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# Real-World Evidence for Chronic Lymphocytic Leukemia in the Era of Targeted Therapies

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## Abstract

The landscape of chronic lymphocytic leukemia (CLL) has transformed in the era of small molecule inhibitor targeted therapies. While randomized controlled trials (RCTs) remain the gold-standard in evaluating new therapies, they are often unable to keep pace with the clinical questions that arise during the use of novel agents. Real-world evidence (RWE) is generated through analysis of data such as electronic medical records, payer claims, and patient registry databases, and can provide invaluable information to supplement RCTs, such as outcomes in patient populations excluded from clinical trials, rates of discontinuation or dose reductions in clinical practice, survival outcomes, and optimal sequencing of novel agents. This review aims to discuss major findings from recent, relevant, real-world evidence publications that have greatly informed our understanding of CLL as it is treated in clinical practice.

### Keywords

Real-world evidence; chronic lymphocytic leukemia; ibrutinib; idelalisib; venetoclax; survival outcome; adverse events

## Real-World Evidence

Randomized controlled trials (RCTs) are the gold standard in providing evidence for Food and Drug Administration (FDA) approval of a medical product; however, study limitations often include inadequate follow-up period, inadequate power, insufficient evidence regarding prescribing practices or patient adherence, and a study population which may not reflect the patients most commonly receiving the product in clinical practice[1]. A large body of real-world data (RWD) is generated with clinical use of a product through electronic medical records (EMR), payer claims, and patient registry databases, all of which can be analyzed to generate real-world evidence (RWE)[1]. RWE is increasingly informing the results of RCTs, lending further insights into issues surrounding routine clinical use, including adverse events, patient adherence, financial toxicity, and population-based outcomes, often at a much more rapid and cost-effective pace than RCTs. Limitations of RWE include low internal

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validity, lack of quality control, and susceptibility to bias. However, despite these limitations, the FDA has stated their intent for greater use of RWE and is consulting with stakeholders to formalize standards and methods for generating RWE to help inform RCTs[1].

## Real-World Evidence in Chronic Lymphocytic Leukemia

RWE has been particularly informative in the field of chronic lymphocytic leukemia (CLL), which has undergone a paradigm shift in the past decade with the advent of several novel, targeted, small molecule therapies. RCTs alone are insufficient to keep pace with the clinical questions that continue to arise in this new and exciting era. RWE has informed our understanding of how to interpret and incorporate traditional prognostic markers, manage toxicities, sequence therapies, and counsel patients on therapy, among others. The remainder of this review will focus on three key areas: (1) Pre-treatment molecular testing patterns in clinical practice (2) RWE regarding dose reductions/interruptions, impact on survival outcomes, and spectrum of adverse events not evaluated in clinical trials of the small molecule inhibitors ibrutinib and venetoclax, and (3) optimal sequencing of novel agents.

## Molecular Testing Patterns in CLL

Given considerable progress in the diagnosis, prognostication, and therapy approaches to CLL in the past decade, Hallek et al published the International Workshop on Chronic Lymphocytic Leukemia in 2008 as a major update to the previously published National Cancer Institute Working Group (NCI-WG) 1996 guidelines, including guidelines regarding molecular testing[2]. iWCLL 2008 guidelines designated molecular cytogenetics testing as “desirable” prior to treatment, though early clinical trials with targeted therapies were already stratifying outcomes based on fluorescence in-situ hybridization (FISH) status[3]. As further evidence supporting molecular profiling for prognostication emerged, Hallek et al published the updated 2018 iWCLL guidelines, which have now been amended to designate molecular cytogenetics, *TP53* mutation and immunoglobulin heavy-chain (IGHV) mutational status as “always” indicated prior to treatment[4]. In 2016, Mato et al conducted a retrospective review of molecular profiling patterns using the CONNECT CLL registry, a multicenter, prospective, observational cohort study of 1494 adult (>18 years old) patients receiving CLL treatment enrolled across 199 participating centers (87.8% community, 10.4% academic, 1.9% government) between 2010–2017[5]. The authors reported metaphase cytogenetics (MC) or FISH were performed at study enrollment in 861 (58%) of patients, with 28% of patients receiving both MC/FISH[5]. When stratified by line-of-treatment, 576 (65%) first-line therapy patients were tested by either FISH/MC before enrollment, versus 130 (50%) of patients on second-line therapy, and 155 (45%) of patients on third-line therapy[5]. The authors performed a univariate analysis of 12 predictors of prognostic testing rates among patients on first-line versus second and third-line therapies, finding FISH/MC were more often performed at (1) academic sites vs community/government centers, (2) younger patients (≤75), (3) white race, (4) private insurance, and (5) Rai stage ≥2[6]. Multivariate analysis retained (1) academic center, (2) white race and (3) private insurance status as independent predictors of FISH/MC testing at first-line therapy[5]. Additionally, only 40% of patients who underwent FISH/MC at enrollment underwent retesting at progression, despite knowledge that somatic mutations may be acquired through the disease course[5].

