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LETTER

The role of trephine bone marrow biopsies in the era of measurable residual disease—Results from the CLL10 trial of the German CLL Study Group (GCLLSG)

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The advent of BCL-2 inhibitor-based time-limited therapies has currently replaced chemoimmunotherapy as one standard of care in chronic lymphocytic leukemia (CLL). Despite many differences in efficacy and safety profile, both treatment approaches achieve similarly high rates of undetectable measurable residual disease (U-MRD).[1,2] U-MRD has been shown to correlate with progression-free survival (PFS) and even with overall survival (OS) within the MURANO trial,[3] as well as in the CLL14 trial.[4] Currently, U-MRD is accepted by the European Medicines Agency (EMA) as intermediate endpoint within clinical trials.[5]

The iwCLL 2018 response criteria require a bone marrow (BM) aspirate and trephine biopsy for confirmation of complete remission, with immunohistochemistry (IHC) recommended as a tool to differentiate between CLL cells versus benign T- and B-cell infiltrates.[6] While the prognostic value of measurable residual disease (MRD) in CLL has been extensively studied before,[7–11] the role of BM assessments by IHC on trephine biopsies has not yet been evaluated. As both BM aspirations and trephine biopsies are collected using an invasive procedure, their added valued remained a matter of debate. Therefore, prognostic value of BM IHC and flow cytometry-based BM MRD assessments is analyzed herein. Moreover, we investigated whether or not sensitive MRD assessments in the peripheral blood (PB) might be able to completely replace the need for BM assessments. Finally, the impact of central versus local pathology investigations are evaluated.

Patient data were derived from the prospective, randomized CLL10 trial of the GCLLSG, in which chemoimmunotherapy with

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fludarabine, cyclophosphamide, and rituximab (FCR) or bendamustine and rituximab (BR) was administered. BM aspiration and biopsy were performed at final staging 2 months (+28 days) after end of therapy. Central assessment of BM trephine biopsy material for IHC was performed by the hematopathology department in Kiel in conjunction with the prior local pathology. To this end, pathologists aim to identify lymphoid cells with a CLL phenotype in aggregates of lymphoid cells according to the current WHO classification[12] by superimposing B-cell distribution pattern detected by CD20, CD19, or CD79a with the staining for CD5 and CD23 on separate slides. B-cell markers were stained according to standard protocols on an automated stainer. MRD was assessed in the central laboratory in Kiel by four-color flow cytometry at a threshold of 10^{-4} as previously described.[13,14]

We compared the impact of MRD and IHC using Kaplan–Meier landmark analyses of PFS and OS from the time point of sample assessment with log-rank tests and Cox proportional hazards

TABLE 1 Basic patient characteristics according to BM infiltration by IHC as assessed in central laboratories.

Baseline characteristics	IHC−	IHC+	Total
Analysis population, *N*	135	74	209
Treatment, *N* (%)	135	74	209
FCR	87 (64.4)	33 (44.6)	120 (57.4)
BR	48 (35.6)	41 (55.4)	89 (42.6)
Time since first diagnosis (months)	134	74	208
Median (range)	22.3 (0.4–218.0)	26.6 (0.5–163.8)	23.9 (0.4–218.0)
Gender, *N* (%)	135	74	209
Male	99 (73.3)	55 (74.3)	154 (73.7)
Age (years)	135	74	209
Median (range)	60 (40–79)	61 (40–79)	60 (40–79)
Binet stage, *N* (%)	135	74	209
A	34 (25.2)	8 (10.8)	42 (20.1)
B	51 (37.8)	33 (44.6)	84 (40.2)
C	50 (37.0)	33 (44.6)	83 (39.7)
Total CIRS score	135	74	209
Median (range)	2 (0–6)	1.5 (0–6)	2 (0–6)
ECOG performance status, *N* (%)	135	74	209
0	92 (68.1)	48 (64.9)	140 (67.0)
1	39 (28.9)	25 (33.8)	64 (30.6)
2	4 (3.0)	1 (1.4)	5 (2.4)
Type according to hierarchical model, *N* (%)	135	74	209
Deletion 17p	0 (0.0)	0 (0.0)	0 (0.0)
Deletion 11q	25 (18.5)	20 (27.0)	45 (21.5)
Trisomy 12	18 (13.3)	5 (6.8)	23 (11.0)
No abnormalities	39 (28.9)	15 (20.3)	54 (25.8)
Deletion 13q sole	53 (39.3)	34 (45.9)	87 (41.6)
IGHV mutational status, *N* (%)	127	74	201
Unmutated	68 (53.5)	46 (62.2)	114 (56.7)
Serum thymidine kinase (U/L)	130	73	203
Median (range)	17.3 (0.0–304.0)	15.9 (3.2–304.0)	16.9 (0.0–304.0)
Serum β2 microglobulin (mg/L)	130	73	203
Median (range)	3.0 (0.0–6.8)	3.3 (1.4–9.0)	3.1 (0.0–9.0)
CLL-IPI risk group, *N* (%)	122	73	195
Low	37 (30.3)	15 (20.5)	52 (26.7)
Intermediate	50 (41.0)	29 (39.7)	79 (40.5)
High	35 (28.7)	29 (39.7)	64 (32.8)
Very high	0 (0.0)	0 (0.0)	0 (0.0)

