Changes in clinical stage identify patients with CLL and different outcome within iwCLL partial response: RESONATE study

Ibrutinib, a first-in-class, oral, once-daily inhibitor of Bruton tyrosine kinase, is indicated for the treatment of patients with chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL) including patients with del(17p) and allows for treatment without chemotherapy. The phase 3 RESONATE™ (PCYC-1112) trial demonstrated superior progression-free survival (PFS), overall survival (OS) and overall response rate (ORR) with ibrutinib compared to ofatumumab in previously treated patients with CLL/SLL (Byrd *et al*, 2014). Most patients treated with ibrutinib achieve partial response (PR), in some cases with rebound lymphocytosis (PR-L). As defined by the 2008 International Workshop on CLL (iwCLL) criteria, PR is heterogeneous, and includes patients with varying outcomes (Hallek *et al*, 2008). Clinical stages reflect tumour load and correlate with OS at diagnosis and over the disease course (Rai *et al*, 1975), as well as after therapy (Montserrat *et al*, 1985). Therefore, clinical stages enable the response to therapy to be charted throughout the clinical course of CLL (Rai *et al*, 1975; Montserrat *et al*, 1985). With this background, we sought to determine whether changes in Binet stage (Binet *et al*, 1981) identify different response categories among partial responders in CLL patients treated with ibrutinib.

The study design for PCYC-1112 (NCT01578707) has been previously described (Byrd *et al*, 2014). Patients with relapsed/refractory CLL/SLL were randomized 1:1 to oral ibrutinib 420 mg once daily until progressive disease or unacceptable toxicities *versus* ofatumumab for up to 24 weeks (300 mg week 1, 2000 mg weekly for 7 weeks, 2000 mg every 4 weeks for 16 weeks). The study was approved by the institutional review board or independent ethics committee at each participating institution and conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines. All patients provided written informed consent.

Patients that achieved PR or PR-L by iwCLL criteria (Binet *et al*, 1989; Mertens & Stilgenbauer, 2014) were retrospectively assessed for Binet stage (Binet *et al*, 1981) based on clinical data at baseline and at the time of first response (ToFR) to ibrutinib. Stage A was defined as no anaemia or thrombocytopenia and <3/5 involved sites (unilateral or bilateral cervical, axillary, and inguinal lymph nodes; liver, spleen) (Binet *et al*, 1981). Stage B was defined as no anaemia or thrombocytopenia and ≥3/5 involved sites (Binet *et al*, 1981). Stage C was defined as anaemia (haemoglobin <100 g/l) and/or thrombocytopenia (platelets $<100 \times 10^9$/l), regardless of involved sites (Binet *et al*, 1981). Binet stage was considered missing if any component of the staging criteria was not available. Kaplan–Meier analyses on PFS and OS were performed based on Binet stage at ToFR as assessed by the investigator. PFS and OS were adjusted using ToFR as baseline instead of date of randomization, because Binet stage was assigned at time of initial response. Data were analysed according to the primary clinical trial analysis (Byrd *et al*, 2014). *P* values are descriptive and were considered significant when <0·05.

Of 195 ibrutinib-treated patients, 162 (83%) had an initial response of PR or PR-L as assessed by the investigator [84 (52%) PR, 78 (48%) PR-L]. At baseline, Binet stage for these 162 patients was A, B and C in 66 (41%), 17 (10%) and 72 (44%) patients, respectively; disease stage was missing in 7 patients (4%). Stage B was uncommon in this relapsed/refractory population, as most patients with ≥3 sites enlarged also had persistent cytopenias. At the time of first PR/PR-L [median 2·5 months (range, 1–11)], Binet stage for these 162 patients had shifted to A, B and C in 106 (65%), 1 (1%) and 44 (27%) patients, respectively, and disease stage was missing in 11 patients (7%). Patients who maintained Stage C at ToFR had a higher percentage of bone marrow infiltration, rate of del(11q) at baseline, and median number of prior therapies compared to patients with Stage A, though differences for each were not statistically significant (Table I). Twenty-one (48%) of 44 patients with PR/PR-L who were Stage C at ToFR resolved their cytopenias and improved from Stage C to A with continued ibrutinib therapy.

Responders who resolved cytopenias showed a statistically significant longer PFS than those with persistent cytopenias at ToFR to ibrutinib ($P = 0{\cdot}0431$, Fig 1). By assessing PFS from the time of first PR/PR-L, a controlled comparison between Stages A and C was achieved where non-responders were eliminated and question of causality was addressed by basing the Kaplan–Meier analysis solely on PFS events after initial response to ibrutinib. Difference in PFS between Stages A and C was demonstrated starting from the first time point that Binet stage was assessed, thereby excluding the preceding timeframe between randomization and first response assessment during which no events occurred. The estimated median PFS for Stage C should be interpreted with caution as an event occurred at the tail end of the curve with

Table I. Baseline characteristics by Binet staging for partial responders on ibrutinib per investigator assessment.

