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A SPECIAL MEETING REVIEW EDITION

Highlights From the XVII International Workshop on Chronic Lymphocytic Leukemia

A Review of Selected Presentations From the XVII International Workshop on Chronic Lymphocytic Leukemia
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Special Reporting on:

- Outcomes of Ibrutinib-Treated Patients With CLL/SLL With High-Risk Prognostic Factors in an Integrated Analysis of 3 Randomized Phase 3 Studies
- Outcomes of Standard-of-Care Regimens in Treatment-Naive Chronic Lymphocytic Leukemia Patients With Unmutated Immunoglobulin Heavy Chain Variable Genes
- The Role of MRD in the Setting of Novel Targeted Therapies
- Ibrutinib, Fludarabine, Cyclophosphamide, and Obinutuzumab (GA101) for Previously Untreated Patients With Chronic Lymphocytic Leukemia With Mutated *IGHV* and Non-Del(17p)
- Characteristics of Patients Treated for CLL in a Real-World Registry: Results From informCLL

PLUS Meeting Abstract Summaries

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Outcomes of Ibrutinib-Treated Patients With CLL/SLL With High-Risk Prognostic Factors in an Integrated Analysis of 3 Randomized Phase 3 Studies

Outcomes in patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) are heavily influenced by genetic abnormalities.[1-3] As described by the Döhner hierarchical classification, the shortest median survival is seen in patients with deletion of chromosome arm 17p (del[17p]), followed by del(11q).[1] The unmutated immunoglobulin heavy chain variable (*IGHV*) gene is a prognostic factor for poor response to chemoimmunotherapy.[2] Patients with del(13q) as their sole abnormality fare better than those with normal cytogenetic profiles.

In the phase 2 PCYC-1102 and PCYC-1103 trials, 5-year follow-up of 132 patients who received treatment with ibrutinib showed that median progression-free survival (PFS) was shortest in those with del(17p), followed by del(11q).[4] In a multivariate analysis that included *IGHV*, complex karyotype, clinical stage, age, and del(17p), only del(17p) was independently associated with PFS or overall survival (OS).

Dr Thomas Kipps presented results of an analysis of pooled data from CLL patients treated with ibrutinib in three phase 3 clinical trials.[5] Each of the phase 3 clinical studies demonstrated superior outcomes in the ibrutinib arm vs the comparator arm. The RESONATE trial (Ibrutinib Versus Ofatumumab in Patients With Relapsed or Refractory Chronic Lymphocytic Leukemia; PCYC-1112) included 391 patients who had received at least 1 prior therapy (mean, 3 prior therapies) and were ineligible for or refractory to purine analogue therapy.[6] Patients were randomly assigned to receive ibrutinib at 420 mg once daily or ofatumumab at an initial dose of 300 mg followed by 11 doses at 2000 mg throughout 24 weeks. In the ofatumumab arm, 131 patients crossed over to ibrutinib following progressive disease. The RESONATE-2 trial (Randomized, Multicenter, Open-Label, Phase 3 Study of the Bruton's Tyrosine Kinase Inhibitor Ibrutinib Versus Chlorambucil in Patients 65 Years or Older With Treatment-Naive Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma [PCYC-1115/1116]) included 269 treatment-naive patients ages 65 years or older. Patients with del(17p) were excluded. Study participants were randomly assigned to receive ibrutinib at 420 mg once daily or chlorambucil at 0.5 mg/kg (up to a maximum of 0.8 mg/kg) on days 1 and 15 of a 28-day cycle. In the extension study, 64 patients in the chlorambucil arm crossed over to ibrutinib.[7] The HELIOS study (A Study of Ibrutinib in Combination With Bendamustine and Rituximab in Patients With Relapsed or Refractory Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma; CLL3001) included 578 patients who had received at least 1 prior therapy (mean, 2 therapies).[8] Patients with del(17p) were excluded. All patients received treatment with bendamustine plus rituximab (BR), and were then randomly assigned to receive ibrutinib (420 mg once daily) or placebo for a maximum of 6 cycles. After disease progression, 142 patients in the placebo arm crossed over to ibrutinib.

