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Utility of Measurable Residual Disease for Predicting Treatment Outcomes with BCR- and BCL2-Targeted Therapies in Patients with CLL

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Abstract

Inhibitors targeting B-cell receptor (BCR) signaling pathway proteins and B-cell lymphoma-2 (BCL2) in chronic lymphocytic leukemia (CLL) are recommended in the first-line and relapsed/refractory disease settings. Measurable residual disease (MRD) is an important prognostic tool in patients treated with the BCL2-targeted agent, venetoclax. We explored the relationship between MRD status and progression-free (PFS)/overall survival (OS) in patients with CLL, following treatment with novel BCR- and BCL2-targeted agents. Compared with chemoimmunotherapy, higher rates of undetectable (u)MRD were achieved with BCL2-targeted therapies; achieving uMRD status was associated with longer PFS and OS than MRD-positivity. Continuous treatment with BCR-targeted agents did not achieve uMRD status in many patients, and outcomes were not correlated with uMRD status. Future clinical trials of targeted treatment combinations could be designed to demonstrate uMRD as a treatment objective, and allow a response-driven, personalized strategy to optimize treatment and improve OS outcomes.

Keywords

Lymphoid leukemia; pharmacotherapeutics; prognostication

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Author contributions

All authors were involved in interpreting the data and writing the manuscript. All authors approved the final version for submission.

Introduction

In trials of chemoimmunotherapy for treatment of patients with chronic lymphocytic leukemia (CLL), achieving undetectable measurable residual disease (uMRD) status at end of treatment (EOT) has been shown to be an independent prognostic marker for longer progression-free (PFS) and overall survival (OS), independent of clinical response status [1–7].

In the phase III CLL8 trial of first-line (1L) rituximab plus fludarabine and cyclophosphamide (FCR), median PFS was 68.7 months in patients who had uMRD status ($<10^{-4}$) 2 months after treatment, compared with 40.5 and 15.4 months in patients with intermediate ($\geq 10^{-4}$ to $<10^{-2}$) or high ($\geq 10^{-2}$) MRD levels, respectively [6]. Median OS was 48.4 months in patients with high MRD and not reached (NR) in those with uMRD or intermediate-MRD [6]. Combined analysis of data from CLL8 and CLL10 (FCR *vs.* bendamustine + rituximab [BR]) showed that MRD quantification improved the predictive value of clinical response for PFS outcome [8]. Moreover, later modeling analyses from the German CLL Study Group based on data from >1000 patients treated in the CLL8, CLL10, and CLL11 (obinutuzumab [G] + chlorambucil [Clb] *vs.* R-Clb *vs.* Clb) trials demonstrated a statistically significant treatment effect on peripheral blood (PB) uMRD and on PFS, supporting the use of MRD as a surrogate endpoint [9].

However, uMRD rates obtained at EOT from the intent-to-treat (ITT) populations in trials of 1L chemoimmunotherapy are relatively low (rates for PB and bone marrow [BM] uMRD ranging from 3%–64% and 1%–36%, respectively) [6,10–13]. Limited data on MRD status following chemoimmunotherapy are available in the relapsed/refractory (R/R) setting; one study of FCR demonstrated PB and BM uMRD in only 24% and 12%, respectively, of patients from the ITT population with complete response (CR) [14].

Several novel agents targeting key CLL pathogenic pathways are now approved, including the B-cell lymphoma-2 inhibitor (BCL2i) venetoclax (Ven), and B-cell receptor (BCR) signaling pathway inhibitors including Bruton's tyrosine kinase inhibitors (BTKi's) ibrutinib (Ibr) and acalabrutinib (Acala), and phosphatidylinositol-3-kinase inhibitors (PI3Ki's) idelalisib (Idela) and duvelisib [15,16]. BTKi's and PI3Ki's are administered continuously until disease progression (PD) [17–20]. This continuous treatment strategy prolongs PFS and OS, but CR rates using the International Workshop on CLL (iwCLL) criteria [21] are low; furthermore, uMRD status is very infrequently attained, thereby reducing the potential for treatment discontinuation and a durable remission off-treatment [22–30]. Therefore, while continuous treatment typically maintains disease control, toxicities, development of resistance, and cost implications of such regimens have led to increasing consideration of fixed-duration therapy options [31].

BCL2i-based therapies result in deep remissions and high uMRD rates, independent of high-risk factors, through fixed-duration treatment [32,33]. Fixed-duration VenG and VenR demonstrated significant efficacy, which was maintained at the 4–5-year follow-ups, with manageable toxicity, in phase III trials in the 1L (CLL14) and R/R (MURANO) settings, respectively [20,32–35]. Unlike continuous BTKi therapy, fixed-duration treatment with

VenG or VenR demonstrates high rates of uMRD in PB and/or BM [32,36–40], with durable remissions off-treatment [32,33]. Thus, the BCL2-targeted treatment strategy is to treat patients for a fixed duration to achieve remission, to monitor their disease during remission, and to plan for re-treatment if/when relapse and progression occur.

Although the association between achieving uMRD status and long-term outcomes has been established for chemoimmunotherapy [5–7], it has been less conclusive with BCL2i-based treatment due to the lesser availability of trial data with targeted agents, and relatively shorter follow-up. We performed a systematic scoping literature review [41] to evaluate and summarize the relationship between MRD response and clinical outcomes (PFS and OS) following treatment with novel BCR- or BCL2-targeted agents in patients with CLL.

Methods

The research question to be investigated was: *does uMRD attainment following BCR-targeted or BCL2-targeted treatment correlate with improved PFS and/or OS in patients with CLL?*

Data Search Strategy

Using Medical Subject Heading terms and keywords, the PubMed, Cochrane, and Embase databases were searched for research articles and published abstracts. Registered clinical trials (within clinicaltrials.gov or EudraCT) were also searched in public domains. Keywords used in the search strings are in Supplemental Table 1 and the full list of inclusion/exclusion criteria is shown in Supplemental Table 2.

All trial publications reporting data on MRD and treatment outcomes, using quantitative and/or qualitative assessments, from January 1, 2010 to December 31, 2021 were included, to capture the relevant phase II/III trials for novel targeted agents (US Food and Drug Administration approval of the first novel targeted agent, Ibr, occurred in 2013).

Data Screening and Extraction

Titles and abstracts of all records (research articles, abstracts, and clinical trial records) were screened in accordance with the inclusion/exclusion criteria by two independent reviewers working in parallel. In cases of discrepancy between the two reviewers, a third reviewer was consulted. Records not meeting the study criteria were excluded. Screening of the full text of ‘included’ publications was then performed by two independent reviewers working in parallel. A third reviewer was used for adjudication in cases of non-alignment between the two reviewers.

The final set of records was then grouped based on the study number/identifier, and key data from these studies were compiled. Details captured from each study were: study population, intervention, doses and treatment duration, MRD assessment method, MRD outcomes, OS, PFS, and key conclusions related to MRD.

Data Summary

A descriptive summary of the findings is presented. Unless otherwise specified, all rates of MRD are given for the ITT population (all enrolled/randomized patients); where not provided in the publication, values were re-calculated as a proportion of the ITT population. Generally, for fixed-duration regimens, uMRD rates were reported at EOT; for continuous treatment regimens, best uMRD rates were reported.

Results

Search and Study Selection

In total, 925 records were obtained from the searches. After excluding duplicates and records not meeting the inclusion criteria, 118 records covering 44 clinical trials were included for analysis (Figure 1). Summary details of the final included studies are provided in Supplemental Tables 3–5. Details of MRD testing methods, cut-offs for uMRD status and concordance between PB and BM uMRD are provided in the Supplemental Results, Supplemental Figure 1, and Supplemental Table 6.

Association Between uMRD Status Achievement with Novel Targeted Therapy and PFS

Details of trials evaluating the association are presented in Table 1.

