Title Page

The efficacy and safety of venetoclax therapy in elderly patients with relapsed, refractory chronic lymphocytic leukaemia

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SUMMARY (95 words)

Elderly CLL patients treated outside of trials have notably greater toxicity with the BTK inhibitor ibrutinib compared to younger patients. It is not known whether the same holds true for the BCL2 inhibitor venetoclax. We provide a comprehensive analysis of key safety measures and efficacy in 342 patients comparing age categories ≥75 and <75 years treated in the relapsed, refractory non-trial setting. We demonstrate that venetoclax has equivalent efficacy and safety in R/R CLL patients who are elderly, the majority of whom are previous ibrutinib exposed and therefore may otherwise have few clear therapeutic options.

SHORT REPORT 1500 words max (words: 1646)

Chronic lymphocytic leukaemia (CLL) is predominantly a disease of the elderly, with a median age of onset of 72 years. In the UK between 2013-2015, 43% of new diagnoses were in patients ≥75 years (https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/leukaemia-cll). Elderly patients typically possess a cumulative burden of comorbidities and are often under-represented within clinical trials. As such, understanding the efficacy and safety of novel agents in elderly patients who are at higher risk of adverse events (AEs) is a key priority. Findings in clinical practice have not consistently paralleled clinical trial outcomes. For example, in contrast to trial reports, large retrospective series have documented higher discontinuation rates attributable to ibrutinib-related AEs (Mato *et al*, 2018a). Maddocks and colleagues (Maddocks *et al*, 2015) showed that age was the only significant independent risk factor of ibrutinib discontinuation for reasons other than progressive disease (PD) (hazard ratio [HR] for 10-year increase, 1.87; 95% confidence interval (CI), 1.33-2.64 [p<0.001].

Venetoclax is a potent, selective and orally bioavailable small-molecule inhibitor of the anti-apoptotic protein BCL2 with high efficacy in treatment-naïve (Fischer *et al,* 2019) and relapsed or refractory (R/R) CLL including

TP53-disrupted disease (Stilgenbauer *et al*, 2016). Phase II trials demonstrate impressive activity in these settings with an overall response rate (ORR) of ~80% in the B-cell receptor inhibitor (BCRi) naïve setting (Stilgenbauer *et al*, 2016) and high response rates (65-67%) post-BCRi (Coutre *et al*, 2018; Jones *et al*, 2017). Progression-free survival (PFS) across a recent pooled analysis of early phase trials (n=436) was ~30 months (Roberts *et al*, 2019) but was dependent on patient and disease characteristics. The median age was 66 years (Roberts *et al*, 2019) across all patients with those ≥70 years achieving similar response depth, duration and MRD-negativity compared to younger patients. AE rates, including grade (G) 3/4 AEs, serious AEs, and AEs leading to venetoclax dose reduction, interruption, or discontinuation did not differ according to age (<75 or ≥75 years) within a pooled analysis of 350 venetoclax-treated trial patients (Davids *et al*, 2018).

Recent large retrospective, multicentre series (Mato *et al*, 2018b; Eyre *et al*, 2019) have demonstrated reassuringly similar efficacy and survival to trial outcomes. A toxicity analysis (including rates of tumour lysis syndrome (TLS), dose interruptions and discontinuations) has been assessed in a recent all-age cohort (Roeker *et al*, 2019) but the specific question of efficacy and tolerability in elderly non-trial patients has not been specifically addressed.

We evaluated an international cohort of 342 venetoclax-treated patients outside of clinical trials to compare the efficacy and safety in patients ≥75 years compared to those <75 years. We analysed response rates and standard survival measures as well as TLS rates, admissions, dose alterations and discontinuation reasons. We included patients from 15 academic and 51 community centres across the US and UK. The study was completed in partnership with the Collaborative Study of Real-World Evidence and the UK CLL Forum and was Institutional Review Board approved.

Data were extracted following medical chart review including details on: baseline characteristics pre-venetoclax; prior lines; *TP53* status pre-venetoclax; ORR (per iwCLL criteria); and survival. For toxicity data, we focused on dosing schedules, TLS events, dose interruptions and permanent discontinuation. TLS events were defined according to Howard criteria, which specify criteria for laboratory and clinical TLS. Toxicity assessment was defined according to the Common Terminology Criteria for AEs (CTCAEv.4.0).

PFS was defined as the time from commencing venetoclax until PD or death from any cause and overall survival (OS) was defined as the time from commencing venetoclax to death from any cause. Survival analyses were calculated by Kaplan-Meier methods. Comparisons were made using Cox regression or log rank tests (Scheumper *et al,* 1996). Cochran-Mantel-Haenszel tests compared baseline characteristics across age groups. Analyses were performed in Stata 15.1 (StataCorp, College Station, TX). Follow-up was censored at the most recent hospital visit or death. The database was locked in 12/2018.