The pooled analysis evaluated the impact of the *IGHV* mutation, del(11q), trisomy 12, and the complex karyotype. (The analysis omitted del[17p] since patients with this

ABSTRACT SUMMARY Phase 2 Study of the Combination of Ibrutinib Plus Venetoclax in Patients With Treatment-Naïve CLL/SLL

PCYC-1142 is a multicenter, double-blind, placebo-controlled, randomized phase 2 study investigating the combination of ibrutinib plus venetoclax in treatment-naive patients with CLL/SLL (Abstract 95). The study is ongoing and has a planned recruitment of approximately 150 patients. The primary objectives are to identify the minimal residual disease (MRD)-negative response rate and to determine whether discontinuation of ibrutinib in patients who achieve MRD negativity impacts disease-free survival. Following treatment with ibrutinib plus venetoclax, patients with a confirmed MRD-negative response after at least 12 cycles of ibrutinib plus venetoclax will be randomly assigned to maintenance therapy with either ibrutinib or placebo. Patients who do not achieve a confirmed MRD-negative response will be randomly assigned to receive open-label treatment with ibrutinib plus venetoclax or ibrutinib alone. The primary endpoint for the initial ibrutinib-plus-venetoclax treatment phase is the MRD-negative response rate. The primary endpoint for the randomized phase of the study is the rate of MRD-negative disease-free survival at 1 year.

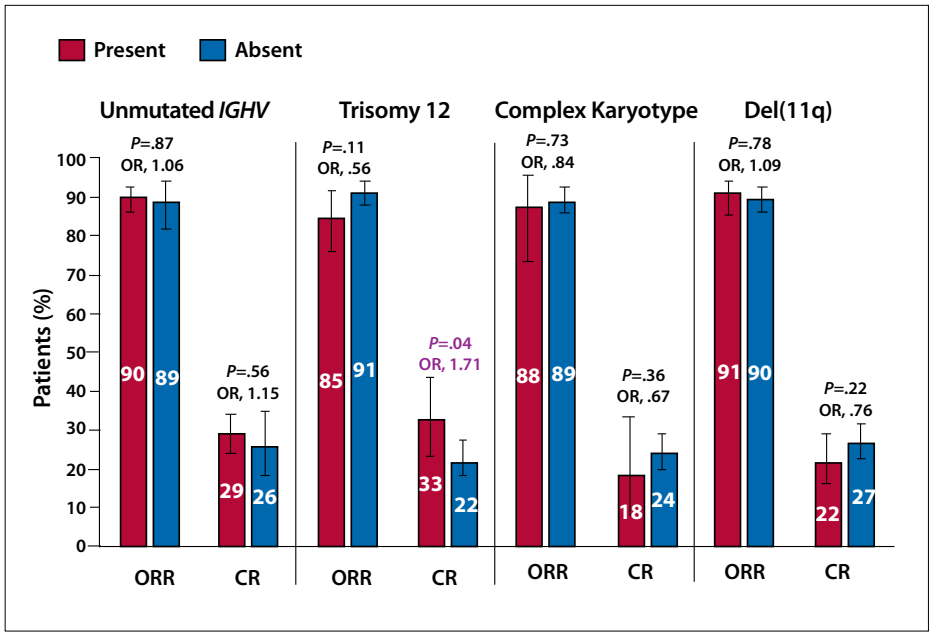

Figure 1. In an analysis of phase 3 trials, genomic risk factors were not associated with inferior response rates among patients treated with ibrutinib. CR, complete response; OR, odds ratio; ORR, overall response rate. Adapted from Kipps TJ et al. Abstract 19. The XVII International Workshop on Chronic Lymphocytic Leukemia.[5]

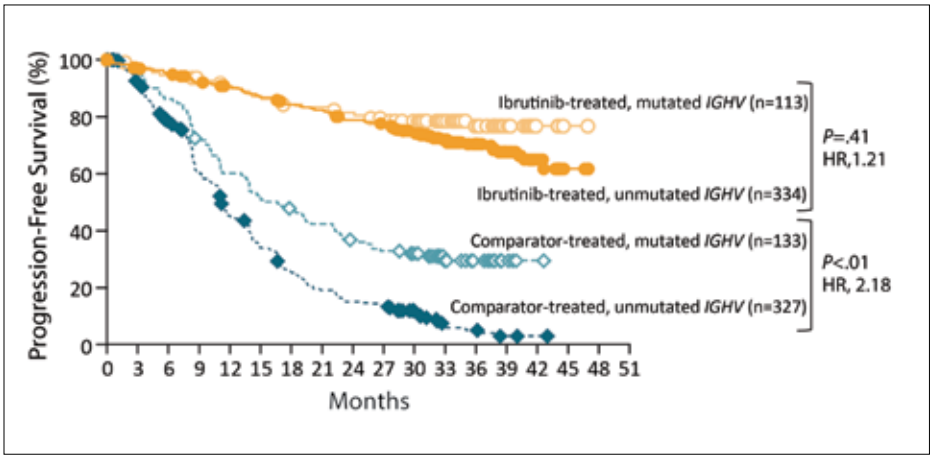

Figure 2. In an analysis of phase 3 trials, presence of the *IGHV* mutation did not impact progression-free survival among patients treated with ibrutinib. HR, hazard ratio. Adapted from Kipps TJ et al. Abstract 19. The XVII International Workshop on Chronic Lymphocytic Leukemia.[5]

mutation were excluded from 2 of the trials.) There were 620 patients treated with ibrutinib and 590 patients in the control arms.