BCR-Targeted Therapy

Data evaluating association between uMRD attainment and PFS were sparse. The 1L E1912 trial of continuous Ibr, with R for cycles 2–7, found no significant difference in PFS between patients achieving or not achieving PB uMRD status [42]. However, when MRD was analyzed as a continuous variable on a $\log_{10}$ scale, patients with higher levels of MRD tended to have shorter PFS for each 10-fold increase in MRD level (HR 2.08; 95% CI [confidence interval], 0.84–5.16 at 12 months) [42].

In the R/R HELIOS study of continuous Ibr until PD or unacceptable toxicity, with BR for cycles 1–6, 3-year PFS rates were numerically higher in patients with uMRD *vs.* those who were MRD-positive (88.6% *vs.* 60.1% respectively) [43].

BCL2-Targeted Therapy

In the 1L CLL14 study (fixed-duration VenG for 12 months), landmark analysis of PFS from EOT demonstrated a HR of 0.10 for patients with uMRD at EOT ($<10^{-4}$) *vs.* those who were MRD-positive; a further landmark analysis showed that patients with uMRD $\leq 10^{-5}$ at EOT had 2-year post-EOT PFS of 93% *vs.* 37% in patients with MRD levels $>10^{-2}$ [34,44].

Median PFS was NR in R/R patients with a best response of PB uMRD during treatment with fixed-duration Ven-monotherapy in the VENICE-1 trial compared with 30.5 months in the overall population [45]. Similarly, median PFS was NR in patients with uMRD after a median 16 months of continuous Ven-monotherapy ($P = .0019$ *vs.* MRD-positive group [median PFS 21.9 months]) in the M14–032 study in patients with R/R CLL progressing after prior Ibr or Idela therapy [46]. Further, the M13–982 trial of continuous Ven-monotherapy in patients with R/R CLL and chromosome 17p deletion (del(17p)) found

that patients who achieved uMRD were less likely to have PD or die compared with patients achieving clinical response but remaining MRD-positive (at median 23 months on therapy) [47].

At the 3-year follow-up of the MURANO trial in patients with R/R disease (fixed-duration VenR for 6 months, followed by Ven-monotherapy up to maximum of 2 years) [36], landmark analysis of PFS from end of combination treatment (EOCT) demonstrated a HR of 0.48 for patients with uMRD *vs.* intermediate-MRD-positive status, 0.15 for uMRD *vs.* high-MRD-positive and 0.24 for intermediate-MRD-positive *vs.* high-MRD-positive status. This was sustained at the 4-year follow-up [48]. At the 5-year follow-up (3 years post-EOT), 32/83 patients (39%) with uMRD at EOT remained in ongoing uMRD status; baseline presence of high-risk prognostic factors was associated with increased risk of MRD conversion and PD [35].

Combination BCR-/BCL2-Targeted Therapy

At 1 year of follow-up in the 1L GLOW trial, PFS was similar for patients with/without uMRD status in the fixed-duration Ven-Ibr arm, while patients treated with G-Clb who achieved uMRD status had longer PFS than those with detectable MRD [49].

Association Between uMRD Status and OS

Findings are available in Table 1.

BCR-Targeted Therapy

No difference in OS in relation to MRD status was observed in patients who responded to Ibr-BR treatment in the HELIOS study on multivariate analysis (median 34.8 months on-study) [43].

BCL2-Targeted Therapy

The fixed-duration regimen studies, CLL14 and MURANO, indicated that achieving uMRD status after VenG or VenR, respectively, was linked to improved OS. A CLL14 *post-hoc* analysis found longer OS in patients with uMRD at EOT (medians NR, median follow-up 39.6 months) [50]. Similarly, in MURANO, achieving uMRD status at EOT with VenR was associated with a trend toward improved OS (OS 3 years post-EOT 95% *vs.* 85% in patients with uMRD *vs.* MRD-positive status at EOT, respectively) [35].

Independence of uMRD from Clinical Response as a Prognostic Marker

BCR-Targeted Therapy—Findings from the 1L E1912 trial showed that MRD-positive patients without CR at 12 months of treatment had significantly worse PFS compared with patients with CR or uMRD status (HR 3.73; 95% CI, 1.14–12.27) [42]. Further, patients with uMRD status had similar PFS regardless of CR status, although patient numbers were small.

BCL2-Targeted Therapy—Landmark analysis of PFS according to uMRD status at EOT in CLL14 showed that the improved PFS with uMRD *vs.* MRD-positive status (HR 0.10;

95% CI, 0.06–0.15) was seen regardless of clinical response (in a combined analysis of patients treated with 1L VenG and G-Clb) [50].

Similarly, at the 3-year follow-up of the MURANO trial [36], improved PFS was observed in R/R patients who achieved uMRD at EOCT, regardless of clinical response or treatment arm at EOCT (Table 1). Landmark analysis showed that VenR-treated patients achieving partial response (PR) and uMRD at EOCT had similar PFS to those achieving CR and uMRD (HR 0.71; 95% CI, 0.24–2.14). Patients with PR and detectable MRD had inferior PFS after EOCT *vs.* those with PR and uMRD in Kaplan–Meier analysis [36]. At 4-years' follow-up, MRD status did not seem to affect PFS in patients achieving CR/CR with incomplete hematologic recovery [48].

Rates of uMRD Achieved with Targeted Therapies

BCR-Targeted Therapy—In the 1L setting (Figure 2A), the lowest rates of PB and BM uMRD were seen in trials of continuous Ibr-monotherapy (e.g. 1% PB uMRD after 1 year, GELLC-7 [51]; 6% after 4 years, NCT01500733) [52]. Rates increased with addition of a CD20 monoclonal antibody (mAb), with a uMRD rate of 30% after ~2.5 years in the iLLUMINATE trial (continuous Ibr with G for cycles 1–6) [30]. BM uMRD rates following 1L treatment were highest in the NCT02007044 trial of IbrR (25%, although numbers were small [$n = 12$]) [53], and the iLLUMINATE trial of IbrG (20%) [30].

In the R/R setting (Figure 2B), rates of PB uMRD ranged from 7% with ublituximab (Ubli)-Ibr after 6 months of follow up to 46% after 42 months of follow-up (GENUINE) [54].

In 1L trials of Ibr that included a response- and/or MRD-guided maintenance component, a substantial number of patients achieved or maintained uMRD following maintenance (Figure 2C).

BCL2-Targeted Therapy—Trials of BCL2-targeted therapies mainly evaluated fixed-duration regimens. PB uMRD rates achieved at EOT in the 1L setting ranged between 38% with BR-VenR (3 cycles BR, followed by 12 Ven-containing cycles; NCT03609593) [55] and 89% with VenG (CLL13) [56] (Figure 3A). Rates were generally lower in the R/R setting, with the highest rate achieved with VenR in the MURANO trial (64%) [32]. BM uMRD rates achieved at EOT in 1L trials ranged from 35% with BR-VenR (NCT03609593) [55] to 73% with VenG (CLL13) [56]. One trial of BCL2-targeted therapy in the R/R setting reported a BM uMRD rate of 50% with atezolizumab-VenG (NCT02846623) [57]. Two trials evaluated continuous treatment with Ven-monotherapy in the R/R setting, demonstrating PB uMRD rates of 22–30% (M14–032 and M13–982); one additional trial had a uMRD rate of 46% with the CD19 mAb tafasitamab (Tafa) plus Ven (COSMOS cohort B) (Figure 3B) [58].

In the HOVON 139/GIVE trial of 1L VenG, following treatment cycle 14, patients with a clinical response were randomized to fixed-duration treatment with 12 cycles of Ven-monotherapy or MRD-guided Ven (in which MRD-positive patients at cycle 14 received 12 cycles of Ven-monotherapy and patients with uMRD status discontinued). Following

12 months of treatment or observation in the MRD-guided group, 57% of patients had maintained or achieved uMRD status (Figure 3C). The IMPROVE trial of Ven-monotherapy in R/R disease showed that 84% of the 19 patients (of 38; 50%) who did not achieve uMRD status following 12 cycles of Ven-monotherapy achieved uMRD status following 12 months' Ven-Ibr maintenance (Figure 3C).