Note: Patients with deletion 17p were ineligible for participation in CLL10.

Abbreviations: BM, bone marrrow; IHC−, no BM infiltration by IHC; IHC+, with BM infiltration by IHC).

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regression modeling. Independent prognostic baseline factors for PFS were identified by multivariable analyses using Cox proportional hazards regression modeling with backward and forward selection. All statistical tests were two-sided and *p* values were descriptive without adjustments for multiple testing. The significance level was set at 0.05.

Out of 561 patients who were enrolled in the CLL10 trial, 310 patients (55.3%) underwent BM examinations by IHC. Of these, samples from 209 patients (67.4%) were centrally evaluated.

FCR was administered in 120 (57.4%) of the 209 patients with centrally assessed IHC and 89 patients (42.6%) were treated with BR. For further patient characteristics see Table 1.

Centrally evaluable samples for BM MRD were available in 168 of 209 patients (80.4%). Out of these 168 samples, seven samples (4.2%) tested IHC positive (+) with BM U-MRD, 77 samples (45.8%) tested IHC negative (−) with BM U-MRD, 53 samples (31.5%) were IHC+ with BM detectable MRD (D-MRD), and 31 (18.5%) had discordantly IHC−/BM D-MRD. Patients with BM U-MRD had an

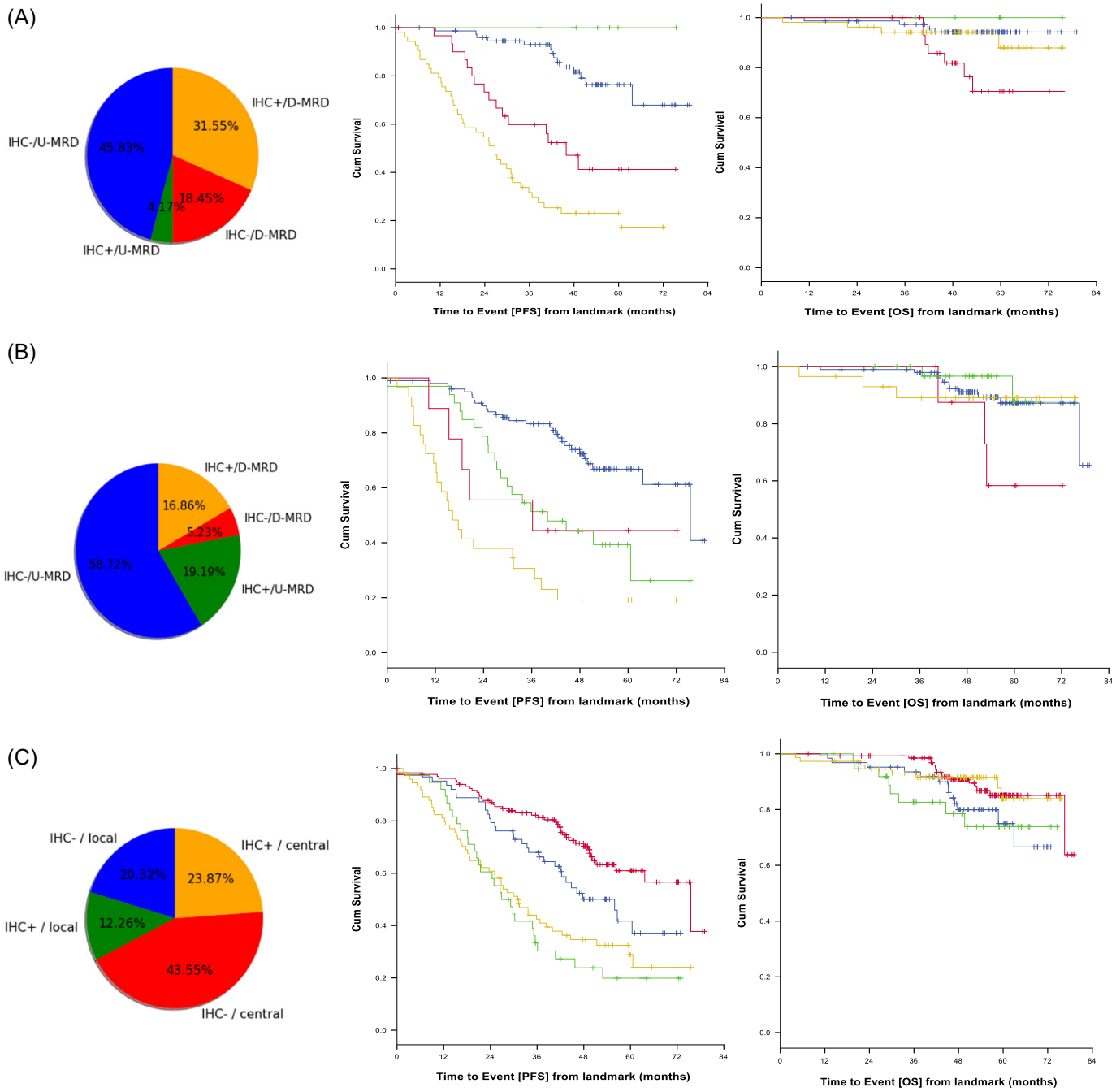


FIGURE 1 (A) Landmark progression-free survival (PFS) and overall survival (OS) according to bone marrow (BM) infiltration by IHC and MRD in BM, analysis population restricted to patients with BM infiltration assessed in central laboratory. (B) Landmark PFS and OS according to BM infiltration by IHC and MRD in PB (analysis population restricted to patients with BM infiltration assessed in central laboratory). (C) Landmark PFS and OS according to BM infiltration by IHC and laboratory (central vs. local). (D-MRD, detectable MRD; PB, peripheral blood; IHC−, no BM infiltration by IHC; IHC+, with BM infiltration by IHC; U-MRD = MRD < 10^{-4}).