In the cohort of patients who received treatment with ibrutinib, the overall response rates (ORRs) and the complete response (CR) rates were similar regardless of the presence of the *IGHV* mutation, del(11q), and the complex karyotype (Figure 1). The CR rate was reduced among patients who lacked trisomy 12 (*P*=.04). OS at 42 months was similar regardless of the presence of mutated *IGHV*, trisomy 12, complex karyotype, and del(11q).

At a median follow-up of 36.4 months, PFS was similar for patients with mutated or unmutated *IGHV* (*P*=.41) in the ibrutinib arm (Figure 2). In the comparator arms, mutated *IGHV* was associated with a superior PFS (*P*<.01). Trisomy 12 did not impact PFS in the ibrutinib or comparator arms. In the ibrutinib arm, presence of the complex karyotype and del(11q) did not impact PFS. In the comparator arms, however, an inferior PFS was seen in patients with complex karyotype (*P*<.01) and del(11q; *P*<.01).

Multivariate analysis did not identify any clear prognostic factors associated with ibrutinib treatment, with the possible exception of 0 vs 1 prior therapy (*P*=.06) and 1 vs 2 prior therapies (*P*=.06). In the comparator arms, a shorter PFS was seen in patients with unmutated *IGHV*, del(11q), complex karyotype, 2 or more prior therapies, bulky disease, and elevated levels of β2-microglobulin (*P*<.05 for each). Genomic risk factors did not alter the ibrutinib safety profile. Across the 3 trials, median exposure to ibrutinib ranged from 33 months to 35 months (range, <1-50 months). Serious adverse events (AEs) were observed

in 60% to 68% of patients. AEs leading to discontinuation were observed in 14% to 22% of patients, and AEs leading to death occurred in 5% to 16% of patients. The results suggest that genomic risk factors identified in patients treated with older therapies have a reduced impact in the ibrutinib setting.

References

1. Döhner H, Stilgenbauer S, Benner A, et al. Genomic aberrations and survival in chronic lymphocytic leukemia. *N Engl J Med*. 2000;343(26):1910-1916.

2. Zenz T, Gribben JG, Hallek M, Döhner H, Keating MJ, Stilgenbauer S. Risk categories and refractory CLL in the era of chemoimmunotherapy. *Blood*. 2012;119(18):4101-4107.

3. Van Dyke DL, Werner L, Rassenti LZ, et al. The Dohner fluorescence in situ hybridization prognostic classification of chronic lymphocytic leukaemia (CLL): the CLL Research Consortium experience. *Br J Haematol*. 2016;173(1):105-113.

4. Coutré SE, Furman RR, Flinn IW, et al. Extended treatment with single-agent ibrutinib at the 420 mg dose leads to durable responses in chronic lymphocytic leukemia/small lymphocytic lymphoma. *Clin Cancer Res*. 2017;23(5):1149-1155.

5. Kipps TJ, Fraser G, Coutre SE, et al. Outcomes of ibrutinib-treated patients with chronic lymphocytic leukemia/small lymphocytic leukemia (CLL/SLL) with high-risk prognostic factors in an integrated analysis of 3 randomized phase 3 studies. Abstract presented at: the XVII International Workshop on Chronic Lymphocytic Leukemia; May 12-15, 2017; New York, NY. Abstract 19.

6. Byrd JC, Brown JR, O'Brien S, et al; RESONATE Investigators. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. *N Engl J Med*. 2014;371(3):213-223.

7. Burger JA, Tedeschi A, Barr PM, et al; RESONATE-2 Investigators. Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. *N Engl J Med*. 2015;373(25):2425-2437.

8. Chanan-Khan A, Cramer P, Demirkan F, et al; HELIOS investigators. Ibrutinib combined with bendamustine and rituximab compared with placebo, bendamustine, and rituximab for previously treated chronic lymphocytic leukaemia or small lymphocytic lymphoma (HELIOS): a randomised, double-blind, phase 3 study. *Lancet Oncol*. 2016;17(2):200-211.