Combination BCR-/BCL2-Targeted Therapy—One 1L trial of fixed-duration combination BCL2 and BCR-targeted therapy demonstrated PB and BM uMRD rates of 88% and 78%, respectively, with Ven-IbrG (CLL13) (Figure 4A) [56].

In the R/R setting, the CLARITY trial showed BM uMRD rates of 35% after 1 year and 44% after 2 years of continuous Ven-Ibr treatment (Figure 4B) [59].

In the 1L CAPTIVATE trial MRD cohort, similar PB uMRD rates were observed in patients following 12 months' maintenance with placebo or Ibr-monotherapy (84% and 77%, respectively) following uMRD achievement with 12 months' combination therapy with Ven-Ibr (Figure 4C) [60]. Similarly, 12 months after randomization to observation or Ibr-monotherapy following achievement of CR plus uMRD at 15 cycles of Ven-Ibr for R/R disease, similar rates of BM uMRD were observed (71% and 75%, respectively) in the VISION-HO141 trial (Figure 4D) [61].

uMRD Rates in Patients with High-Risk Genetic Features

BCR-Targeted Therapy—Most BCR-targeted therapy trials showed similar rates of uMRD in patients with high-risk genetics compared with the overall population (Table 2). Multivariate analysis from the E1912 trial (IbrR) found that having mutated IGHV was associated with achieving uMRD status [42].

BCL2-Targeted Therapy—Similar to findings with BCR-targeted therapy, the rates of uMRD achieved by BCL2-targeted therapies were generally comparable between patients with high-risk genetics and the overall population (Table 2). In the 1L setting, this was observed in the CLL14 and CLL2-BAG trials [33,50,62]. In the R/R setting, the MURANO trial (VenR) found that uMRD status at EOT was not associated with four major cytogenetic alterations (del(17p), chromosome 11q deletion, Trisomy 12, or chromosome 13q deletion) [36,48]. High and low karyotypic complexity (≥3 or ≥5 structural and/or numerical chromosomal aberrations, respectively [63]) correlated with MRD-positive status at EOT; 36% of patients without complex karyotype (CK) were MRD-positive, compared with 42% and 50% of patients with low and high CK, respectively [56,64,65]. Further, patients treated with VenR who had *TP53, NOTCH1, XPO1*, or *BRAF* mutations had numerically lower rates of uMRD.

Combination BCR-/BCL2-Targeted Therapy—Similar patterns were found when BCR and BCL2-targeted therapies were given in combination, with the exception of the AVO (Acala-VenG) trial in 1L [66], which reported lower rates of uMRD in patients with high-risk genetics compared with the overall study population. A univariate analysis using data from patients treated with Ven-IbrG in the OSU-14266 trial found no association

between high-risk genetic markers including unmutated IGHV, presence of del(17p), or CK and achievement of uMRD status [67].

MRD Responses Below 10^{-4} Following Treatment with Novel Oral Targeted Agents

BCR-Targeted Therapy—At EOT in the ICLL-07 trial (following 9 months of IbrG and 6 months of Ibr plus FCG therapy [iFCG; in 92% of patients]) [68], 67% of patients had BM uMRD at a cutoff $<10^{-6}$ (79% $<10^{-4}$). In a phase II trial in 45 patients (NCT02629809) [69], BM uMRD $<10^{-5}$ assessed via next-generation sequencing (NGS) was achieved after three cycles of iFCG by 56% of patients and by 42% at $<10^{-6}$ (87% $<10^{-4}$ by flow cytometry), increasing to 71% and 47%, respectively (89% $<10^{-4}$) after a further three cycles of IbrG, and 78% and 51%, respectively, after a further six cycles of Ibr-monotherapy or IbrG (91% $<10^{-4}$) [69,70].

BCL2-Targeted Therapy—In CLL14 [44], at 3 months post-EOT, 42% of VenG-treated patients had PB uMRD $<10^{-6}$ (75% $<10^{-4}$).

Combination BCR-/BCL2-Targeted Therapy—The CLARITY study reported that, after 12 months of Ven-Ibr in R/R patients, 29% of patients had uMRD $<10^{-5}$ (35% $<10^{-4}$) [71].

uMRD Response Duration

BCR-Targeted Therapy—Of 61 patients who began Ibr maintenance with BM uMRD status following iFCR in the NCT02251548 trial, 13 (21%) had recurrent BM MRD positivity; median time to MRD recurrence NR [72]. In a phase II trial of Ubli plus umbralisib (U2)-Ibr, of 16 patients who entered treatment-free observation (15 due to achievement of uMRD), no progression was observed at median 242 days off treatment [73].

BCL2-Targeted Therapy—In CLL14, uMRD was sustained in many patients throughout treatment up to month 18 of follow-up [44]; PB uMRD was achieved by 75% of VenG-treated patients 3 months post-EOT, 81% 12 months post-EOT, 47% 18 months post-EOT, and 27% 30 months post-EOT [74]. At 12 months post-EOT, the HR for MRD conversion was 0.19 (95% CI, 0.12–0.30). At a median follow-up of 39.6 months, 10 of 90 patients with uMRD $<10^{-6}$ at EOT converted to MRD positivity, including one patient with PD; 18-month conversion-free survival was 88%.

In MURANO [32,48], 62% of patients had uMRD at EOCT (after 6 months' VenR) and 48% had uMRD at EOT (after 2 years' Ven). Of the 83 patients who completed 2 years of Ven and had uMRD at EOT, 70% had uMRD status at a median 9.9 months post-EOT, and 39% had ongoing uMRD status at 3 years post-EOT [32,35,36,48].

Combination BCR-/BCL2-Targeted Therapies—In GLOW [75], 55% of patients receiving 1L fixed-duration Ven-Ibr achieved uMRD status 3 months post-EOT, of whom 85% maintained uMRD status to 12 months post-EOT [49,75]. In the 1L cohort of the NCT02756897 trial [76], after a median follow-up of 12.4 months, 8/53 (15%) patients with

uMRD after 24 cycles of Ven-Ibr had MRD recurrence, five of whom had first achieved uMRD status at completion of 24 cycles. In a phase II trial of Ven-Ibr from the MD Anderson Cancer Center, at a median follow-up of 29 months, 29/45 (64%) patients have achieved uMRD, with two patients subsequently progressing [77]. Of the patients receiving U2-Ven in the NCT03801525 trial, 45% (18/40) had PB uMRD at EOT; 18% (7/40) had uMRD 6 months post-EOT, and 10% (4/40) had uMRD 12 months post-EOT [78,79].

Discussion

We explored whether attaining uMRD status following treatment with BCR- or BCL2-targeted therapies, either as fixed-duration or continuous treatment regimens, including regimens with an MRD-guided treatment component (for 1L treatment or R/R disease), correlated with longer PFS and OS in patients with CLL, compared with an MRD-positive status. BCR-targeted therapies resulted in low rates of uMRD attainment; however, achievement of uMRD was associated with improved PFS *vs.* MRD-positivity. BCL2-targeted agents generally achieved deep, durable responses, with high rates of uMRD; achievement of uMRD was associated with prolonged PFS, independent of clinical response status, and prolonged OS.

BCR-Targeted Therapy

Achievement of PB uMRD $<10^{-4}$ was infrequent in patients treated with Ibr in 1L (rate with Ibr-monotherapy, 1–6%), although rates were increased with the addition of a CD20 mAb, in particular G (30% after 2.5 years with IbrG in iLLUMINATE) [30], and prolonged duration of treatment. BM uMRD rates showed a similar pattern. In patients with R/R disease, the highest rate of BM uMRD was achieved by Ubli-Ibr in the GENUINE trial (46% after 42 months' follow-up) [80]. BM uMRD data were sparse in R/R trials.