Though mutational status helps drive treatment decisions at both initiation and progression, real-world practices reflect a dearth of adequate genetic testing by FISH/MC in patients both at first and subsequent lines of therapy[5]. Seymour et al used Surveillance, Epidemiology, and End Results (SEER) Patterns of Care data to compare molecular testing patterns among adult CLL patients diagnosed in 2008 (1008 patients) vs 2014 (1367 patients)[7]. Encouragingly, they found an increase (53% to 62%) in FISH testing among treated patients and an increase (6.1% to 10.5%) in IGHV mutation status testing among diagnosed patients between 2008 to 2014[7]. Notably, Seymour et al found greater rates of FISH testing than Mato and colleagues, which may be accounted for by the different patient populations and different sources used (e.g. prospective registry vs. SEER data).

Mato and colleagues recently published an updated interim analysis of 840 adult CLL patients using the informCLL registry, a multicenter, prospective, observational registry of CLL patients enrolled since 2015 across 194 participating sites. Despite consensus iwCLL 2018 guideline recommendations for molecular profiling, FISH, *TP53* and IGHV mutational status were only queried for 262 (31%), 89 (11%), and 94 (11%) patients, respectively[8]. Furthermore, of 70 patients who tested positive for *TP53* mutation/del(17p), 34% received chemoimmunotherapy, despite the National Comprehensive Cancer Network (NCCN) guideline recommendations for targeted therapies given many prior studies establishing poorer outcomes with chemoimmunotherapy in this patient population[9].

While several clinical trials[10–12] are increasingly supporting the use of targeted therapy as front-line across all treatment groups regardless of molecular characteristics, the prognostic and treatment implications of molecular profiling have not been obviated and are still informative for guiding management decisions. The above RWE studies have highlighted disparities in testing patterns that are an opportunity for education and improvement.

## Ibrutinib in Clinical Practice

### Survival Outcomes in Patients Excluded from Landmark Trials

Ibrutinib, an irreversible small molecule inhibitor of Bruton's tyrosine kinase (BTKi), has been approved for both first-line and relapsed/refractory treatment of CLL. Burger and colleagues published results of the RESONATE-2 phase III clinical trial that led to the approval of ibrutinib in the first-line setting for CLL by 2016[13]. Patients were included in the trial if they were treatment-naïve, older than 65 with adequate performance status and organ function, though importantly, were excluded if they carried a del(17p) [13]. Notably, *TP53* mutational status was not reliably reported. Burger et al demonstrated significant improvements over chemotherapy in overall response rate (ORR), progression-free survival (PFS) and overall survival (OS). To inform our understanding of patient populations excluded from either trial, Mato and colleagues performed a retrospective cohort study of 391 adult CLL patients receiving first-line ibrutinib monotherapy across 20 academic and community centers, with 41% of patients aged < 65, 29.8% with del(17p), and 20% with *TP53* mutation[14]. ORR was similar for both age < 65 and del(17p) cohorts as compared to ORR for all cohorts in landmark clinical trials, and PFS/OS were similar across all age cohorts. Comparatively, the del(17p) cohort evidenced inferior PFS (87% vs 92% across all cohorts at 1 year) and OS (89% vs 95% across all cohorts at 1 year)[14]. These findings

further validate the inferior PFS experienced by the del(17p)/*TP53* cohort in an NIH study (5 year PFS 58.2% vs 81.2% in elderly cohort)[15] (Table 1). ORR and PFS/OS are still remarkably improved with targeted therapy over chemoimmunotherapy in this traditionally high-risk patient population, and RWE supports their use in these patient cohorts.