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estimated 3-year PFS rate from landmark of 100% if simultaneously IHC+ and an estimated 3-year PFS rate from landmark of 92.9% if IHC− (log-rank $p = 0.202$). Thus, IHC does not seem to contribute to identification of low-risk disease once BM U-MRD is known. In BM D-MRD patients, simultaneous IHC+ showed an estimated 3-year PFS rate from landmark of 31.7%, compared to concordant IHC− with an estimated 3-year PFS rate from landmark of 59.8% (HR = 2.062, 95% confidence interval [CI]: 1.155–3.683, $p = 0.014$). Detecting CLL by IHC in BM D-MRD patients might contribute to identify patients suffering from persistent high-level disease with a poor PFS (Figure 1A). However, very high-risk disease might be identified in the BM and PB with similar accuracy using an additional cut-off at an MRD threshold of 10^{-2}.[7] The estimated 3-year OS-rate from landmark was 100.0% for patients with IHC+/BM U-MRD, whereas patients with IHC−/BM U-MRD had an estimated 3-year OS-rate from landmark of 97.3% (log-rank $p = 0.537$). For patients with IHC+/BM D-MRD, the estimated 3-year OS-rate from landmark was 94.1% versus 100.0% in patients with IHC−/BM D-MRD (HR = 0.368; 95% CI: 0.108–1.258, $p = 0.111$) (Figure 1A).

Analyzing patients with U-MRD in the PB, the estimated 3-year PFS rate was 51.3% for 33 IHC+ patients, compared to 101 patients with IHC− who had an estimated 3-year PFS rate of 83.3% (HR = 2.646, 95% CI: 1.488–4.705, $p < 0.001$). For 29 patients with IHC+ and PB D-MRD, the estimated 3-year PFS rate was 30.7% compared to 55.6% in nine patients with IHC−/PB D-MRD (HR = 2.035, 95% CI: 0.772–5.368, $p = 0.151$) (Figure 1B). The estimated 3-year OS-rate was 100.0% for patients with IHC+/PB U-MRD and 98.0% for patients with IHC−/PB U-MRD (HR = 0.668, 95% CI: 0.146–3.050, $p = 0.602$). Patients with IHC+/PB D-MRD had an estimated 3-year OS-rate from landmark of 89.1% and patients with IHC−/PB D-MRD of 100.0% (HR = 0.364, 95% CI: 0.073–1.807, $p = 0.216$) (Figure 1B).