Deep responses were achievable in a proportion of patients who received Ibr plus chemotherapy, with uMRD $<10^{-6}$ rates of 42–67% reported in patients who received iFCG in the ICLL-07 and NCT02629809 trials [68,70]. Rates of uMRD achieved were generally comparable between patients with high-risk cytogenetics and the overall trial populations, although no data on depth of response were available in high-risk patients.

Data on association between uMRD and PFS with BTKi's were limited, and likely impacted by the low rates of uMRD attainment. One trial evaluated PFS outcomes in patients with uMRD at $<10^{-4}$ and MRD-positive patients following 1L IbrR (E1912), and found no significant difference between the groups at any timepoint, although PFS was longer in patients with MRD < *vs.* $>10^{-1}$ [42]. However, in the R/R HELIOS trial, after a median of 35 months on therapy, Ibr-BR was shown to improve PFS over placebo-BR in patients with uMRD, intermediate-MRD-positive status, and high-MRD-positive status. Multivariate analysis from HELIOS showed no difference in OS among these response categories.

BCL2-Targeted Therapies

High PB uMRD rates were seen following fixed-duration BCL2-targeted therapy with Ven-containing regimens in the 1L and R/R settings. Trials of VenG and VenR demonstrated rates of 72–89% [33,56,81], with the exception of the NCT03609593 trial [55], which had a lower

PB uMRD rate of 38% following BR-VenR treatment, perhaps due to compromised Ven delivery owing to myelosuppression with the addition of bendamustine. BM uMRD rates followed a similar pattern. Fewer data were available in the R/R setting, with the highest PB uMRD rates observed with VenR in the MURANO trial [32]. Rates of PB uMRD in patients treated with continuous Ven-monotherapy were lower, ranging from 22 to 30%, although a small trial of Tafa-Ven demonstrated a uMRD rate of 46% after 15 months [58]. There was a lack of data on MRD-guided maintenance following Ven-based treatment; one small study in R/R CLL found that 16 of 19 patients who did not achieve uMRD with VenG went on to attain uMRD status following 12 months' Ibr maintenance [82].

Similar to BCR-targeted therapies, most trials reported comparable uMRD rates in patients with high-risk genetics *vs.* the overall study population. However, earlier reemergence of MRD and shorter PFS have been observed for patients with high-risk biological features treated with fixed-duration Ven-based regimens, indicating more rapid kinetics of disease regrowth [74]. Notably, genomic complexity has not been associated with significantly inferior outcomes in 1L Ven-based treatment, but more so in the R/R setting [48,83]. Longer follow-up is needed, as divergence in outcomes based on presence/absence of genomic complexity may subsequently emerge, but this suggests that early Ven treatment may overcome this risk feature to some degree.

uMRD status achieved with fixed-duration Ven-based regimens was typically sustainable for more than 12 months post-EOT in the majority of patients, with prolonged PFS even after patients stopped therapy. Data from the CLL14 and MURANO trials indicate that uMRD achievement following fixed-duration Ven-based therapies is associated with prolonged PFS, and potentially OS; however, it is still too early to accurately assess the impact on OS, given the overall good prognosis, few deaths, and availability of effective salvage regimens for patients receiving targeted therapies. Therefore, longer follow-up of these clinical trials is needed. This aligns with findings from a quantitative meta-analysis of 11 chemotherapy and chemoimmunotherapy studies (median follow-up 28 months–12.8 years) showing significant association between uMRD status and OS, which was not maintained when considering only patients who achieved CR [4]. As clinical trials with extended follow-up indicate that patients achieving a deep response with uMRD have better long-term survival than those with persistent MRD [39], therapy directed at eradication of detectable MRD may become a desirable goal in clinical practice.

Combination BCR- and BCL2-Targeted Therapies

Data on association between uMRD attainment and PFS in patients treated with combination BCR- and BCL2-targeted therapies are limited to date. Early data from the 1L GLOW trial of Ven-Ibr found similar PFS of 90% at 12-months post-EOT; although in the chemoimmunotherapy comparator arm, it was seen that MRD-positive patients relapsed more quickly than those with uMRD [49].

The CLL13 trial demonstrated high PB and BM uMRD rates following 1L Ven-IbrG of 88% and 78%, respectively [56]. The highest rates of PB and BM uMRD seen in the R/R setting with a continuous treatment regimen were with Ven-Ibr in the CLARITY trial [59], although rates were lower than those achieved with fixed-duration VenR in MURANO [32].

MRD Assessment Methodology

Flow cytometry (mainly 4-color [sensitivity 10^{-4}] [84] and 8-color [sensitivity 10^{-5}] [85]), was the most commonly used method for MRD detection for clinical trials included in this analysis. This fits with the recent review by Al Sawaf et al. [86] which highlights harmonization efforts by the European Research Initiative on CLL [87] for flow cytometry MRD assessment across trials, and compares with polymerase chain reaction and NGS testing. While deeper response levels (MRD levels $<10^{-5}$ or lower) are informative for greater depth of remissions, allowing serial tracking of response kinetics (and re-growth), currently the $<10^{-4}$ threshold should be maintained, as it is most robustly correlated with long-term clinical outcomes from the chemoimmunotherapy era. However, future investigations of more potent novel targeted treatment combinations in clinical trials should explore the potential impact of deeper responses. Furthermore, to be relevant for standard-of-care treatment, and particularly in relation to MRD-directed therapy, future clinical investigations will need to utilize MRD methodology that meets the regulatory standards. Although few studies assessed concordance levels between MRD assessment based on PB and BM, reported concordance levels were high. This suggests that assessment of MRD in PB, which is more convenient than BM sampling, is highly reliable and also appropriate for serial clinical trial assessments.

Limitations

Due to variations in study protocols/methodology across the final set of studies considered in this review, conclusive evidence on the research question could not be established. Risk of bias is inherent with this type of analysis; however, to reduce this risk, first- and second-pass screening was carried out by two independent reviewers, and results were subject to adjudication and reconciliation at each stage. However, publication bias could not be excluded. Immortal-time bias may also be present, particularly for studies that did not clearly define the starting point for time-to-event endpoint calculations.

Clinical Perspective

Approved fixed-duration targeted therapy for CLL currently consists of Ven-based regimens. Trials of MRD-directed therapy are lacking generally; no such trials have been conducted for chemoimmunotherapy, and data are very limited for Ven-based treatment. Yet, as outlined in this article, an MRD-guided strategy may provide additional benefits to fixed-duration or continuous treatment regimens in terms of improved efficacy and quality of life, or reduced toxicity and exposure. Clinical trials are needed to address this question. The use of Ven-based consolidation strategies is also relevant, with the aim of deepening remission by converting continuous treatment to fixed-duration treatment.

A substantial body of evidence correlates uMRD status with longer PFS and OS following fixed-duration Ven-based treatment, irrespective of whether Ven is used as monotherapy, or in combination with a CD20 mAb. It remains to be seen whether Ven in combination with other targeted agents (BTKi’s or PI3Ki’s) achieves long-term survival.

Targeted therapy with BCR signaling pathway small molecule inhibitors (BTKi’s and PI3Ki’s) is administered continuously without expectation of uMRD in a notable proportion

of patients. Thus, if a patient on such treatment achieves uMRD status, an option may be to discontinue treatment.

The question remains as to whether MRD testing should be recommended outside of clinical trials. Our review does not address the limitations of using MRD to assess clinical outcome in the community practice setting, nor does it address the implications of MRD assessment for patients of different genetic high-risk subgroups. However, uMRD achievement in the context of fixed-duration Ven-based treatment has stronger prognostic value than iwCLL response, since it is much more widely evaluated and independently validated (with iwCLL response being largely based on consensus regarding arbitrary cut-offs rather than disease biology). Already, MRD status has current clinical implications where prognostication is desired e.g. at EOT, and therefore wider adoption of MRD assessment warrants consideration.