## Equivalent Survival Outcomes for Dose-Reduced Ibrutinib

While not reported in RESONATE-2[13], Ahn et al reported 10.5% of patients required a dose reduction of ibrutinib due to intolerable toxicities in their landmark analysis[15]. Mato and colleagues evaluated the survival impact of dose reductions or interruptions through a retrospective chart review of 197 patients (81% relapsed/refractory, 19% first-line) across 3 academic centers[16]. 37 patients (19%) received reduced-dose ibrutinib, defined as any dose < 420 mg/day sustained for > 2 months within 3 months of drug initiation[16]. At a median reduced dose of 4.3 mg/kg/day vs 5.1 mg/kg/day standard dosing, the authors were unable to find a difference in PFS/OS[16], which correlates with findings by Ahn et al in their landmark analysis[15]. Notably, subset analysis was not performed for first-line vs relapsed/refractory patients. These findings were further supported in a subsequent retrospective single-center review of 70 CLL patients, again majority relapsed/refractory, of which 23 (31.3%) received reduced-dose ibrutinib at a median dose of 140 mg daily at any point in their treatment course[37]. The authors reported no statistically significant difference in ORR, median PFS, or OS between full and reduced-dose cohorts, regardless of whether a dose reduction was performed within three months of initiating therapy or later, up to a median follow up of 21 months[37]. Winqvist et al recently reported 30-month follow up data of the Swedish Compassionate Use cohort, in which 25 relapsed/refractory CLL patients received dose reductions that did not impact their PFS or OS, further confirming earlier findings[38]. While several studies have now reported equivalent survival outcomes in a majority relapsed/refractory population, Rhodes et al reported an inferior 12 month PFS of 71% versus 93% for patients receiving first-line, reduced-dose ibrutinib as compared to patients receiving first-line, full-dose ibrutinib in a retrospective review of 391 first-line CLL patients, of whom 30 (7.6%) initiated treatment doses < 420 mg daily[36]. Of note, the authors found dose interruptions > 8 days occurred in 22% of their patients, which ultimately did not impact 12 month PFS[36]. Though difficult to draw definitive conclusions given several study limitations including small sample sizes and limited follow up periods, providers should feel comfortable discussing dose reductions and interruptions with patients if needed, given evidence to suggest long-term outcomes may not be significantly affected, especially in the relapsed/refractory population.

## Adverse Events Related to Ibrutinib in Clinical Practice

Several retrospective reviews have reported higher rates of adverse events and ibrutinib discontinuation in clinical practice than reported in clinical trials[14,17]. RESONATE-2 only reported adverse events that occurred in patients with a frequency of > 15% during a follow up period of 17 months, with the most common adverse events reported as diarrhea (57%, n=42) and fatigue (41%, n=30). Notably, only 9% of study participants required ibrutinib discontinuation, and only 4% of patients required dose reductions due to adverse events[13]. A similar adverse event profile was reported by the NIH[15].

To characterize adverse events leading to drug discontinuation in clinical practice, Mato et al performed a retrospective chart review of adverse events documented in 616 patients (87% relapsed/refractory, 13% first-line) across 9 academic centers and the CONNECT CLL registry, 88% of whom were off-trial, with a median follow up of 17 months[17]. In contrast to low discontinuation rates on clinical trial, 41% of patients discontinued ibrutinib with a median time to discontinuation of approximately 6–7 months[17] (Table 2). Toxicity was the most common reason for discontinuation in all patients (63% in first-line, 50.2% in relapsed/refractory patients). Discontinuations due to progressive disease were far lower: 15.8% in first-line and 20.9% in relapsed/refractory. Common adverse events leading to discontinuation included arthralgia and atrial fibrillation in both first-line and relapsed/refractory patients[17] (Table 3). The relapsed/refractory cohort additionally experienced high rates of pneumonitis (9.9%), infection (10.7%), and bleeding (9%)[17] (Table 3). Overall, longer follow up time with less stringent reporting criteria for adverse events using RWE suggests a higher incidence of adverse events, a wider range of adverse events (including serious immunologic effects such as pneumonitis), and a much higher rate of discontinuation (majority due to toxicity) in clinical practice than previously reported by trial data. Given previous findings showing equivalent survival outcomes with dose-reduced or interrupted ibrutinib in clinical practice, future studies can explore time-limited therapy to minimize toxicity while improving current adverse event recognition and management.

