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Tumour debulking and reduction in predicted risk of tumour lysis syndrome with single-agent ibrutinib in patients with chronic lymphocytic leukaemia

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Ibrutinib, a first-in-class, once-daily inhibitor of Bruton tyrosine kinase, is approved in the US for treatment of chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma (SLL). Single-agent ibrutinib given continuously confers prolonged progression-free survival (PFS) with high overall response rates in relapsed/refractory (R/R) and treatment-naïve (TN) patients with CLL (Burger*, et al* 2015, Byrd*, et al* 2014, Byrd*, et al* 2013). Complete remission is infrequent early on and increases with ongoing treatment (Barr*, et al* 2018, O'Brien*, et al* 2018), but few patients ever achieve undetectable minimal residual disease (MRD) (Burger*, et al* 2015). The oral BCL2 inhibitor, venetoclax, has demonstrated efficacy and deep responses in patients with R/R del(17p) CLL (Stilgenbauer*, et al* 2016), with up to an 83.5% undetectable MRD rate achieved in peripheral blood in combination with rituximab (Seymour*, et al* 2018). Together with preclinical data suggesting combinatorial synergy (Cervantes-Gomez*, et al* 2015), these results have prompted ongoing investigations into the potential combination of ibrutinib plus venetoclax to confer even deeper responses and potentially allow for finite treatment duration with durable PFS (e.g., NCT02427450, NCT02910583, EudraCT2015-003422-14, NCT3462719, NCT02756897).

Although the risk of tumour lysis syndrome (TLS) with venetoclax is greatly reduced by following United States Prescribing Information and Summary of Product Characteristics recommendations, a recent retrospective analysis suggests that compliance with label recommendations may not be as stringent in real-world clinical experience as in clinical trials, with TLS remaining as an adverse event in up to 13.4% of patients (Mato*, et al* 2018). Current label recommendations describe TLS risk assessment based on lymph node (LN) bulk and absolute lymphocyte count (ALC) with gradual venetoclax dose

ramp-up and risk-adapted prophylaxis, monitoring and treatment (https://www.rxabbvie.com/pdf/venclexta.pdf). Given that ibrutinib rapidly reduces LN bulk (Byrd*, et al* 2013), ibrutinib lead-in is predicted to reduce the tumour burden sufficiently to reduce TLS risk prior to initiating venetoclax.

In this post hoc analysis, TLS risk categories (defined according to venetoclax labelling: ALC ≥25×10^9/l and diameter of largest lymph node [LDi] ≥5 cm-<10 cm and ≥10 cm) (**Supplementary Methods**) were assessed in 162 TN and 262 R/R patients treated with single-agent ibrutinib in several clinical studies (**Table SI**). Changes were also assessed in sub-populations defined by *IGHV* mutation status and fluorescence *in situ* hybridisation (FISH) cytogenetics.

At baseline, elevated ALC was observed more frequently in TN than R/R patients, while bulky LN were more common in R/R patients (**Table I**); similar percentages of TN and R/R patients were assessed as high risk for TLS (28% and 33%, respectively). More patients with unmutated *vs* mutated *IGHV* had the LDi ≥5 cm TLS risk factor; comparable proportions of patients with unmutated and mutated *IGHV* had ALC ≥25×10^9/l. More patients with del(11q) had high baseline TLS risk and LDi ≥5 cm than other cytogenetic subgroups.

Among patients with baseline LDi ≥5 cm, bulky disease resolved (LDi <5 cm) in 90% of TN and 85% of R/R patients during ibrutinib treatment, with 78% and 65% reduction, respectively, observed at first assessment (2-4 months). LDi reductions from baseline were generally greater in TN than R/R patients and occurred irrespective of *IGHV* mutation status or cytogenetic profile (**Fig 1A-1B; S1A-1D**).

Consistent with the known ibrutinib pharmacodynamic effect, median ALC increased within 1-2 weeks, peaked on Weeks 3 (R/R) and 5 (TN), and then gradually declined to ≤25x10^9/l by Weeks 12 (R/R) and 17 (TN) (**Fig S2A**); this pattern occurred regardless of *IGHV* mutation status (**Fig 1C**) or cytogenetic subgroup, with the exception of patients with trisomy 12, who showed no prominent ALC increase and shorter median resolution times (TN, 29 days; R/R, 40 days) (**Fig S2B-S2C**).