Conclusions

MRD status is an important prognostic tool in patients with CLL receiving fixed-duration therapy. BCL2-targeted therapy achieves uMRD status in a high proportion of patients with fixed-duration treatment, and uMRD status is correlated with longer PFS and OS than MRD-positive status, as with chemoimmunotherapy. Compared with chemoimmunotherapy, higher rates of uMRD are achieved with Ven-based targeted therapies. However, as data are limited, we can only determine that the association of uMRD status and PFS is independent of CR in Ven-based studies.

BCR pathway inhibitor-based treatment (BTKi's and PI3Ki's) is continuous and does not achieve uMRD status for the vast majority of patients. Thus, consideration of the association of uMRD status with outcome is less relevant for these agents. Combination targeted trials (BTKi's plus BCL2i) have often used fixed-duration treatment and have achieved high uMRD rates, but follow-up is too short to allow firm correlations to be drawn. Future clinical trials of novel targeted treatments should explore MRD-guided therapy approaches and include longer follow-up to assess the impact of uMRD with targeted treatments on OS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

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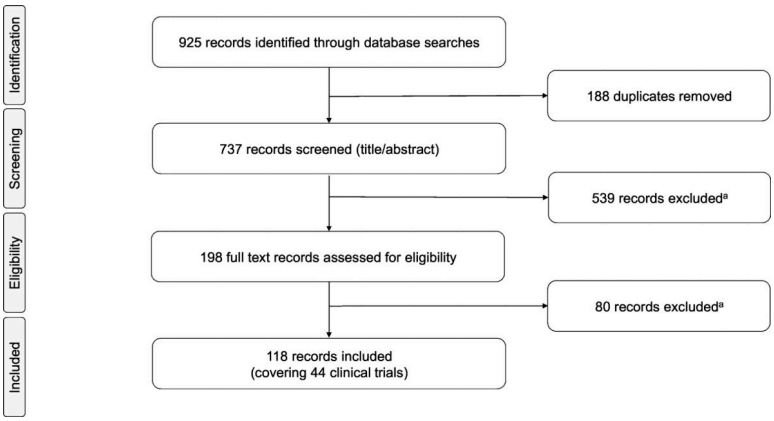


Figure 1.

PRISMA flow chart detailing numbers of included records at each step and reasons for exclusion.

[a]Reasons for exclusion: ineligible population (e.g. non-chronic lymphocytic leukemia histology), study designs, interventions or with non-relevant (non-measurable residual disease-related) outcomes, phase I trial, real-word evidence study, non-original data.

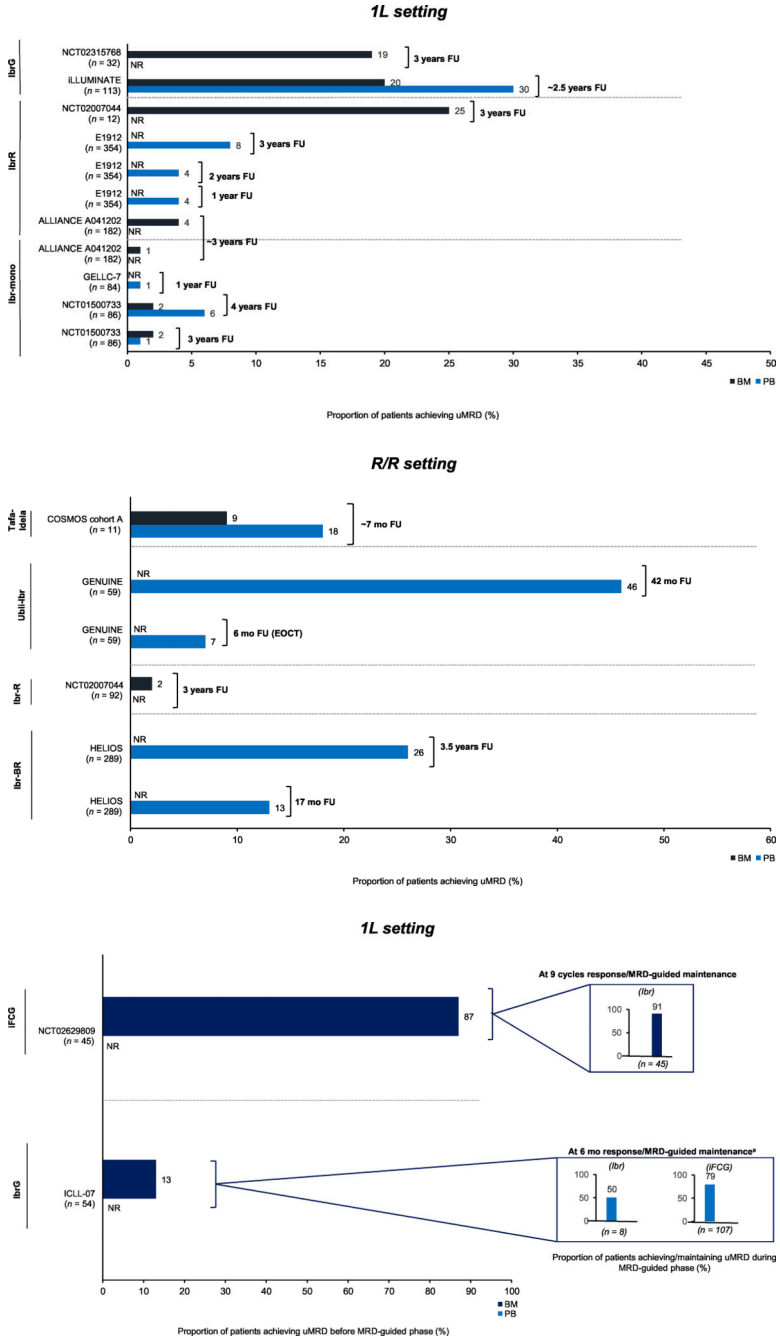


Figure 2.

Rates of uMRD during continuous BCR-targeted therapy in the 1L setting (A), for R/R disease (B) and in trials with an MRD- or response-guided component (C) (ITT populations).

1L, first-line; B, bendamustine; BCR, B-cell receptor; BM, bone marrow; EOCT, end of combination treatment; FU, follow-up; G, obinutuzumab; Ibr, ibrutinib; Idela, idelalisib; iFCG, ibrutinib plus fludarabine, cyclophosphamide, and G; ITT, intent-to-treat; mono, monotherapy; MRD, measurable residual disease; mo, months; NR, not reported;

PB, peripheral blood; R, rituximab; R/R, relapsed/refractory; Tafa, tafasitamab; Ubli, ublituximab; uMRD, undetectable MRD.

Details of treatment regimens and MRD analysis methodology are provided in Tables S3–5.