342 patients with R/R CLL receiving venetoclax as monotherapy (79%) or in combination (21%) were evaluated. 271 patients were <75 years and 71 patients were ≥75 years at time of initiation of venetoclax. 69% were male.

Patients received a median of 3 prior therapies (range 0-15), 78% received prior ibrutinib, 43% were 17p deleted and 39% had a complex karyotype (CK) (≥3 cytogenetic aberrations). The groups were well balanced for prior treatment lines, prior ibrutinib, *TP53*/17p aberrations, *NOTCH1* and *IGVH* status (Table IS). Older patients received a higher proportion of venetoclax monotherapy (p=0.05) and had advanced Rai stage (p=0.03). Across all patients, TLS risk groups were low (38%), medium (34%) and high (28%) respectively, with no significant differences according to age. Older patients did however have a significantly lower creatinine clearance (Table IS).

The median follow-up of the whole cohort was 11.6 months. The median follow-up according to age was 11.5 months (<75 years) and 12.2 months (≥75 years) respectively. "The duration of follow up was similar in the two age groups (≥75 vs. < 75 years) using reverse censoring for PFS or OS events gave log-rank p=0.41 and p=0.66, respectively. ORR for patients <75 years was 82.0% (complete response (CR) 32.6%) and for patients ≥75 years was 81.6% (CR 35.2%). There was no difference between the 1-year PFS (<75 years: 73% (95% CI:67-79%) vs ≥75 years: 79% (95% CI:66-87%)) (Figure 1A) or 1-year OS (<75 years:83% (95% CI:78-88%) vs ≥75 years: 77% (95% CI:65-86%)) (Figure 1B) across cohorts. Age ≥75 years (vs. <75 years) did not impact PFS (HR 0.89, 95% CI 0.53-1.52, p=0.67) or OS (1.25 95% CI 0.72-2.16, p=0.42) in unadjusted analysis and when adjusted for mono vs. combination venetoclax-based therapy (PFS HR 1.0, 95% CI 0.62-1.84, p=0.81, OS HR 1.26, 95% CI 0.72-2.18, p=0.42).

Toxicity was assessed by measuring the number of dose reductions, biochemical and clinical TLS events, cytopenias (CTCAE G≥3), and neutropenic fever. Clinical TLS was 3% in both cohorts. Across age categories, we observed no statistically significant differences in toxicity (Table 1). Older patients required a similar number of planned admissions during the initial ramp-up phase and required a similar proportion of dose reductions, with 66% obtaining a stable dose of 400mg o.d.. Reassuringly, although rates of G≥3 thrombocytopenia and G≥3 neutropenia were higher (p=0.13 in both) in older patients, this did not clearly translate into higher rates of neutropenic infection (9% <75 years vs. 4% ≥75 years; p=0.51).

Across all patients, 141 (41%) patients discontinued venetoclax. The proportion discontinuing venetoclax due to toxicity (n=28; 20% of discontinuations) was considerably lower than discontinuing due to PD or Richter's transformation (n=67; 48% of discontinuations). Overall, 18/271 (6.6%) of younger patients stopped due to toxicity compared to 10/71 (14%) of older patients (p=0.07). While specific AEs leading to discontinuation were captured, given the small number (n=10) in ≥75 years cohort who discontinued due to toxicity, meaningful comparison of unique AEs could not be made.

Although the proportion of ≥75 years stopping due to toxicity was proportionally higher than <75 years, there were considerably more reasons for younger patients to discontinue therapy, for example, CAR-T or stem-cell transplantation (16%; n=18/112). Overall, 56/271 (20.7%) of younger patients stopped due to PD or Richter's transformation compared to 10/71 (14%) of older patients (p=0.28). Only 3 patients ≥75 years receiving

venetoclax in combination discontinued therapy to date, therefore comparison of AEs of monotherapy vs. combination was not performed.

The provision of effective and tolerable therapy in elderly patients is a clear priority for the CLL community. This large international cohort suggests that venetoclax provides reassuringly similar efficacy and toxicity profiles in the 'elderly', defined in this cohort as ≥75 years of age at the time of starting venetoclax. We chose this age cut off to provide consistency with the recent analyses of toxicities in venetoclax-treated clinical trial patients (Davids *et al*, 2018) which demonstrated no significant difference in toxicity profile need for dose modifications in those <75 or ≥75 years. While rates of AEs and dose modifications were similar, older patients discontinued therapy more frequently due to toxicity. This is consistent with prior reports with immunochemotherapy and ibrutinib (Maddocks *et al*, 2015; Woyach *et al*, 2018) where tolerance may be inferior in elderly patients. We speculate that the maximal tolerated dose in the elderly may be lower. Alternate dosing strategies and further study of drug-drug interactions should be conducted in elderly patients to possibly mitigate toxicity.