After ibrutinib (2-4 months), the percentage of patients classified as high baseline TLS risk decreased (TN: 28% [46/162] to 7% [11/162]; R/R: 33% [86/262] to 13% [35/262]), the percentage with medium risk remained stable, and percentage with low risk increased in both groups (**Fig 1D**). Due to the transient increase in ALC shortly after ibrutinib, a few patients increased from low to medium risk (TN, 8/162 [5%]; R/R, 16/262 [6%]) or from medium to high risk (TN, 0%; R/R, 7/262 [3%]). Most meaningfully, among 46 TN and 86 R/R patients at high baseline TLS risk, 76% (35/46) TN and 65% (56/86) R/R shifted to a lower risk category, including 24% (11/46) TN and 15% (13/86) R/R who shifted to low risk. Among 86 TN patients at medium baseline TLS risk, 33% (28/86) shifted to low and 60% (52/86) remained at medium risk. Among 118 R/R patients at medium baseline risk, 37% (44/118) decreased to low and 52% (61/118) remained at medium. The high and medium TLS risk categories each can be subdivided by their two defining criteria of ALC and/or LDi (**Fig S3**). In patients with baseline high-risk TLS due to the combination of elevated ALC and bulky LN, the shift to medium-risk TLS at first assessment was largely due to LN bulk reduction (LDi <5 cm), with less frequent ALC decreases (<25×10^9/l).

Hospitalisation is recommended for patients with high-risk TLS with venetoclax administration, and considered for patients with medium-risk TLS and renal dysfunction (creatinine clearance <80 ml/min) (https://www.rxabbvie.com/pdf/venclexta.pdf). The number of patients meeting these hospitalisation criteria decreased from baseline to first assessment (TN: 115 to 64; R/R: 157 to 97), with proportionally greater reduction in patients with baseline high-risk TLS (TN: 46 to 11; R/R: 86 to 35) than with medium-risk TLS and creatinine clearance <80 ml/min (TN: 69 to 53; R/R: 71 to 62).

In summary, these results support the value of single-agent ibrutinib lead-in for tumour debulking to reduce TLS risk prior to initiating venetoclax for CLL, including for patients with compromised kidney function. This 2- to 4-month ibrutinib lead-in reduced LN bulk and ALC, resulting in reduced TLS risk categorization. Reduced TLS risk with ibrutinib lead-in may lead to fewer hospitalisations for TLS prophylaxis, monitoring and management. Our analysis serves to inform ongoing prospective studies of ibrutinib plus venetoclax and provides additional information regarding these effects in patients with genomic high-risk CLL (i.e., *IGHV* unmutated, FISH abnormalities).

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Conflict of Interest Statement

WGW received research funding from AbbVie, Genentech and Pharmacyclics LLC, an AbbVie Company. **JCB** received research funding from Acerta, Genentech, Janssen and Pharmacyclics LLC, an AbbVie Company. **SO** served in a consultancy/advisory role with AbbVie, Alexion, Amgen, Aptose Biosciences, Inc., Astellas, Celgene, Gilead, GlaxoSmithKline, Janssen Oncology, Pfizer, Pharmacyclics LLC, an AbbVie Company, Sunesis, TG Therapeutics and Vaniam Group LLC; and received research funding from Acerta, Gilead, Kite, Pfizer, Pharmacyclics LLC, an AbbVie Company, Regeneron, Sunesis and TG Therapeutics. **SEC** received honoraria from Janssen and Pharmacyclics LLC, an AbbVie Company; served in a consultancy/advisory role for AbbVie, BeiGene and Janssen; and received research funding from AbbVie, Acerta, Gilead, Janssen and Pharmacyclics LLC, an AbbVie Company. **PMB** served in a consultancy/advisory role for AbbVie, Celgene, Novartis, Genentech, Verastem, Gilead, Merck and

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Authorship Contributions

WGW, DFJ, JN and CZ designed the analyses and interpreted the data. WGW, JCB, SO, SC, PMB, RRF, TJK, JAB, DAS, JS, PG, IWF and CST enrolled patients and collected data; CZ conducted statistical analyses; CZ and JN analysed and collated the data; all authors had access to the data files and contributed to the data interpretation; all authors participated in manuscript preparation and revisions, and approved the final version of the manuscript for submission.

