%)	32 (30%)
No	40 (65%)	19 (73%)	7 (70%)	6 (100%)	73 (70%)
***~~TP53~~ TP53-*disrupted**					
Yes	36 (58%)	10 (38%)	4 (36%)	0 (0%)	50 (48%)
No	24 (39%)	16 (62%)	6 (64%)	6 (100%)	53 (50%)
Not ~~K~~known	2 (3%)	0 (0%)	0 (0%)	0 (0%)	2 (2%)
Prior BTKi					
Duration of prior BTKi (**n = 73**) (median and range in months)	16 (1-48)	N/A	9 (0.25-35)*	N/A	15 (0.25-48)
Reasons for stopping BTK~~T~~i					
PD	42 (68%)	N/A	4 (36%)	N/A	46 (64%)
Toxicity	20 (32%)	N/A	7 (64%)*	N/A	27 (36%)
Deeper response required	0 (0%)	N/A	0 (0%)	N/A	0 (0%)
Prior Pi3Ki					
Duration of prior Pi3Ki (**n = 36**)* (median and range in months)	N/A	8 (1-27)	9.5 (1-26)*	N/A	8.5 (1-27)
Reasons for stopping Pi3Ki					

PD	N/A	8 (31%)	5 (50%)	N/A	13 (36%)
Toxicity	N/A	16 (62%)	5 (50%)	N/A	21 (58%)
Deeper response required	N/A	2 (8%)	0 (0%)	N/A	2 (6%)
Prior BCRi					
Duration of prior BCRi (**n = 109**)* (median and range in months)	N/A	N/A	N/A	N/A	12 (0.25-48)
Reasons for stopping BCRi					
PD	N/A	N/A	N/A	N/A	59 (54%)
Toxicity	N/A	N/A	N/A	N/A	48 (44%)
Deeper response required	N/A	N/A	N/A	N/A	2 (2%)
TLS group					
High	28 (45%)	12 (46%)	4 (40%)*	5 (83%)	50 (48%)
Intermediate	16 (26%)	6 (23%)	4 (40%)	0 (0%)	26 (25%)
Low	18 (29%)	7 (27%)	2 (20%)	1 (17%)	28 (27%)
Not known	0 (0%)	1 (4%)	0 (0%)	0 (0%)	1 (1%)
Doses of rasburicase* **	2 (0-17)	2 (0-7)	2 (0-7)	1 (0-3)	2 (0-17)
Number of elective admissions (median and range)	1 (0-6)	2 (0-6)	2 (0-4)	0.5 (0-3)	1 (0-6)
Number of unplanned admissions (median and range)	0 (0-6)	0 (0-6)	0 (0-5)	0 (0-1)	0 (0-6)
Additional therapy alongside Venetoclax					
Bridging Steroids	3	1	1	0	5
Rituximab	5	1	1	0	7
Other**	3	0	1	0	4
Venetoclax dose attenuation					
Yes	28 (45%)	8 (31%)	4 (36%)	3 (50%)	43 (41%)
No	34 (55%)	18 (69%)	7 (64%)	3 (50%)	62 (59%)
Venetoclax stopped permanently due to related AE					
~~Y~~es	6 (10%)	2 (8%)	0 (0%)	0 (0%)	8 (8%)
~~N~~o	56 (90%)	24 (92%)	11 !100%)	6 (100%)	97 (92%)

*=1 patient in blinded trial of idelalisib therefore uncertain whether received

Abbreviations: AE: adverse event; BCRi: B cell receptor inhibitor; BTKi: Bruton tyrosine kinase inhibitor; ECOG PS: Eastern Cooperative Oncology Group performance status; N/A: not applicable; PD: progressive disease; Pi3Ki: phosphoinositide 3-kinase inhibitor; TLS: tumour lysis syndrome~~BTKi: Bruton tyrosine kinase inhibitor; BCRi: B cell~~

receptor inhibitor; Pi3Ki: phosphoinositide 3-kinase inhibitor; TLS: tumour lysis syndrome; AE: adverse event; PD: progressive disease; ECOG: Eastern cooperative oncology group