	All (N = 162)	Stage A at response (n = 106)	Stage C at response (n = 44)
Bone marrow infiltration, (%)			
n (patients)	112	75	27
Mean (standard deviation)	71 (25)	68 (25)	78 (25)
Del(11q), *n*/*N* (%)			
Yes	54/159 (34)	32/104 (31)	18/43 (42)
No	105/159 (66)	72/104 (69)	25/43 (58)
Del(17p), *n* (%)			
Yes	53 (33)	36 (34)	14 (32)
No	109 (67)	70 (66)	30 (68)
Bulky disease ≥5 cm, *n* (%)			
Yes	107 (66)	69 (65)	29 (66)
No	55 (34)	37 (35)	15 (34)
Number of prior therapies, median (range)	3 (1–12)	2 (1–12)	3 (1–10)
Median age, years (range)	66 (30–86)	65·5 (30–85)	66·5 (51–79)
IGHV mutation, *n*/*N* (%)			
Unmutated	82/109 (75)	54/73 (74)	21/28 (75)
Mutated	27/109 (25)	19/73 (26)	7/28 (25)

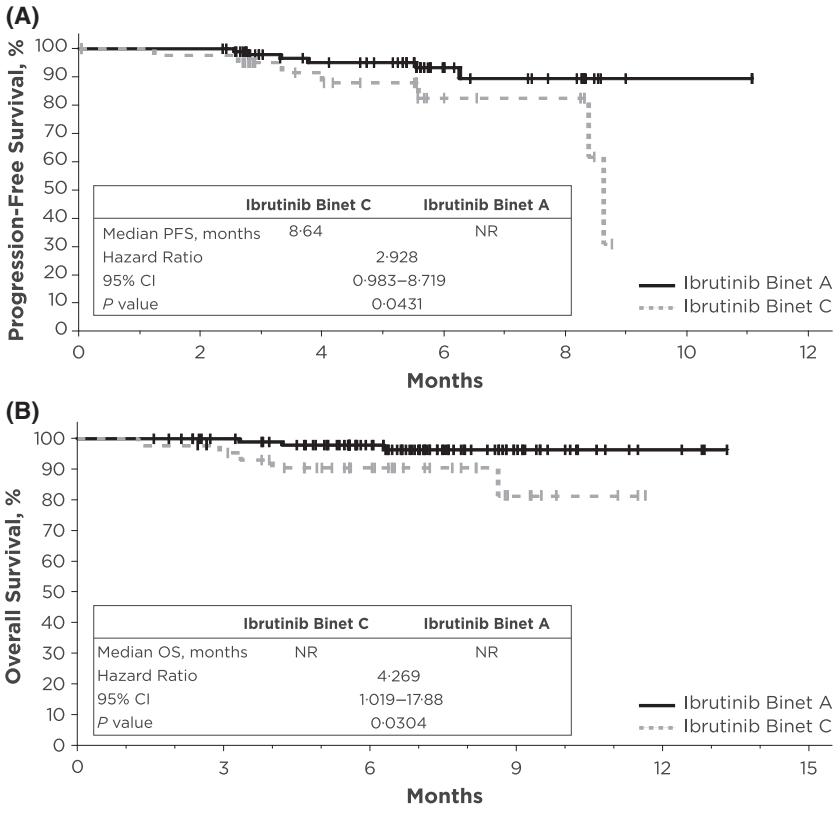

Fig 1. Kaplan–Meier curves of survival by Binet stage for ibrutinib partial responders starting after first response. (A) progression-free survival (PFS) and (B) overall survival (OS). CI, confidence interval; NR, not reached.

only 2 patients at risk. Responders with Stage A also showed a longer OS than those with Stage C at ToFR to ibrutinib (P = 0·0304). These findings were consistent with Kaplan–Meier analyses based on date of randomization, rather than time after first tumour response, which indicated longer PFS (P = 0·0314) and OS (P = 0·0281) among responders with Stage A compared to those with Stage C. Although of interest, a subgroup analysis of patients with complete response (CR) *versus* CR with incomplete haematopoietic recovery (CRi) was not feasible due to the small number of patients attaining CR/CRi (n = 1) at first response assessment.

These results show that changes in clinical stage separate the iwCLL PR/PR-L response category into different,

clinically meaningful, subgroups and reinforces the notion that improving cytopenias is a desirable goal of CLL therapy (Barrientos *et al*, 2014). Changes in clinical stage could be a useful and inexpensive method to evaluate treatment response at different time points over the course of the disease. This is a concept with important potential clinical implications in the management of patients treated with continuous therapies mostly resulting in iwCLL PR/PR-L, a broad and heterogeneous response group category. Further studies along the lines of our analysis are warranted.

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Authorship contributions

As study investigators, CM, JD, JCB, and EM collected data and contributed to the analysis and interpretation of data. SS, EH, and DFJ analysed and interpreted data. All authors were involved in manuscript preparation and approved the final version of the manuscript.

Disclosure of Conflicts of Interest

CM: consulting or advisory role with Janssen, Abbvie and Gilead, research funding from Gilead and Roche; JD: honoraria from and consulting/advisory role for Gilead, Janssen, and Roche, research funding from Roche; JCB: research funding from Genentech, Acerta, and Pharmacyclics; WLZ: no relevant conflicts of interest to disclose; SS: employment and equity ownership with Iovance Biotherapeutics Inc., consulting/advisory role with Pharmacyclics LLC, an AbbVie Company; EH, DFJ: employment with Pharmacyclics LLC, an AbbVie Company, equity ownership with AbbVie; EM: equity ownership with Vivia Biotech, honoraria from Janssen, consultancy/advisory role with Janssen, Morphosys, and Pharmacyclics LLC, an AbbVie Company, travel expenses from Janssen.

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