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Table I. Baseline measurements by genomic characteristics

Baseline measurements	***IGHV mutation status***		**FISH cytogenetics***				**Overall**
TN patients	**Mutated (n=54)**	**Unmutated (n=71)**	**Del(17p) (n=2)**	**Del(11q) (n=29)**	**Trisomy 12 (n=26)**	**Other (n=105)**	**(n=162)**
ALC ≥25×10^9/l, n (%)	40 (74)	51 (72)	2 (100)	18 (62)	21 (81)	75 (71)	116 (72)
Bulky disease (LDi ≥5 cm), n (%)	11 (20)	34 (48)	0 (0)	17 (59)	7 (27)	34 (32)	58 (36)
LDi ≥10 cm	1 (2)	6 (8)	0 (0)	3 (10)	0 (0)	5 (5)	8 (5)
LDi ≥5 cm to <10 cm	10 (19)	28 (39)	0 (0)	14 (48)	7 (27)	29 (28)	50 (31)
TLS risk category, n (%)							
High risk	8 (15)	28 (39)	0 (0)	13 (45)	7 (27)	26 (25)	46 (28)
Medium risk	35 (65)	32 (45)	2 (100)	10 (34)	14 (54)	60 (57)	86 (53)
Low risk	11 (20)	11 (15)	0 (0)	6 (21)	5 (19)	19 (18)	30 (19)
R/R patients	**Mutated (n=47)**	**Unmutated (n=150)**	**Del(17p) (n=86)**	**Del(11q) (n=68)**	**Trisomy 12 (n=12)**	**Other (n=96)**	**(n=262)**
ALC ≥25×10^9/l, n (%)	25 (53)	72 (48)	43 (50)	38 (56)	4 (33)	39 (41)	124 (47)

Bulky disease (LDi ≥5 cm), n (%)	25 (53)	95 (63)	49 (57)	48 (71)	4 (33)	58 (60)	159 (61)
LDi ≥10 cm	1 (2)	8 (5)	6 (7)	4 (6)	0 (0)	3 (3)	13 (5)
LDi ≥5 cm to <10 cm	24 (51)	87 (58)	43 (50)	44 (65)	4 (33)	55 (57)	146 (56)
TLS risk category, n (%)							
High risk	11 (23)	52 (35)	27 (31)	30 (44)	1 (8)	28 (29)	86 (33)
Medium risk	29 (62)	66 (44)	40 (47)	28 (41)	6 (50)	44 (46)	118 (45)
Low risk	7 (15)	32 (21)	19 (22)	10 (15)	5 (42)	24 (25)	58 (22)

*By Dohner hierarchy categorization. FISH Cytogenetic subgroups presented in a hierarchy of CLL chromosomal abnormalities are based on Dohner subgroups: del(17p), del(11q) but not del(17p), trisomy 12 but not del(11q) or del(17p), or "other", including all patients without del(17p), del(11q), or trisomy 12.

ALC, absolute lymphocyte count; FISH, fluorescence *in situ* hybridisation, *IGHV*, immunoglobulin heavy chain variable; LDi, largest diameter of lymph node; R/R, relapsed/refractory; TLS, tumour lysis syndrome; TN, treatment-naïve.