## Venetoclax in Clinical Practice

### Equivalent Survival Outcomes for Monotherapy versus Combination Therapy

Venetoclax, a BH3-mimetic and inhibitor of the anti-apoptotic B-cell lymphoma-2 (BCL-2) protein, is approved for use in relapsed/refractory CLL as of June 2018 based on the results of the multinational, randomized, open-label phase III MURANO clinical trial demonstrating superior survival outcomes in relapsed/refractory CLL patients treated with venetoclax in combination with rituximab versus bendamustine with rituximab[18]. Venetoclax monotherapy has also shown promising ORR, PFS and OS in prospective clinical trials, even in heavily pre-treated and traditionally high-risk patient populations, such as del(17p) or *TP53* mutated CLL[19,20,21,39]. Combinations of venetoclax with other targeted therapies are being explored[22,23]; however, the efficacy of combination therapy over monotherapy remains unknown, and is not planning to be explored in prospective, head-to-head clinical trials[24]. While combination therapy has improved outcomes in the chemoimmunotherapy era, its additive effect is not apparent in the era of small molecule inhibitors, as recent data[25,26] have failed to show survival benefit with the addition of anti-CD20 activity to a BTKi. In light of these findings, RWE provides an opportunity to investigate the clinical efficacy of venetoclax monotherapy versus combination therapy.

Mato et al conducted a retrospective cohort review of 321 relapsed/refractory CLL (270 venetoclax monotherapy, 51 venetoclax combination therapy, ~80% off clinical trial) patients across 24 US and 42 United Kingdom (UK) academic and community centers to investigate outcomes for venetoclax mono versus combination therapy[24]. Of note, over 70% of patients in either monotherapy or combination therapy arm had prior BTKi exposure, representing a much higher proportion of patients than in landmark clinical trials[18,20,21].

Patient characteristics between cohorts were modestly balanced; the monotherapy group contained a greater proportion of complex karyotype (43% vs 25%), median prior therapies (3 vs 2), *TP53* mutation (37% vs 25%) than the combination therapy cohort, suggesting more aggressive disease with possible anti-CD20 resistance[24]. For the entire cohort, ORR, 12-month PFS and OS were similar across both monotherapy and combination therapy cohorts[24] (Table 4). In bivariate analysis controlling for pre-venetoclax prognostic factors such as complex karyotype, number of prior therapies, presence of del(17p), del11q, or IGHV mutation, prior ibrutinib exposure, and prior chemoimmunotherapy exposure, PFS and OS remained comparable between cohorts[24]. The investigators could not find a group that benefited from combination therapy, even when adjusting for observed differences between cohorts, such as complex karyotype and number of prior therapies. Eyre et al recently published the largest UK review series to date of 105 relapsed/refractory CLL patients outside of a clinical trial across both academic and community centers on venetoclax monotherapy[27]. Patients were heavily pre-treated and had high risk clinical features, such as *TP53* mutation, complex karyotype and del(17p), and the majority had prior BTKi, phosphoinositide 3-kinase (PI3K) inhibitor or exposure to both. Despite these high-risk features, the authors showed comparable ORR, PFS and OS to clinical trial cohorts [19,20,28] and US-based RWE[24] (Table 4). Thus, RCTs and RWE are generating a growing body of evidence supporting venetoclax monotherapy in relapsed/refractory CLL, and furthermore highlight the importance of including a venetoclax monotherapy control arm in future clinical trial design.

## Dose Reductions, Interruptions and Discontinuations are Similar in Clinical Practice and May Not Affect Clinical Outcomes