Outcomes of Standard-of-Care Regimens in Treatment-Naive Chronic Lymphocytic Leukemia Patients With Unmutated Immunoglobulin Heavy Chain Variable Genes

Chemoimmunotherapy is the standard of care for patients with CLL. Several studies have demonstrated that CLL patients with unmutated *IGHV* genes have inferior response rates and survival outcomes following treatment with fludarabine, cyclophosphamide, and rituximab (FCR), BR, or rituximab and chlorambucil.[1-4] In CLL patients with mutated *IGHV* but without del(11q) or del(17p), treatment with FCR conferred a life expectancy similar to that seen in an age-matched population.[5] In the RESONATE-2 trial, ibrutinib led to an 83% reduction in the risk of disease progression or death compared with chlorambucil in patients with mutated *IGHV* and a 93% risk reduction in patients with unmutated *IGHV*.[6]

Dr Paolo Ghia presented an analysis of published outcomes in CLL patients who received treatment with FCR, BR, or ibrutinib in the CLL8, CLL10, and RESONATE-2 studies.[1,3,6,7] Estimated PFS rates were obtained from Kaplan-Meier curves that were digitized from the original publications. In the 3 studies, the proportion of patients with unmutated *IGHV* ranged from 43% to 68%. Most patients were male (65% to 74%). The median age was 61 to 62 years in CLL8 and CLL10, and 73 years in RESONATE-2. In CLL8, 10% of patients had del(17p). Patients with del(17p) were excluded from CLL10 and RESONATE-2.

In the RESONATE-2 trial, Kaplan-Meier analysis of patients treated with ibrutinib showed similar rates of PFS over time, regardless of *IGHV* status. In contrast, the Kaplan-Meier curves did not overlap for patients in the chemoimmunotherapy arm stratified by *IGHV* mutation status. Among the BR-treated patients from CLL10, those with mutated *IGHV* had a superior PFS vs those with unmutated *IGHV*. Similarly, among the FCR-treated patients from CLL8 and CLL10, PFS was superior in patients with mutated *IGHV* genes. Among patients with mutated *IGHV* in all 3 trials—who were treated with ibrutinib, FCR, or BR—the Kaplan-Meier curves overlapped through 36 months, at which point the data for ibrutinib-treated patients were not available. After 36 months, PFS was superior for FCR compared with BR.

The estimated 30-month PFS rates for patients with mutated *IGHV* were 81% for ibrutinib-treated patients, 84% for FCR-treated patients from CLL8, 87% for FCR-treated patients from CLL10, and 83% for BR-treated patients from CLL10 (Figure 3). A comparison of Kaplan-Meier curves from patients with unmutated *IGHV* showed overlapping curves for patients from CLL8 or CLL10 who received treatment with FCR, a superior PFS for ibrutinib-treated patients with