[a]92% of patients also received four cycles of standard-dose FCG

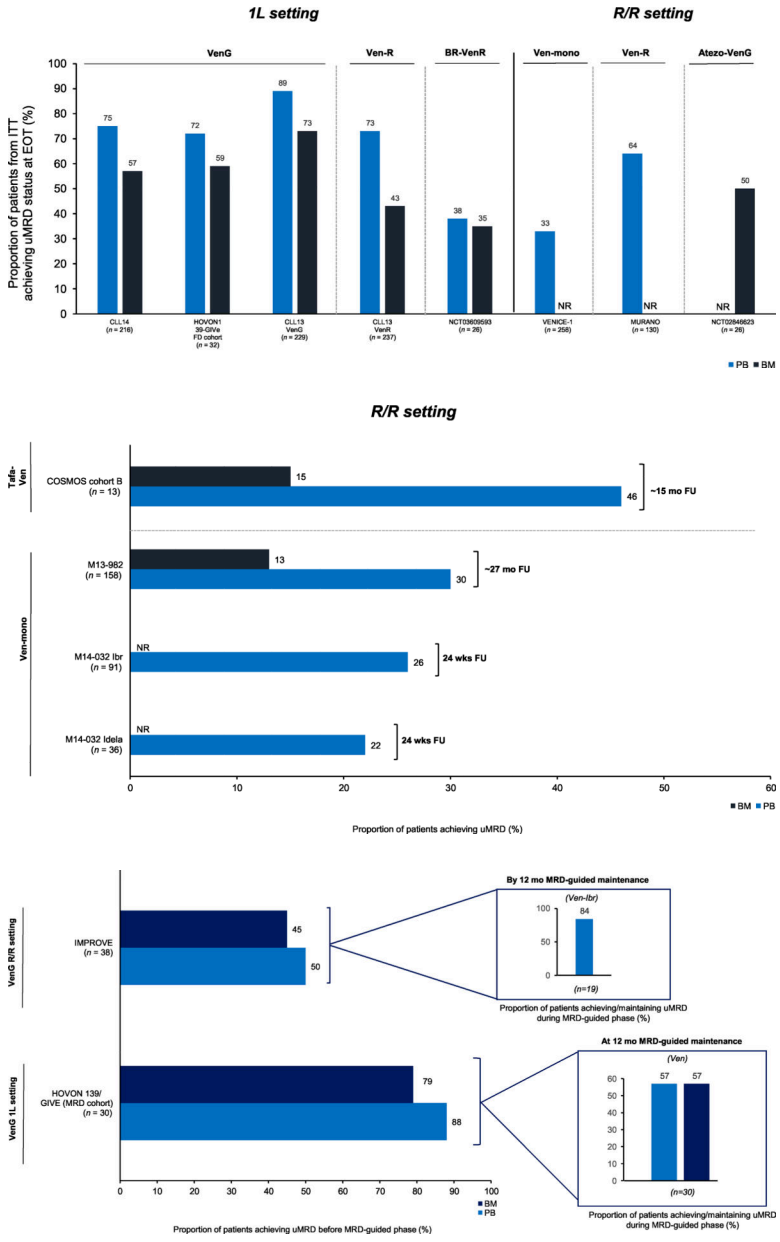


Figure 3.

Rates of uMRD at EOT[a] following fixed-duration BCL2-targeted therapy (A),[b] during continuous BCL2-targeted therapy (B), and in trials with an MRD- or response-guided component (C)[c] (ITT populations).

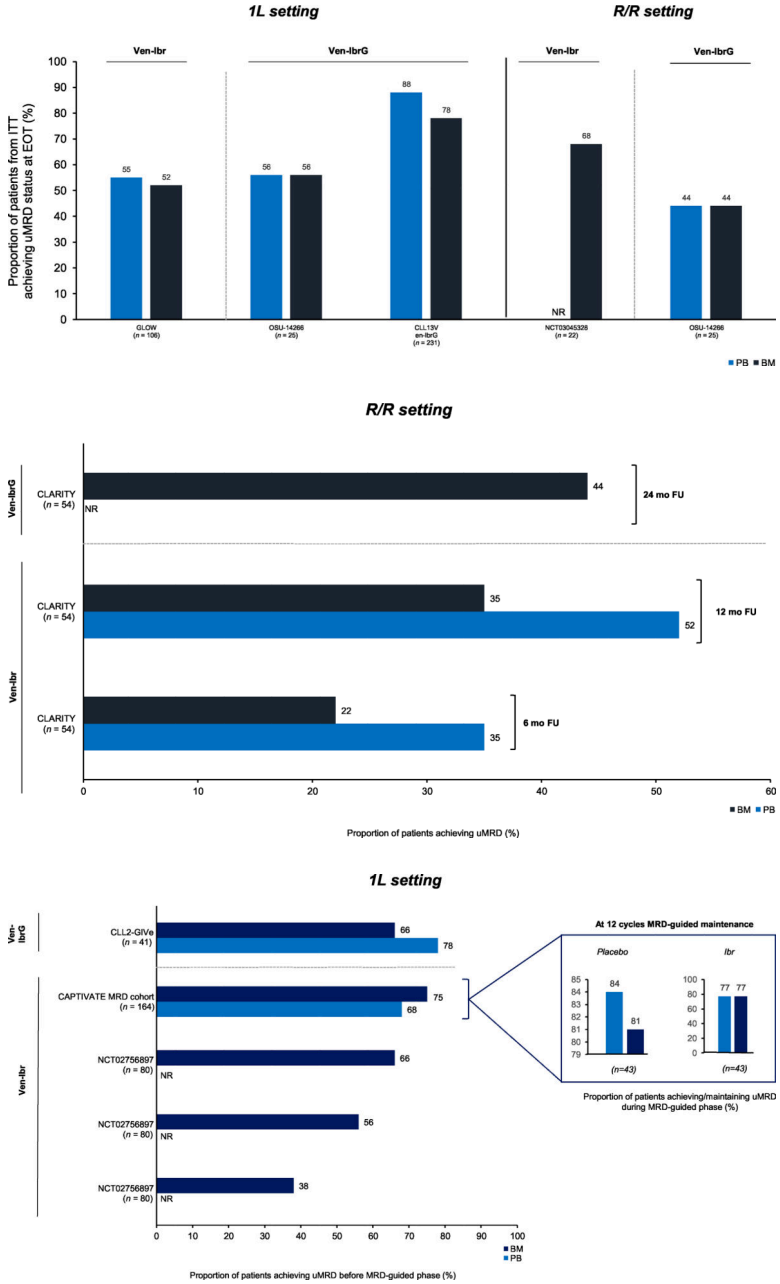
1L, first-line; Atezo, atezolizumab; B, bendamustine; BCL2, B-cell lymphoma-2; BM, bone marrow; EOT, end of treatment; FU, follow-up; G, obinutuzumab; Ibr, ibrutinib; ITT, intent-to-treat; mo, months; mono, monotherapy; MRD, measurable residual disease; NR, not reported; PB, peripheral blood; R, rituximab; R/R, relapsed/refractory; Tafa, tafasitamab; uMRD, undetectable MRD; Ven, venetoclax; wks, weeks.

Details of treatment regimens and MRD analysis methodology are provided in Tables S3–5.

[a]Values within 3 mo of EOT are included.

[b]MURANO trial: n represents the number of patients who completed the full 2 years of Ven treatment; HOVON 139/GIVE trial: n represents the number of patients randomized to Arm A: fixed-duration Ven maintenance for 12 cycles following induction; values reported are at end of maintenance.

[c]HOVON 139/GIVE trial: Only two patients randomized to the MRD-guided arm actually received Ven due to MRD-positivity.



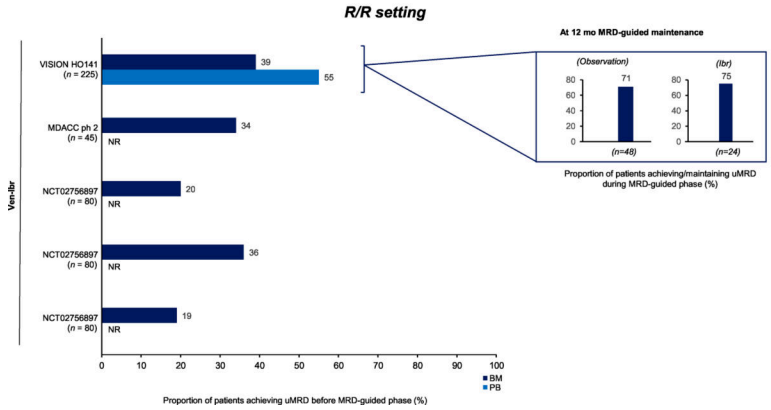


Figure 4.