Davids et al reported comprehensive venetoclax safety data in a pooled analysis of 350 patients with CLL using an integrated data set from three phase I/II clinical trials[29]. The authors reported a dose reduction, interruption, or discontinuation secondary to adverse events in 45 (13%), 120 (34%), and 35 (10%) of patients, respectively[29]. Given prior evidence regarding higher rates of BTKi discontinuation in clinical practice[14,16,17], Mato et al performed a multicenter, retrospective cohort safety review study of 141 patients with CLL treated with either venetoclax monotherapy or combination therapy (139 relapsed/refractory, 2 first-line) across 19 academic and community centers[30]. 18.4% of patients received venetoclax combination therapy, most commonly in combination with ibrutinib (36%); notably, almost 89% of patients had had prior BTKi exposure, and almost every patient harbored at least one traditionally poor risk feature[30]. Dose interruptions occurred in 30% of patients and 21% required dose reduction, with tumor lysis syndrome (TLS) occurring in 13.4% of patients[30]. Furthermore, venetoclax was permanently discontinued in 29% of patients; of those patients, this was most commonly due to disease progression (53.8%), followed by toxicity (20.5%)[30]. Roeker et al performed a recent multinational, retrospective cohort safety evaluation study of 297 patients with CLL (96% relapsed/refractory, 4% first-line) across 15 academic and 51 community centers in the US and UK[31]. Venetoclax was given as monotherapy (80%) or combination (20%); in combination therapy, an anti-CD20 monoclonal antibody was most commonly used (75%). Dose reductions and interruptions occurred for 29% and 32% of patients, respectively, with a median length of dose interruption of 7 days. Venetoclax was discontinued in 40% of patients, most

commonly for CLL progression (35.3%), followed by toxicity (19.3%)[31] (Table 5). RWE shows modestly higher rates of dose reduction than in landmark clinical trials, but overall the incidence of interruptions and reductions were consistent with published trial data (Table 5). Reassuringly, Kaplan-Meier estimates of survival demonstrated that dose interruption or reduction did not impact PFS to a median follow up of 12 months[31], similar to prior findings in the patients treated with BTK inhibitors.

### Adverse Events and Tumor Lysis Syndrome May be More Frequent in Clinical Practice

In their pooled analysis, Davids et al reported the most common adverse events of any grade were diarrhea (41%), neutropenia (40%), nausea (39%), anemia (31%), fatigue (28%), and upper respiratory tract infection (25%). The most common grade 3/4 adverse events were hematologic, majority neutropenia (37%). Roeker et al reported a very similar rate of grade 3/4 neutropenia at 39.6%, though observed rates of thrombocytopenia (29.2%) and diarrhea (6.9%) were higher in their retrospective cohort study[31] (Table 6).

Davids et al further reported a clinical and laboratory incidence of TLS of 0% and 1.2% respectively in their pooled analysis of patients receiving 5-week ramp-up dosing[29]. Comparatively, Roeker et al reported a total of 25 (8.4%) incidences of TLS for all patients, with a higher incidence of clinical TLS (2.7%) and laboratory TLS (5.7%) than previously reported in clinical trials[18,29,31]. Higher rates of TLS may have been due to variations in adherence to FDA guidelines; for example, 12% of the high-risk for TLS group were not hospitalized during venetoclax initiation, though FDA guidelines recommend universal admission[31]. Roeker et al further identified impaired renal function, defined as a creatinine clearance less than 80 mL/min, as a new clinical risk factors for TLS in univariate analysis of pre-treatment variables including sex, age at venetoclax initiation, number of prior therapies, prior ibrutinib, cytogenetics, *IGHV* mutational status, creatinine clearance, venetoclax monotherapy vs. combination therapy, and TLS risk group as defined by the FDA package insert[31]. In a multivariable analysis adjusted for patient age at venetoclax initiation, FDA-defined TLS risk group and creatinine clearance (categorized by <80 and ≥80 mL/min) also independently predicted TLS development[31].

Interestingly, Roeker et al identified very conservative TLS management in the FDA-designated low-risk TLS patient cohort. 85% of patients received intravenous normal saline and 57% had at least one planned hospitalization during dose-ramp up, though FDA package insert guidelines state that for low risk TLS patients, oral hydration and outpatient ramp-up is appropriate[31]. While reasons for conservative treatment are not readily apparent through retrospective review, this may be an area for cost-effective intervention. Overall, RWE has supported the safety and efficacy of venetoclax in clinical practice, with opportunities for improvement in TLS risk stratification and prevention.

## Sequencing of Targeted Therapies

As targeted therapies gain wider FDA approval in CLL, their optimal sequencing has emerged as a new clinical challenge. Few prospective studies have compared novel agents to contemporary, clinically relevant controls, and follow-up is limited once patient data is

censored on trial. RWE has provided our greatest insight into this area of unmet clinical need.