Table II: Best Objective Response and outcomes With Venetoclax

	~~Post~~ Post-BTKi alone (n = 62)	~~Post~~ Post-Pi3Ki alone (n = 26)	~~Post~~ Post-BTKi and -Pi3K (n = 10)*	~~BCRi~~ BCRi-naïve (n = 6)	All patients (n = 105)
~~Time on venetoclax, median (range) in months~~	-	-	-	-	-
Overall response rate					
CR	14 (23%)	10 (38%)	2 (20%)	5 (83%)	31 (30%)
Clinical PR / PR	39 (62%)	14 (54%)	6 (60%)	1 (17%)	61 (58%)
Clinical SD / SD	2 (3%)	1 (4%)	1 (10%)	0 (0%)	4 (4%)
Clinical PD / PD	7 (11%)	1 (4%)	1 (10%)	0 (0%)	9 (9%)
ORR	53 (85%)	24 (92%)	8 (80%)	6 (100%)	92 (88%)
Ongoing patients on venetoclax	33 (53%)	14 (54%)	7 (70%)	6 (100%)	60 (58%)
Reasons for permanent discontinuation of venetoclax					
CLL PD	9 (15%)	1 (4%)	3 (27%)	0 (0%)	13 (12%)
AlloSCT	4 (6%)	4 (15%)	1 (9%)	0 (0%)	9 (9%)
Richter~~'s~~ transformation (biopsy confirmed or suspected)	7 (11%)	2 (8%)	0 (0%)	0 (0%)	9 (9%)
toxicity**	6 (10%)	2 (8%)	0 (0%)	0 (0%)	8 (8%)
other	1 (2%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)
unrelated deaths	2 (3%)	3 (12%)	0 (0%)	0 (0%)	5 (5%)
Death					
Yes	21 (34%)	8 (31%)	3 (30%)	0 (0%)	33 (31%)
No	41 (66%)	18 (69%)	7 (64%)	6 (100%)	72 (69%)

*=1 patient in blinded trial of idelalisib therefore uncertain if received

** = 1 patient that stopped due to toxicity subsequently developed Richter Transformation

Abbreviations: AE: adverse event; AlloSCT: allogeneic stem cell transplantation; BCRi: B-cell receptor inhibitor; BTKi: Bruton tyrosine kinase inhibitor; CLL: chronic lymphocytic leukaemia; CR: complete response; ORR: overall response rate; PD: progressive disease; Pi3Ki: phosphoinositide 3-kinase inhibitor; PR: partial response; SD: stable disease; TLS: tumour lysis syndrome.~~BTKi: Bruton tyrosine kinase inhibitor; BCRi: B cell receptor inhibitor; Pi3Ki: phosphoinositide 3-kinase inhibitor; TLS: tumour lysis syndrome; AE: adverse event; PD: progressive disease; ECOG: Eastern cooperative oncology group; AlloSCT: allogenic stem cell transplantation; CR: complete response; PR: partial response; SD: stable disease; ORR: overall response rate~~

Figure legends

Figure 1. Survival curves for all patients.
A: Progression-free survival of all patients
B: Overall survival of all patients
CI: confidence interval; OS: overall survival; PFS: progression-free survival.

Figure 2. Duration of response and overall survival.
A: duration of response according to remissions status
B: overall survival according to response
*clinical complete responses (without bone marrow biopsy confirmation) were assigned as partial responses in line with iwCLL criteria (Hallek *et al* 2018)
CI: confidence interval; CR: complete response; OS: overall survival; PD: progressive disease; PR: partial response; SD: stable disease.

Figure 3. Survival according to B cell receptor inhibitor.
A: Progression-free survival according to prior B cell receptor inhibitor exposure
B: Overall survival according to prior B cell receptor inhibitor exposure
C: Progression-free survival according to reason for stopping prior B cell receptor inhibitor
BCRi: B-cell receptor inhibitor; BTKi: Bruton tyrosine kinase inhibitor; CI: confidence interval; HR: hazard ratio; PD: progressive disease; Pi3Ki: phosphoinositide 3-kinase.

Figure 4. Overall survival following progression on venetoclax.
A: Overall survival following progression on venetoclax
B: Overall survival following progression on venetoclax according to cause of progression
CI: confidence interval; CLL: chronic lymphocytic leukaemia; OS: overall survival;