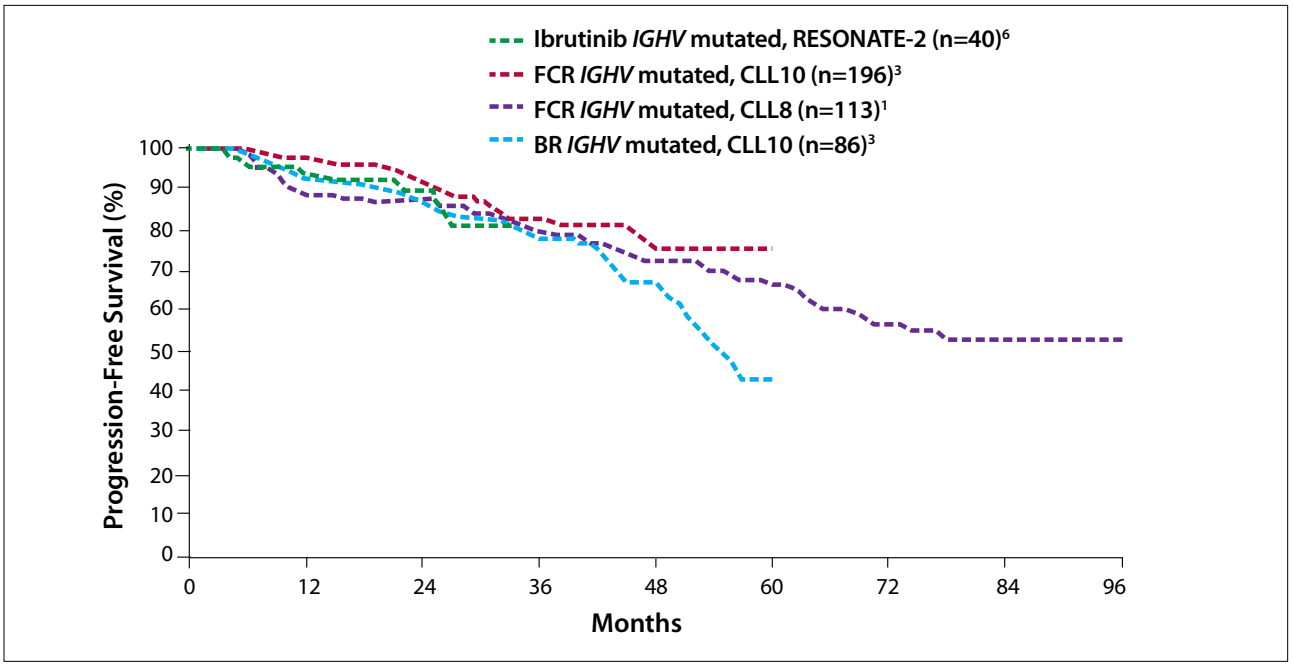

Figure 3. Rates of progression-free survival among patients with CLL and the *IGHV* mutation from 3 clinical trials. BR, bendamustine/rituximab; CLL, chronic lymphocytic leukemia; FCR, fludarabine/cyclophosphamide/rituximab; RESONATE-2, Randomized, Multicenter, Open-Label, Phase 3 Study of the Bruton's Tyrosine Kinase Inhibitor Ibrutinib Versus Chlorambucil in Patients 65 Years or Older With Treatment-Naive Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma (PCYC-1115/1116). Adapted from Ghia P et al. Abstract 188. The XVII International Workshop on Chronic Lymphocytic Leukemia.[7]

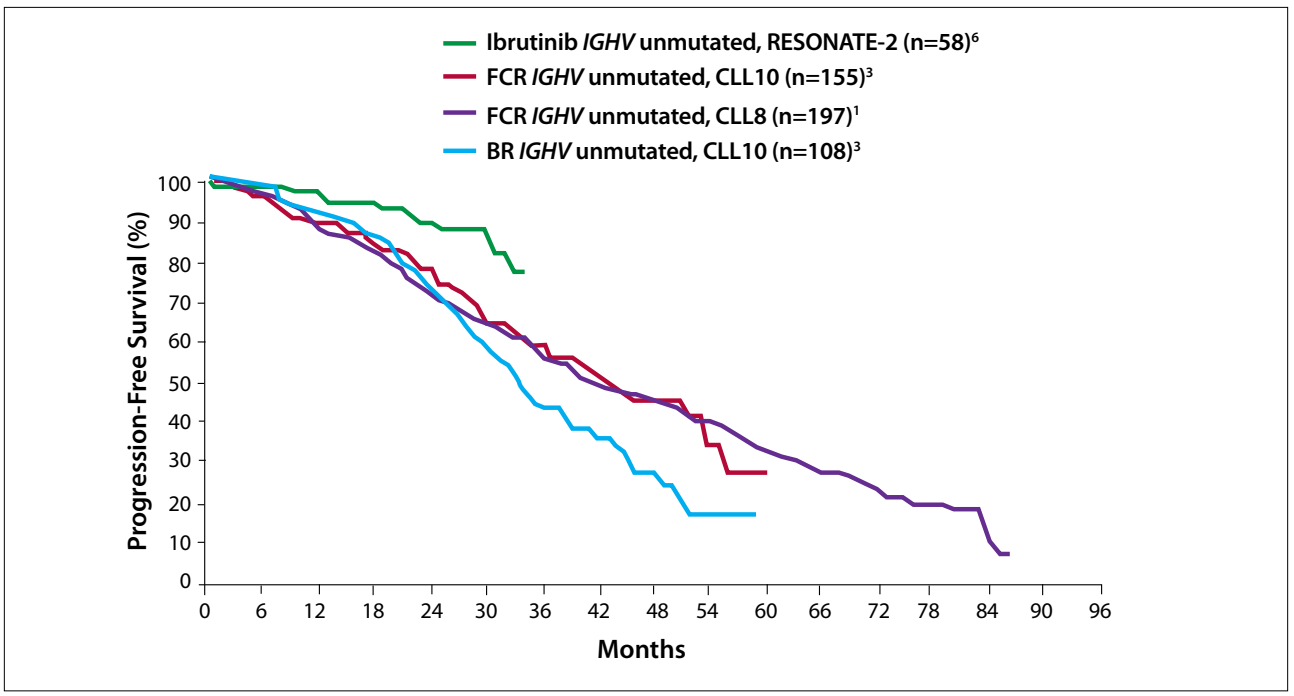

Figure 4. Rates of progression-free survival among patients with CLL and without the *IGHV* mutation from 3 clinical trials. BR, bendamustine/rituximab; CLL, chronic lymphocytic leukemia; FCR, fludarabine/cyclophosphamide/rituximab; RESONATE-2, Randomized, Multicenter, Open-Label, Phase 3 Study of the Bruton's Tyrosine Kinase Inhibitor Ibrutinib Versus Chlorambucil in Patients 65 Years or Older With Treatment-Naive Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma (PCYC-1115/1116). Adapted from Ghia P et al. Abstract 188. The XVII International Workshop on Chronic Lymphocytic Leukemia.[7]

unmutated *IGHV*, and the lowest PFS rate for patients treated with BR (Figure 4). Estimated 30-month PFS rates for patients with unmutated *IGHV* were 87% for ibrutinib-treated patients, 64% for FCR-treated patients from CLL8, 65% for FCR-treated patients from CLL10, and 59% for BR-treated patients from CLL10. OS was similar regardless of the presence of the *IGHV* mutation until approximately 15 months, at which point it decreased for patients with unmutated *IGHV* and remained lower through 96 months. The cross-trial comparisons suggest that patients with mutated or unmutated *IGHV* can experience a durable PFS with ibrutinib. In contrast, patients with unmutated *IGHV* experience inferior outcomes after chemoimmunotherapy vs those with mutated *IGHV*.