Many patients are still being treated with chemoimmunotherapy in the first-line, and robust evidence suggests improved response rates and survival outcomes with use of a targeted therapy at progression instead of re-challenging with chemoimmunotherapy[32,33,34]. Ibrutinib monotherapy, idelalisib with rituximab, or venetoclax with or without rituximab would all be reasonable options for this patient population, as no prospective studies have confirmed which small molecule inhibitor is best.

A retrospective review of 683 CLL patients treated with either ibrutinib, idelalisib, or venetoclax across 9 academic centers and the CONNECT CLL registry sought to answer optimal sequencing of targeted therapies in the first-line and at progression[33]. 14% of patients had received kinase inhibitor therapy in the first-line, and only 19% were on clinical trial. Notably, though patients were well-balanced between ibrutinib versus idelalisib-based therapy groups, there were significantly more patients who had received ibrutinib than idelalisib (611 versus 62, respectively)[33]. The authors reported superior PFS with initial ibrutinib versus idelalisib-based therapy in both first-line (HR 2.8, CI 1.3–6.3, $p < 0.01$), relapsed/refractory (HR 2.8, CI 1.9–4.1, $p < 0.001$), del17p (HR 2.0, CI 1.2–3.4, $p < 0.008$), or complex karyotype cohorts (HR 2.5, CI 1.2–5.2, $p < 0.02$). These findings differ from an earlier, smaller cohort study of 178 CLL patients who had discontinued ibrutinib (n= 143) or idelalisib-based (n = 35) therapy, in which initial kinase inhibitor did not impact PFS (HR 1.2, CI 0.8–1.8) or OS (HR 0.8, 95% CI 0.4–1.5)[35].

Growing evidence supports the use of venetoclax after progression on a kinase inhibitor. Mato et al first demonstrated this in their retrospective review of 167 patients who received a second line therapy after a first-line kinase inhibitor, reported as either kinase inhibitor-based therapy, venetoclax or chemoimmunotherapy combinations[33]. The ORRs (CR rate) to venetoclax, kinase inhibitor-based therapy, or chemoimmunotherapy combinations were 73.6% (31.5%), 58.5% (4.1%), and 49.9% (2.1%), respectively, indicating superior outcomes with venetoclax following progression on a kinase inhibitor. Jones et al recently published data further supporting the use of venetoclax in patients whose disease progresses on a kinase inhibitor in their interim analysis of a multicenter, open-label, non-randomized, phase II trial of 127 relapsed/refractory CLL patients receiving venetoclax after progressing on ibrutinib[19]. The investigators noted a high ORR of 65%, even for patients with historically poor outcomes such as *TP53* mutated and complex karyotype[19]. Optimal therapy following progression on venetoclax remains an area of active research, with very limited data to guide medical decision making.

## Conclusions

The treatment of CLL is being advanced at a breakneck pace, and many challenges regarding the sequencing, safety, and durability of emerging therapies have emerged. RWE can provide insights into these challenges and guidance regarding clinical practice, often more rapidly than can be provided through randomized, controlled clinical trials, and in patient populations that hold more clinical relevance outside of a trial setting. However,

RWE is susceptible to limitations given its retrospective nature, heterogeneity, lack of internal validity, susceptibility to bias, and often inconsistent data reporting on available platforms, among others. As we increasingly garner information from RWE, we must continue to improve the rigor of RWE studies, with steps towards standardization of research methods and data reporting, regulatory oversight, and validation in prospective clinical trials.

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**Table 1**

Comparison of RWE ORR PFS and OS in Landmark Clinical Trials

| Study Cohort | ORR | CR | PFS | OS |
|---|---|---|---|---|
| RESONATE-2[13] | 86% | 4% | 96% (30 mo) | 97% (3 y) |
| NIH dell7p/TP53 mutated [5] | 95.8% | 29.2% | 58.2% (5 y) | 75.7% (5 y) |
| NIH >age 65 y[15] | 93.9% | 27.3% | 81.2% (5 y) | 83.8% (5 y) |
| Mato all patients[14] | 81.8% | 17.4% | 92% (1 y) | 95% (1 y) |
| Mato age <65 y[14] | 85.3% | 20.4% | 92% (1 y) | 95% (1 y) |
| Mato del 17p present[14] | 82.3% | 21.2% | 87% (1 y) | 89% (1 y) |