Rates of uMRD during combination BCR- and BCL2-targeted therapy of fixed duration (A), as continuous treatment (B) and in trials with an MRD- or response-guided component (C and D) (ITT populations).

1L, first-line; BCL2, B-cell lymphoma-2; BCR, B-cell receptor; BM, bone marrow; EOT, end of treatment; FU, follow-up; G, obinutuzumab; Ibr, ibrutinib; ITT, intent-to-treat; mo, months; MRD, measurable residual disease; NR, not reported; PB, peripheral blood; R/R, relapsed/refractory; uMRD, undetectable MRD; Ven, venetoclax.

Details of treatment regimens and MRD analysis methodology are provided in Tables S3–5.

Table 1.

Details of trials evaluating PFS and OS association with uMRD status following treatment with novel agents.

Study	No. of pts in ITT	uMRD cut-off	PFS in uMRD	OS in uMRD
BCR-targeted therapies				
1L setting				
NCT01500733 [52][a] (Continuous treatment)	Ibr-mono, *n* = 86	$<10^{-4}$ Low-MRD+: $<10^{-2}$; High-MRD+: $\geq 10^{-2}$	*Median FU 57 mo* No difference in PFS between low-MRD+ and high-MRD+ patients at 3 yrs	
E1912 [42] (Continuous treatment)	IbrR, *n* = 354	$<10^{-4}$ Int-MRD+: 10^{-4} to $<10^{-2}$ High-MRD+: $\geq 10^{-2}$	No significant difference in PFS between pts with or without PB uMRD status $<10^{-4}$ at any of the timepoints studied Also no clear separation of PFS curves when pts split into Int-MRD+ and High-MRD+ groups	
R/R setting				
HELIOS [43] (Continuous treatment)	Ibr-BR, *n* = 289 Placebo-BR, *n* = 289	$<10^{-4}$ Int-MRD+: 10^{-4} to $<10^{-2}$ High-MRD+: $\geq 10^{-2}$	*Median 35 mo on therapy* In MRD-evaluated pts, Ibr-BR showed improved PFS over Placebo-BR at each MRD level: uMRD HR 0.121 95% CI, 0.036–0.408; Int-MRD+ HR of 0.153 95% CI, 0.063–0.374; High-MRD+ HR of 0.110 95% CI, 0.035–0.348. 3-yr PFS 88.6% (95% CI, 76.8–94.6) in Ibr-BR-treated pts with uMRD and 60.1% (95% CI, 52.6–66.8) in MRD+ pts	MVA showed no difference in OS depending on MRD status in responders.
BCL2-targeted therapies				
1L setting				
CLL14 [34,44,50,86,88] (Fixed-duration)	VenG, *n* = 216 G-Clb, *n* = 216	$<10^{-4}$, $<10^{-5}$, $<10^{-6}$ Int-MRD+: 10^{-4} to $<10^{-2}$ High-MRD+: $\geq 10^{-2}$	Landmark analysis from EOT found pts with uMRD ($<10^{-4}$) at EOT had longer PFS *vs.* Int-MRD+ or high-MRD+ (**HR 0.10; 95% CI, 0.06–0.15**), regardless of clinical response at EOT (combined analysis of VenG and G-Clb arms) Landmark analysis from EOT found pts with uMRD ($\leq 10^{-5}$) at EOT had 2-yr PFS **93**% *vs.***37**% in MRD+ ($>10^{-2}$) pts	*Post-hoc* analysis found that pts with uMRD at EOT also had longer OS *vs.* MRD+ (medians NR).
R/R setting				
VENICE-1 [45] (Fixed-duration)	Ven-mono, *n* = 258	$<10^{-4}$	Median PFS NR in pts with best response of PB uMRD during treatment or CR/CRi *vs.* 30.5 months overall 2-year PFS 87.9% in pts with uMRD status; 82.8% in pts with Int-MRD+ and 58.7% in pts with high-MRD+ status	
M14–032 (cohort progressing after Ibr) [46,89] (Continuous treatment)	Ven-mono, *n* = 91	$<10^{-4}$	*Median 14 mo on therapy* Median PFS NR in pts with uMRD and 24.7 mo (95% CI, 15.4–NR) in MRD+ pts, *P* = .01 by log-rank test *Median 16 mo on therapy*[b] Median PFS NR in pts with uMRD and 21.9 mo in MRD+ pts, *P* = .0019 by log-rank test	
M13–982[c] [47] (Continuous treatment)	Ven-mono, *n* = 158	$<10^{-4}$	*Median 23 mo on therapy* Pts achieving uMRD were less likely to have PD or die compared with patients achieving response but MRD+; 18-mo PFS from date of MRD assessment 78% (95% CI, 54–91) for pts with uMRD *vs.* 51% (95% CI, 32–68) for MRD+ Landmark analysis of patients who were	

Study	No. of pts in ITT	uMRD cut-off	PFS in uMRD	OS in uMRD
			assessed at 36±4 wks on therapy found median PFS NR for either patients with uMRD or MRD+; 1/12 pts (8%) with uMRD had PD *vs.* 6/28 (28%) MRD+ pts	
MURANO [35,36,48] (Fixed-duration)	VenR, *n* = 194 BR, *n* = 195	$<10^{-4}$Int-MRD+: 10^{-4} to $<10^{-2}$ High-MRD+: $\geq 10^{-2}$	*3-year FU* In landmark PFS from EOCT, pts with uMRD at EOCT had longer PFS *vs.* Int-MRD+ (**HR 0.48, 95% CI, 0.24–0.98**) and *vs.* High-MRD+ (**HR 0.15 95% CI, 0.06–0.40**) Pts with Int-MRD+ had longer PFS than those with High-MRD+ (**HR 0.24 95% CI, 0.08–0.72**)[d] Pts with INV-assessed PR at EOCT + uMRD had PFS outcomes similar to those with CR + uMRD (**HR 0.71 95% CI, 0.24–2.14**); pts with PR and MRD+ had poorer PFS than those with PR + uMRD from 18 mo after EOCT; pts with CR + MRD+ had similar PFS to those with CR + uMRD (**HR 1.07 95% CI, 0.12–9.55**) *4-year FU (median 22 mo post-EOT)* In landmark PFS from EOCT, pts with uMRD at EOCT had longer PFS *vs.* Int-MRD+ regardless of treatment arm (**HR 0.50, 95% CI, 0.28–0.89**) and *vs.* High-MRD+ (**HR 0.15 95% CI, 0.06–0.36**); Int-MRD+ *vs.* High-MRD+ (**HR 0.25 95% CI, 0.10–0.66**) MRD status did not appear to affect PFS in pts achieving CR/CRi at this FU	*5-year FU* At 3 yrs post-EOT, improved OS was seen in pts who reached EOT without PD and were uMRD (83/118) *vs.* those with MRD+ (35/118); 3-yr post-EOT OS of **95%** (95% CI, 90–100) *vs.***85%** (95% CI, 73–97), respectively
Combination BCL2 and BCR-targeted therapies				
1L setting				
GLOW [49] (Fixed-duration)	Ven-Ibr, *n* = 106 G-Clb, *n* = 105	$<10^{-4}$	In the Ven-Ibr arm, during 12 mo' follow-up post-EOT, PFS was 90% for pts with or without PB uMRD status at EOT; similar trends in BM In the G-Clb arm, pts with detectable MRD relapsed more quickly than those with uMRD.	

1L, first-line; B, bendamustine; BCL2, B-cell lymphoma-2, BCR, b-cell receptor; BM, bone marrow; CI, confidence interval; Clb, chlorambucil; CR, complete response; CRi, CR with incomplete hematologic recovery; del(17p), chromosome 17p deletion; EOCT, end of combination treatment; EOT, end of treatment; FU, follow-up; G, obinutuzumab; HR, hazard ratio; Ibr, ibrutinib; Int, intermediate; INV, investigator, ITT, intent-to-treat; mo, months; mono, monotherapy; MRD, measurable residual disease; MVA, multivariate analysis; NR, not reached; OS, overall survival; PB, peripheral blood; PD, progressive disease; PFS, progression-free survival; PR, partial response; pts, patients; R, rituximab; R/R, relapsed/refractory; uMRD, undetectable MRD; Ven, venetoclax; Wk, Week, yrs, years.