References

1. Stilgenbauer S, Schnaiter A, Paschka P, et al. Gene mutations and treatment outcome in chronic lymphocytic leukemia: results from the CLL8 trial. *Blood*. 2014;123(21):3247-3254.
2. Thompson PA, Wierda WG. Eliminating minimal residual disease as a therapeutic end point: working toward cure for patients with CLL. *Blood*. 2016;127(3):279-286.
3. Eichhorst B, Fink AM, Bahlo J, et al; international group of investigators; German CLL Study Group (GCLLSG). First-line chemoimmunotherapy with bendamustine and rituximab versus fludarabine, cyclophosphamide, and rituximab in patients with advanced chronic lymphocytic leukaemia (CLL10): an international, open-label, randomised, phase 3, non-inferiority trial. *Lancet Oncol*. 2016;17(7):928-942.
4. Foà R, Del Giudice I, Cuneo A, et al. Chlorambucil plus rituximab with or without maintenance rituximab as first-line treatment for elderly chronic lymphocytic leukemia patients. *Am J Hematol*. 2014;89(5):480-486.
5. Rossi D, Terzi-di-Bergamo L, De Paoli L, et al. Molecular prediction of durable remission after first-line fludarabine-cyclophosphamide-rituximab in chronic lymphocytic leukemia. *Blood*. 2015;126(16):1921-1924.
6. Burger JA, Tedeschi A, Barr PM, et al; RESONATE-2 Investigators. Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. *N Engl J Med*. 2015;373(25):2425-2437.
7. Ghia P, Hillmen P, Moreno C, et al. Outcomes of standard of care regimens in treatment-naïve chronic lymphocytic leukemia (CLL) patients with unmutated immunoglobulin heavy chain variable (*IGHV*) genes. Abstract presented at: the XVII International Workshop on Chronic Lymphocytic Leukemia; May 12-15, 2017; New York, NY. Abstract 188.

The Role of MRD in the Setting of Novel Targeted Therapies

Dr Peter Hillmen presented an overview of the expanding role of minimal residual disease (MRD) assessment in the era of targeted treatment.[1] MRD is used as a means to evaluate treatment efficacy in patients with CLL and has traditionally been used as a binary marker that indicates a positive or negative result. Patients who are MRD negative following treatment have longer remissions than patients who are MRD positive. With the introduction of newer agents, MRD may be used to guide duration of therapy. Moreover, because MRD reflects the level of disease, it could be used for early detection of relapse.

The multicenter, open-label, phase 2b ARCTIC (Attenuated Dose Rituximab With Chemotherapy in CLL) and ADMIRE (Does the Addition of Mitoxantrone Improve Response to FCR?) trials included 415 treatment-naive CLL patients who received FCR-like therapy at 60 treatment centers across the United Kingdom.[2,3] ARCTIC was a noninferiority trial that compared standard FCR vs fludarabine, cyclophosphamide, and mitoxantrone, plus low-dose rituximab. ADMIRE was a superiority trial that evaluated FCR with or without mitoxantrone. In both trials, bone marrow MRD was assessed 3 months after cessation of chemoimmunotherapy and 9 months after randomization. Patients who were MRD negative had a superior PFS and OS compared with those who were MRD positive. Because these trials ended in 2012, the study participants were unlikely to have received targeted therapies.

MRD negativity is associated with a superior PFS. However, MRD negativity does not necessarily reflect disease eradication, given the technological limitations in detecting small numbers of CLL cells after treatment. Patients who are MRD negative at the end of treatment can still relapse. Tumor cells with a shorter doubling time will cause earlier relapse. These parameters and others are being assessed in mathematical models that aim to describe the normal distribution of patients with various tumor types and thus predict the proportion of patients who are likely to achieve cures with a given treatment. Higher cure rates will require larger log reductions in the population of viable cancer cells. Therefore, therapies associated with a higher proportion of MRD negativity will increase the time that patients spend off-treatment, as well as the proportion of patients who achieve true cures. Modeling of MRD data from the ADMIRE and ARCTIC trials predicted that approximately 16% of MRD-negative patients would achieve a cure and that approximately 38% of MRD-negative patients would relapse.