**Table 2**

Rates of Ibrutinib Dose Reduction or Discontinuation

| | RESONATE-2[13] | NIH[15] | Mato et al. All Patients[20] | Mato et al. FL[20] | Mato et al. R/R[20] |
|---|---|---|---|---|---|
| Patients requiring dose reduction due to adverse events | 4% | 10.5% (n = 9) | 18.7% (n = 119) | 15% (n = 12) | 20% (n = 107) |
| Patients requiring discontinuation | Not reported | 5.8% (n = 5) | 41% (n = 250) | Not reported | Not reported |
| Discontinuation due to toxicity | 9% | 60% (n = 3) | 20.8% (n = 128) | 63.1% (n = 12) | 50.2% (n = 116) |
| Discontinuation due to progression of disease | Not reported | 0% (n = 0) | 8.4% (n = 52) | 15.8% (n = 3) | 20.9% (n = 49) |
| Discontinuation due to all other | Not reported | 40% (n = 2) | 11.4% (n = 70) | 21.2% (n = 4) | 71.1% (n = 66) |

FL indicates first-line.

## Table 3

Adverse Events Leading to Discontinuation of Ibrutinib

| Adverse Event | RESONATE-2[13] | NIH[15] | Mato et al. FL[20] | Mato et al. R/R[20] |
|---|---|---|---|---|
| Atrial fibrillation | 1% | 0% | 25% | 12.3% |
| Major hemorrhage | 1% | 0% | Not reported | 9% |
| Arthralgia | Not reported | 0% | 41.6% | Not reported |
| Rash | Not reported | 0% | 10.7% | |
| Pneumonitis | Not reported | 1.2% | Not reported | 9.9% |
| Diarrhea | Not reported | 1.2% | Not reported | 6.6% |
| Progressive multifocal leukoencephalopathy | Not reported | 1.2% | Not reported | Not reported |

FL indicates first-line.

**Table 4**

Representative Treatment Response to Venetoclax Monotherapy Versus Combination Therapy

| Study Cohort | ORR | CR | PFS | OS |
|---|---|---|---|---|
| Jones et al., VEN$^{m}$, post-BTKi[22] | 65% (n = 59) | 9% (n = 8) | 75% (12 mo) | 91% (12 mo ) |
| Stilgenbauer et al., VEN$^{m}$, dell7p[25] | 77% (n = 122) | 20% | 54% (24 mo) | 73% (24 mo) |
| Seymour et al., VEN$^{c}$[21] | 92.3% | 26.8% | 84.9% (24 mo) | 91.9% |
| Eyre et al., VEN$^{m}$ All patients[31] | 88% (n = 92) | 30% (n = 31) | 60.9% (15.6 mo) | 69.5% (15.6 mo) |
| Eyre et al., VEN$^{m}$ Post-BTKi[31] | 85% (n = 53) | 23% (n = 14) | Not statistically significantly different than all | Not statistically significantly different than all t |
| Eyre et al., VEN$^{m}$ Post-PI3Ki[31] | 92% (n = 24) | 38% (n = 38) | Not statistically significantly different than all | Not statistically significantly different than all |
| Eyre et al., VEN$^{m}$ KI naive[31] | 100% (n = 6) | 83% (n = 5) | 100% (15.6 mo) | 100% (15.6 mo) |
| Mato et al., VEN$^{c+m}$ All patients [28] | 82% | 33% | 74% (12 mo) | 82% (12 mo) |
| Mato et al., VEN$^{c}$, [28] | 84% | 32% | Not statistically significantly different than all patients | Not statistically significantly different than all patients |
| Mato et al., VEN$^{m}$, [28] | 81% | 34% | Not statistically significantly different than all | Not statistically significantly different than all |

KI indicates kinase inhibitor; P13K, phosphoinositide 3-kinase inhibitor; VEN$^{C}$, venetoclax + anti-CD20 antibody; VEN$^{m}$, venetoclax monotherapy.