Next, we investigated whether PB MRD assessments could completely replace both BM investigations, thus obviating the need for this invasive procedure. In univariable analysis, treatment arm, BM infiltration by IHC and MRD in PB and BM, as well as del(11q) status, IGHV mutational status, and serum thymidine kinase at baseline, were identified as prognostic factors for PFS. When considering all these variables in the multivariable analysis, flow MRD in the BM as well as IGHV mutational status were suggested as independent prognostic factors for PFS. We conclude that for better prognostication a flow-based MRD assessment of a BM aspirate remains necessary. Once BM MRD is known, there seems to be no added value of a trephine biopsy, which might be omitted. When excluding MRD from multivariable analysis, treatment arm, IGHV mutational status, and BM infiltration by IHC were identified as independent prognostic factors. Thus, if no MRD assessments are available, a BM examination seems to contribute to prognostication. Multivariable analysis for OS was not performed as BM infiltration by IHC was not significantly associated with landmark OS in univariable analyses.

Within the total population of 310 patients with both locally and centrally assessed IHC, we found that IHC+, evaluated as a single parameter, was associated with shorter PFS as the estimated 3-year PFS rate from landmark was 39.3% versus 77.5% in IHC− (HR = 2.671, 95% CI: 1.942–3.674, $p < 0.001$). We thereafter evaluated the prognostic value of IHC when assessed in local versus central laboratories. Interestingly, IHC− patients with IHC evaluated in a local laboratory (estimated 3-year PFS-rate 68.0%) carried a poorer prognosis compared to patients with IHC tested in the central laboratory (estimated 3-year PFS-rate 82.2%, HR = 1.756, 95% CI: 1.108–2.782, $p = 0.017$). This finding suggests a better specificity of the reference laboratory for IHC− results. The estimated 3-year PFS-rate from landmark for patients with IHC+ was 33.3% for local versus 42.5% for the central laboratory (HR = 1.160, 95% CI: 0.733–1.834; $p = 0.527$) (Figure 1C). The difference between local and central laboratory in IHC− samples might be explained by the fact that there was no common standard when evaluating the local samples. Thus, whenever a trephine biopsy is taken, an assessment in a reference pathology laboratory is advisable.

When investigating OS from landmark time point of sample assessment according to BM infiltration by IHC and local versus central laboratory, no significant differences were detected. This might be explained by effective subsequent treatments. The estimated 3-year OS-rate from landmark for patients with IHC− was 93.5% if assessed by local laboratory and 98.5% by central laboratory (HR = 1.983, 95% CI: 0.943–4.170, $p = 0.071$). The estimated 3-year OS-rate from landmark for patients with IHC+ was 82.6% for local laboratory and 93.1% for central laboratory (HR = 2.114, 95% CI: 0.793–5.639, $p = 0.135$) (Figure 1C).

In summary, we could confirm that MRD seems to be a valid prognostic parameter for PFS for time-limited therapies, although these data comprise only chemoimmunotherapies and should be re-evaluated for targeted agents if data on both, MRD and IHC, are available. This is consistent with a pooled analysis of phase 3 trials based on chemoimmunotherapy combinations (CLL8, CLL10, CLL11), which has also shown a significant relationship between MRD in the PB and PFS.[11] Within this patient population of the CLL10 trial, no statistically relevant difference in OS could be shown. IHC was confirmed as an independent prognostic marker in multivariable analysis for PFS when flow cytometry-based MRD was excluded.

Although both methods, flow MRD as well as IHC, add valuable information on depth of response, the results of the multivariable analyses indicate that flow MRD in BM provides the prognostic information needed and patients may be spared an additional biopsy. If a biopsy is performed, we recommend to evaluate the histology centrally to improve the prognostic value of the assessment.

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Nadine Kutsch, Sandra Robrecht, Sebastian Böttcher, Wolfram Klapper, Barbara Eichhorst conceived and designed the analysis. Nadine Kutsch, Anna Fink, Elisabeth Lange, Rudolf Weide, Michael G. Kiehl, Martin Sökler, Rudolf Schlag, Ursula Vehling-Kaiser, Georg Köchling, Christoph Plöger, Michael Gregor, Torben Plesner, Michael R. Clausen, Marco Herling, Kirsten Fischer, Hartmut Döhner, Clemens-Martin Wendtner, Michael Hallek, Barbara Eichhorst collected the data. Ilske Oschlies, Matthias Ritgen, Karl-Anton Kreuzer, Stephan Stilgenbauer, Sebastian Böttcher, Wolfram Klapper contributed data or analysis tools. Sandra Robrecht performed the statistical analysis. Nadine Kutsch wrote the first draft of the paper. All authors contributed to manuscript revision, read, and approved the submitted version.

CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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