[a] Not reported separately for 1L and R/R (53/86 [62%] patients were 1L).

[b] Data reported for pts refractory to either Ibr or Idela.

[c] Following a protocol amendment, 1L patients with del(17p) could be enrolled.

[d] 6 patients with High-MRD+ at EOCT in the VenR arm.

Table 2.

Rates of uMRD in patients with high-risk genetics compared with the overall population.

Study identifier	ITT population	PB uMRD rate in high-risk pts	uMRD rate in ITT	uMRD rate in evaluated patients	Timing and method of evaluation
BCR-targeted therapies					
1L setting					
CLL2-BIG[a] [90] (Fixed-duration)	IbrG, *n* = 30	1/8 (13%) del(17p)[c] 7/14 (50%) del(11q)[c] 7/12 (58%) Trisomy 12[c] 8/31 (26%) del(11q)[c]	16/30 (53%)	NA	Final restaging, 3 mo post-EOI, flow cytometry
iLLUMINATE[a] [30] (Continuous treatment)	IbrG, *n* = 113	20/73 (27%) del(17p), *TP53*mut, del(11q), or IGHVunmut	34/113 (30%)	NA	Timing not specified, flow cytometry
ICLL-07[b] [68,91] (MRD-guided component)	IbrG, *n* = 135	23/59 (39%) IGHVmut 26/74 (35%) IGHVunmut	49/115 (43%) iFCG 0/10 (0%) Ibr	49/74 (66%) iFCG 0/7 (0%) Ibr	Month 40, flow cytometry
NCT02251548[b] [92] (MRD-guided component)	iFCR, *n* = 85	38/46 (83%) IGHVunmut	71/85 (84%)	NA	Best response, flow cytometry
CLL2-BIO[a] [93] (Fixed-duration)	Ofa-Ibr, *n* = 39	0/12 (0%) del(17p)[c] 4/45 (9%) IGHVunmut[c]	7/39 (18%)	NA	End of induction, flow cytometry
NCT02158091[b] [28,94] (Fixed-duration)	Duv-FCR, *n* = 32	12/18 (67%) IGHVunmut	21/32 (66%)	NA	Best response, flow cytometry
R/R setting					
M14–032 (Idela)[a] [95] (Continuous treatment)	Ven-mono, *n* = 36	5/22 (23%) IGHVunmut 1/8 (13%) del(17p) 1/5 (20%) *TP53*mut	8/36 (22%)	8/17 (40%)	Week 24, flow cytometry
GENUINE[a] [80,96] (Continuous treatment)	Ubli-Ibr, *n* = 59	3/21 (14%) high-risk[d]	3/41 (7%)		Within 6 mo of starting therapy, flow cytometry
VISION HO141[a] [61]	Ven-Ibr, *n* = 225	25/54 (46%) *TP53*mut/del 72/144 (50%) IGHVunmut	112/225 (50%)	NA	EOCT, flow cytometry
BCL2-targeted therapies					
1L setting					
CLL14[a] [33,50] (Fixed-duration)	VenG, *n* = 216	12/17 (71%) del(17p) 17/25 (68%) *TP53*del/mut	163/216 (75%)	NA	3 mo post-EOT, ASO-PCR

Leuk Lymphoma. Author manuscript; available in PMC 2024 November 21.

Study identifier	ITT population	PB uMRD rate in high-risk pts	uMRD rate in ITT	uMRD rate in evaluated patients	Timing and method of evaluation
		96/121 (79%) IGHVunmut 27/34 (79%) CK			
HOVON139/GIVE [81,97] (Fixed-duration)	VenG, *n* = 67	6 pts with high-risk genetics (del(17p) and/or *TP53*mut)[e]	24/30 (80%)	24/29 (83%)	EOI, flow cytometry
CLL2-BAG[a] [62] (Fixed-duration)	VenG, *n* = 35	5/6 (83%) del(17p) or *TP53*mut	31/35 (89%)	31/34 (91%)	End of induction, flow cytometry
R/R setting					
MURANO[a] [36,64] (Fixed-duration)	VenR, *n* = 194	75/123 (61%) IGHVunmut 41/72 (57%) del(17p)/*TP53*mut 24% *NOTCH1*mut	121/194 (62%) 83/130 (64%)	NA	EOCT, ASO-PCR EOT, ASO-PCR
CLL2-BAG[a] [62] (Fixed-duration)	VenG, *n* = 31	8/11 (73%) del(17p) or *TP53*mut	24/31 (77%)	24/29 (83%)	End of induction, flow cytometry
Combination BCL2 and BCR-targeted therapy					
1L setting					
GLOW[b] [75] (Fixed-duration)	Ven-Ibr, *n* = 106	58.2% IGHVunmut	55/106 (52%)	NA	3 mo post-EOT, NGS
CAPTIVATE FD[a] [98,99] (Fixed-duration)	Ven-Ibr, *n* = 159	22/27 (81%) del(17p)/*TP53*mut	122/159 (77%)	NA	Best rate, flow cytometry
CAPTIVATE[b] [60] (MRD-guided component)	Ven-Ibr, *n* = 164 (MRD cohort)	18/26 (69%) del(17p) 21/32 (66%) del(17p)/*TP53*mut 22/28 (79%) del(11q) 76/99 (77%) IGHVunmut	112/164 (68%)	112/155 (72%)	At any time, flow cytometry
NCT02756897[b] [100] (MRD-guided component)	Ven-Ibr, *n* = 80	9/14 (64%) del(17p) 8/12 (67%) CK 42/63 (67%) IGHVunmut 5/11 (45%) *TP53*mut 12/22 (55%) *NOTCH1*mut	53/80 (66%)	NA	EOT, flow cytometry
AVO[a] [66,101] (MRD-guided component)	Acala-VenG, *n* = 44	9/17 (53%) del(17p) and/or *TP53*mut	37/44 (84%)	NA	Cycle 16, flow cytometry

1L, first-line; Acala, acalabrutinib; ASO-PCR, allele-specific oligonucleotide polymerase chain reaction; B, bendamustine; BCL2, B-cell lymphoma-2; BCR, b-cell receptor; BM, bone marrow; CK, complex karyotype; Clb, chlorambucil; CLL, chronic lymphocytic leukemia; del(11q), chromosome 11q deletion; del(17p), chromosome 17p deletion; Duv, duvelisib; EOCT, end of combination treatment; EOI, end of induction; EOT, end of treatment; FC, flow cytometry; FD, fixed-duration; G, obinutuzumab; Ibr, ibrutinib; Idela, idelalisib; iFCR, ibrutinib plus FCR; IGHV, variable region of the immunoglobulin heavy chain; ITT, intent-to-treat; mo, months; mono, monotherapy; MRD, measurable residual disease; mut, mutated; NA, not assessed; NGS, next-generation sequencing; Ofa, ofatumumab; PB, peripheral blood; PCR, polymerase chain reaction; pts, patients; R, rituximab; R/R, relapsed/refractory; Ubli, ublituximab; uMRD, undetectable MRD; unmut, unmutated; Ven, venetoclax.

uMRD defined as $<10^{-4}$

[a] PB uMRD rate.

[b] BM uMRD rate.

[c] uMRD rates in high-risk patients reported for 1L and R/R combined.

[d] At least one of del(17p), del(11q), and/or TP53mut.

[e] Authors noted that MRD positive disease was not found more frequently in patients with high-risk baseline characteristics (unmutated IGVH, del17p/TP53mut, CG) – reported for both arms combined (MRD-guided and fixed-duration).