**Table 5**

Rates of Venetoclax Dose Reduction or Discontinuation

| | MURANO[21] | Davids et al.[33] | Mato et al.[34] | Roeker et al.[35] |
|---|---|---|---|---|
| Patients requiring dose reduction due to adverse events | 13.9% (n = 27) | 13% (n = 45) | 20.5% (n = 24) | 29% (n = 51) |
| Patients requiring dose interruption due to adverse events | 69.6% (n = 135) | 34% (n = 120) | 29.6% (n = 40) | 32% (n = 58) |
| Patients requiring discontinuation due to adverse events | 12.9% (n = 25) | 10% (n = 35) | 6.4% (n = 9) | 7.7% (n = 23) |

**Table 6**

Adverse Events Related to Venetoclax

| Adverse Event | MURANO[21] | Davids et al.[33] | Mato et al.[34] | Roeker et al.[35] |
|---|---|---|---|---|
| Grade 3 or 4 | | | | |
| Neutropenia | 57.7% (n = 112) | 37% (n = 128) | Not reported | 39.6% |
| Infections | 17.5% (n = 34) | Not reported | Not reported | 25% |
| Anemia | 10.8% (n = 21) | 17% (n = 60) | Not reported | Not reported |
| Thrombocytopenia | 5.7% (n = 11) | 14% (li = 49) | Not reported | 29.2% |
| Febrile neutropenia | 3.6% (n = 7) | Not reported | Not reported | 7.9% |
| Pneumonia | 5.2% (n = 10) | Not reported | Not reported | Not reported |
| TLS | 3.1% (n = 6) | 0% (n = 0) | Not reported | 8.1% |
| Diarrhea | Not reported | Not reported | Not reported | 6.9% |
| Serious adverse events | | | | |
| Pneumonia | 8.2% (n = 16) | 7% (n = 24) | Not reported | Not reported |
| Febrile neutropenia | 3.6% (n = 7) | 5% (n = 17) | Not reported | Not reported |
| Pyrexia | 2.6% (n = 5) | 3% (n = 12) | Not reported | Not reported |
| Anemia | 1.5% (n = 3) | Not reported | Not reported | Not reported |
| Sepsis | 0.5% (n = 1) | Not reported | Not reported | Not reported |
| TLS | 2.1% (n = 4) | Not reported | Not reported | Not reported |
| Fatalities | 5.2% (n = 10) | 3% (n = 15) | Not reported | Not reported |
| Autoimmune hemolytic anemia | Not reported | 3% (n = 10) | Not reported | Not reported |
| Any grade | | | | |
| Diarrhea | 39.7% (n = 77) | 41% (n = 145) | Not reported | Not reported |
| Neutropenia | 60.8% (n = 118) | 40% (n = 141) | 47.4% (n = 65) | Not reported |
| Nausea | 21.1% (n = 41) | 39% (n = 137) | Not reported | Not reported |
| Anemia | 15.5% (n = 30) | 31% (n= 109) | Not reported | Not reported |
| Fatigue | 17.5% (n = 34) | 28% (n = 99) | Not reported | Not reported |
| Upper respiratory tract infection | 22.2% (n = 43) | 25% (n = 86) | Not reported | Not reported |
| Thrombocytopenia | 13.4% (n = 26) | 21% (n = 74) | 36.0% (n = 49) | Not reported |
| Pyrexia | 14.9% (n = 29) | 17% (n = 60) | Not reported | Not reported |
| Cough | 18% (n = 35) | 18% (n = 63) | Not reported | Not reported |
| Constipation | 13.9% (n = 27) | 16% (n = 56) | Not reported | Not reported |
| Pneumonia | 9.3% (n = 18) | 11% (n = 40) | Not reported | Not reported |
| Infusion reaction | 8.2% (n = 16) | Not reported | Not reported | Not reported |
| Headache | 10.8% (n = 21) | 18% (n = 62) | Not reported | Not reported |
| Vomiting | 8.2% (n = 16) | 16% (n = 55) | Not reported | Not reported |
| Rash | 7.2% (n = 14) | Not reported | Not reported | Not reported |
| Bronchitis | 10.3% (n = 20) | Not reported | Not reported | Not reported |
| Insomnia | 10.8% (n = 21) | Not reported | Not reported | Not reported |
| Nasopharyngitis | 11.3% (n = 22) | Not reported | Not reported | Not reported |
| Febrile neutropenia | 3.6% (n = 7) | 5% (n = 17) | 11.6% (n = 16) | Not reported |
| TLS | Not reported | 1.2% (n = 2) | 13.4% (n= 18) | Not reported |