Ibrutinib treatment induces immediate lymphocytosis that persists for several months in most patients. Obinutuzumab is a second-generation anti-CD20 antibody that rapidly reverses peripheral blood lymphocytosis and eradicates MRD in some patients. The IcICLLe (Assessment of the Mechanism of Action of Ibrutinib [PCI-32765] in B-Cell Receptor Pathway Inhibition in CLL) extension study is evaluating the efficacy and safety of continuous oral therapy with ibrutinib plus 6 cycles

ABSTRACT SUMMARY A Comparative Analysis of Six Prognostic Models to Predict Time-to-First-Treatment in Patients With Chronic Lymphocytic Leukaemia in Early Phase

Six prognostic models were evaluated for their ability to predict time-to-first-treatment in patients with newly diagnosed Binet stage A CLL (Abstract 139). All patients were prospectively enrolled into the O-CLL1 protocol at several Italian institutions. The models included various combinations of factors, including *IGHV* status, β2-microglobulin levels, and clinical and genetic parameters. The study included 337 patients, of whom 28.1% had unmutated *IGHV*, 4.5% had del(11q), and 2.6% had del(17p) and/or *TP53* mutation. After a median follow-up of 42 months (range, 1-82 months), the projected probability of remaining free from therapy at 5 years was 65%. All 6 prognostic models showed a moderate discriminating value, with areas under the receiver operating characteristic curves ranging from 0.65 to 0.78. At 12 months after diagnosis, models that included both clinical and genetic variables reached and maintained the area under the curve threshold level of 0.70. The authors concluded that these findings support the clinical practice of initiating treatment only in CLL patients who have active disease.

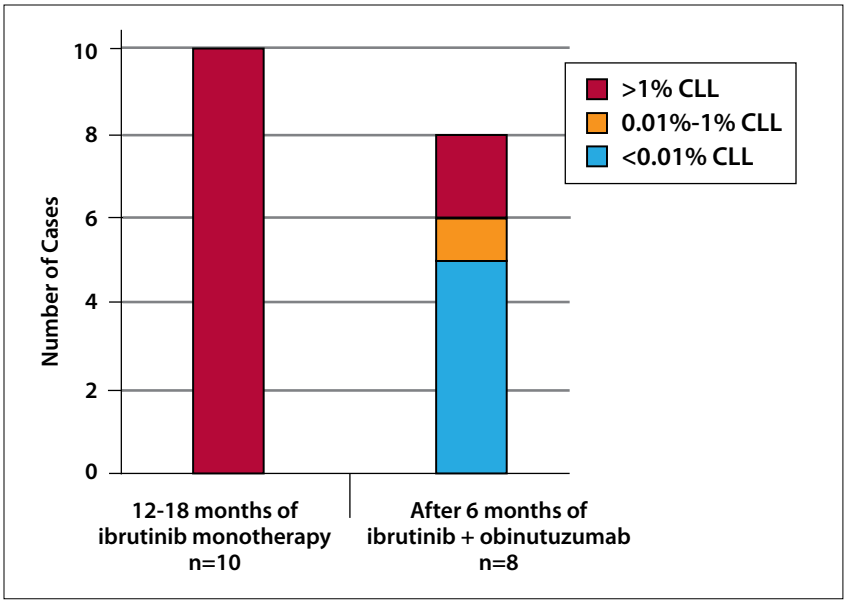

Figure 5. Minimal residual disease in the bone marrow in the IcICLLe Extension study, which evaluated ibrutinib plus obinutuzumab after ibrutinib monotherapy. CLL, chronic lymphocytic leukemia. Adapted from Rawstron A et al. Abstract 242. The XVII International Workshop on Chronic Lymphocytic Leukemia.[4]

of obinutuzumab in patients with relapsed/refractory CLL.[4] Among the 40 enrolled patients, 30 will not have received prior treatment with ibrutinib and 10 will have received at least 1 year of ibrutinib while enrolled in the IcICLLe study. The primary outcome of the extension study is the proportion of patients achieving MRD-negative remission based on criteria from the International Workshop on Chronic Lymphocytic Leukemia (iwCLL).