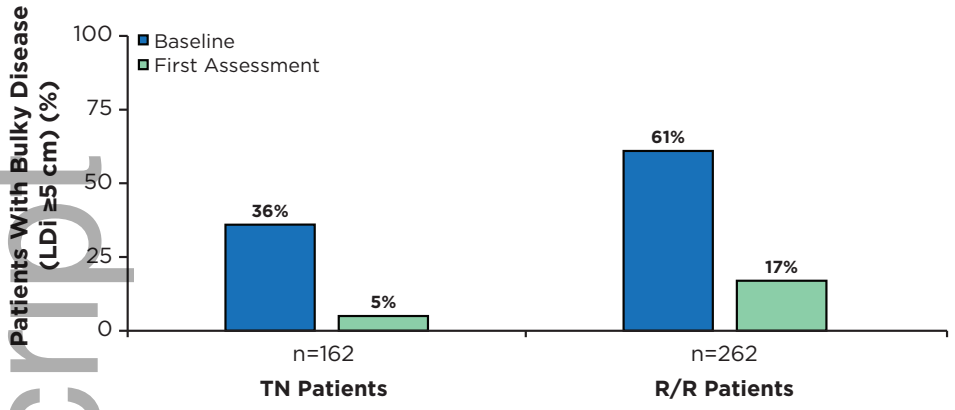
FIGURE LEGENDS

Fig 1. Change in lymph node bulk, absolute lymphocyte count and tumour lysis syndrome risk category after ibrutinib in treatment-naïve or relapsed/refractory patients. Change in the proportion of patients with bulky disease (LDi ≥5 cm) from baseline to first response assessment after initiating ibrutinib treatment in (A) all TN or R/R patients or (B) TN and R/R patients subdivided by *IGHV* mutation status. (C) Median change (95% CI) from baseline in ALC over time inTN or R/R patients, subdivided by *IGHV* mutation status. (D) Shift in the distribution of TLS risk category from baseline to first assessment in ibrutinib-treated TN (left) and R/R (right) patients based on established standards: High, any LDi≥10 cm or ALC ≥25×10^9/l and LDi ≥5 cm; Medium, ALC ≥25×10^9/l or LDi ≥5 cm but <10 cm; Low, ALC <25×10^9/l and LDi <5 cm. See Figure S2 for TLS risk category shifts further subdivided by ALC and bulky disease (LDi). First assessment computed tomography scans post-baseline were scheduled on Day 56 for PCYC-1102, Day 78 for RESONATE, and Day 113 for RESONATE-2.

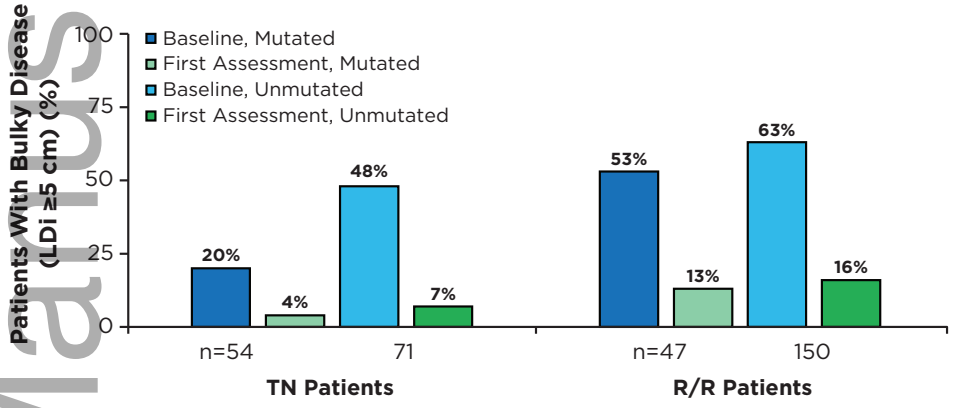
ALC: absolute lymphocyte count; CI: confidence interval; LDi: largest diameter of lymph node; n: total evaluable patients in each category at time of assessment; R/R: relapsed/refractory; TLS: tumour lysis syndrome; TN: treatment-naïve

Figure 1

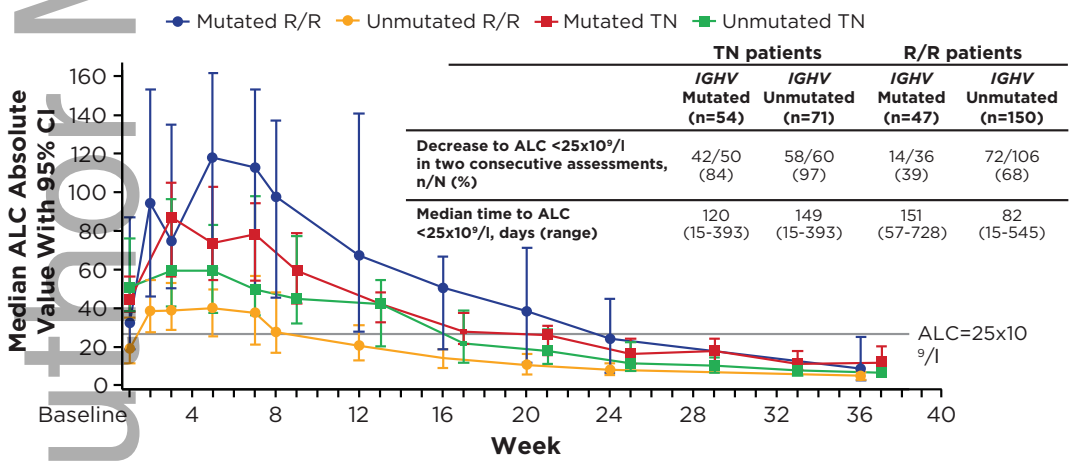
A.



B.



C.



	TN patients		R/R patients	
	IGHV Mutated (n=54)	*IGHV* Unmutated (n=71)	*IGHV* Mutated (n=47)	*IGHV* Unmutated (n=150)
Decrease to ALC <25x10⁹/l in two consecutive assessments, n/N (%)	42/50 (84)	58/60 (97)	14/36 (39)	72/106 (68)
Median time to ALC <25x10⁹/l, days (range)	120 (15-393)	149 (15-393)	151 (57-728)	82 (15-545)

D.