As a novel agents including ibrutinib and venetoclax rapidly move from the relapsed setting into the frontline elderly CLL setting (Moreno *et al*, 2019; Fischer *et al*, 2019), selecting which agent(s) to utilise up-front will be challenging and debated. The tolerability profile of venetoclax in elderly patients demonstrated in this analysis and in pooled trial data is encouraging and may inform its use in the elderly.

We recognise that our study includes the intrinsic biases associated with retrospective data reporting, missing data, the lack of centralized pathology review or formalized radiological reporting, the potential for overestimating CR (per iwCLL) and prospective AE reporting. Reporting of G1-2 AEs were not recorded and as such an accurate representation of the burden of low grade toxicities could not be reported. Twenty-one percent of patients received concurrent therapy, predominantly with an anti-CD20 monoclonal antibody. We were unable to provide a detailed analysis of the contribution towards the toxicity profile of additional therapy given. We also cannot exclude the possibility of some selection bias within the population receiving venetoclax, and we have not collected detailed comorbidity indices to correlate with toxicity. Additionally, while efficacy and safety appear to be similar, the small sample size and retrospective nature of the data do not imply assumptions of equivalence. Findings should be considered hypothesis generating only.

Despite these limiting factors, these data provide a comprehensive analysis of key safety measures and demonstrate that venetoclax appears to have similar efficacy and safety in R/R elderly CLL patients and who otherwise may have few clear therapeutic options. Analyses such as these may inform prescribing choices in the elderly in the future.

Complication(s)	**<75 years (n=271)**	**≥ 75 years (n=71)**	**P value (Cochran-Mantel-Haenszel test)**	**Total (n=342)**

Number of admissions				
0	60/232 (26%)	15/71 (21%)		75/303 (25%)
1	56/232 (24%)	13/71 (18%)	0.54	69/303 (23%)
2	60/232 (26%)	23/71 (32%)		83/303 (27%)
3	16/232 (7%)	7/71 (10%)		23/303 (8%)
4+	40/232 (17%)	13/71 (18%)		53/303 (18%)
No. of dose reductions				
0	126/169 (75%)	30/43 (70%)		156/212 (74%)
1	33/169 (20%)	9/43 (21%)	0.48	42/212 (20%)
2	7/169 (4%)	4/43 (9%)		11/212 (5%)
3	3/169 (2%)	0/43 (0%)		3/212 (1%)
Stable Venetoclax dose obtained				
50mg or less	6/167 (4%)	3/44 (7%)		9/211 (4%)
100mg	11/167 (7%)	1/44 (2%)		12/211 (6%)
200mg	21/167 (13%)	8/44 (18%)	0.54	29/211 (14%)
300mg	10/167 (6%)	3/44 (7%)		13/211 (6%)
400mg	119/167 (71%)	29/44 (66%)		148/211 (70%)
Tumour lysis syndrome (TLS (composite endpoint))	28/268 (10%)	7/71 (10%)		35/339 (10%)
Biochemical TLS			0.78	
Clinical TLS	21/268 (8%)	5/71 (7%)		23/339 (7%)
	7/269 (3%)	2/71 (3%)		12/339 (4%)
Neutropenia (grade ≥3)	68/187 (36%)	23/46 (50%)	0.13	91/233 (39%)
Thrombocytopenia (grade ≥3)	49/186 (26%)	18/46 (39%)	0.13	67/232 (29%)
Neutropenic Fever/infection (grade ≥3)	16/186 (9%)	2/46 (4%)	0.51	18/232 (8%)
Venetoclax Discontinuation	112/271 (41%)	29/71 (41%)	0.95	141/342 (41%)
Reasons for discontinuation				
(N and % of discontinuation events)				
Adverse event	18 (16%)	10 (34%)		28 (20%)
Progressive disease (PD)	47 (42%)	5 (17%)		53 (38%)
Richter's transformation	9 (8%)	5 (17%)		14 (10%)
Stem Cell Transplant	14 (13%)	0 (0%)	-	14 (10%)
CAR-T cell therapy	4 (4%)	0 (0%)		3 (2%)
Cost	0 (0%)	0 (0%)		0 (0%)
Death unrelated to PD or toxicity	7 (6%)	4 (14%)		11 (8%)
Doctor/Patient Preference	2 (2%)	2 (7%)		4 (3%)
Secondary Malignancy	4 (4%)	1 (3%)		5 (4%)
Other	7 (6%)	2 (7%)		9 (6%)

Table I: Treatment complications comparing age categories

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