Data were available for 20 patients who received ibrutinib monotherapy in the IcICLLe trial and 27 patients who received ibrutinib plus obinutuzumab in the IcICLLe extension study. Peripheral CLL counts fell below baseline after 1 week of combination therapy, but remained above baseline for at least 3 months in patients treated with ibrutinib monotherapy. After 6 months of ibrutinib monotherapy, 13 of 19 evaluable patients had a B-cell count of greater than 5×10^9/L, and no patients had a peripheral blood CLL level of less than 0.01%. In contrast, after 6 months of ibrutinib plus obinutuzumab, all 20 evaluable patients (all of whom were ibrutinib-naive at baseline) had a B-cell count of less than 5×10^9/L, and 5 of 20 patients had a peripheral blood CLL level of less than 0.01%. After 1 month of therapy, patients receiving ibrutinib plus obinutuzumab showed a median 32% decrease in the proportion of CLL cells in the bone marrow compared with baseline (P<.001). Among patients treated with ibrutinib monotherapy, there was a 1% increase from baseline (P=.6). There were 8 patients who had received 12 to 18 months of ibrutinib monotherapy followed by 6 months of ibrutinib plus obinutuzumab, and 5 had a bone marrow MRD of less than 0.01% (Figure 5). Among 10 patients who had received 12 to 18 months of ibrutinib monotherapy only, all had a bone marrow MRD of greater than 1%.

The CLARITY trial (Assessment of Venetoclax in Combination With Ibrutinib in Patients With Chronic Lymphocytic Leukaemia) is a feasibility study evaluating the combination of ibrutinib plus venetoclax, an oral inhibitor of BCL-2, in patients with relapsed or refractory CLL.[5] Patients receive treatment with daily ibrutinib monotherapy (420 mg) for 2 months, and then daily venetoclax is added. The initial venetoclax dose was 10 mg daily and escalated weekly to 20 mg, 50 mg, 100 mg, 200 mg, and 400 mg. The primary endpoint is MRD at 12 months, with MRD at 6 months and

Table 1. Peripheral Blood CLL Responses in the CLARITY Trial

Time Point		Patients (n)	Mean ($\times 10^9$/L)	Median ($\times 10^9$/L)	25th Percentile ($\times 10^9$/L)	75th Percentile ($\times 10^9$/L)
Screening		29	62.6	50	9.6	92
Day 0	Before ibrutinib	29	64.4	45	8.4	97
Week 8	Before venetoclax	23	78.6	60	7.0	119
Week 12	End of venetoclax escalation	28	11.7	1.35	0.43	7.95
Month 4	After 8 weeks of venetoclax	28	0.51	0.029	0.0035	0.22
Month 5	After 12 weeks of venetoclax	24	0.31	0.012	0.0024	0.0865

CLARITY, Assessment of Venetoclax in Combination With Ibrutinib in Patients With Chronic Lymphocytic Leukaemia.

Adapted from Muñoz-Vicente S et al. Abstract 249. The XVII International Workshop on Chronic Lymphocytic Leukemia.[5]

24 months as secondary endpoints. Forty-five patients were recruited from May 2016 to March 2017. Among the 26 patients who had completed the venetoclax dose escalation, 1 developed laboratory tumor lysis syndrome. CLL in the peripheral blood increased during the 8 weeks of ibrutinib treatment. After 8 weeks of combination treatment, patients showed a median 3-log reduction in CLL levels (Table 1). The initial bone marrow responses are anticipated after 6 months of combination therapy.

The phase 3 FLAIR trial (First-Line Assessment of Ibrutinib Plus Rituximab) is comparing FCR vs ibrutinib and rituximab as first-line treatment in patients with CLL.[6] In this multicenter, open-label, parallel-group study, patients will be assessed every 6 months for peripheral blood MRD. In the ibrutinib-plus-rituximab arm, treatment will be stopped for patients with a negative MRD at 2 consecutive assessments. The primary endpoint is PFS, with secondary endpoints of OS, MRD, iwCLL response rate, safety, quality of life, and cost effectiveness. The trial protocol was amended to include an arm to evaluate ibrutinib monotherapy and another arm to evaluate ibrutinib plus venetoclax, using the same dosing schedule as the CLARITY trial, with treatment lasting up to 6 years based on MRD results. Recruitment will continue until 2020, with more than 1500 patients enrolled into the 4 arms.

ABSTRACT SUMMARY Evaluation of the International Prognostic Index for Chronic Lymphocytic Leukemia (CLL-IPI) in Previously Untreated CLL Patients Receiving Chemo-Immunotherapy as First-Line Approach: Analysis of 529 Cases

The ability of the CLL International Prognostic Index to predict OS was investigated in a cohort of treatment-naive CLL patients (Abstract 143). Patients received first-line treatment with FCR or BR and had data available for the 5 CLL International Prognostic Index factors at the time of progression, including *IGHV* and *TP53* status, clinical stage, age, and β2-microglobulin level. The 529 patients had a median age of 63 years. After a median follow-up of 3.4 years (range, 3 months-15.7 years), the 3-year OS probability was 98.5% for low-risk patients, 93.7% for intermediate-risk patients, 87.8% for high-risk patients, and 65.6% for patients at very high risk. The Harrell C statistic was 0.70 (P<.0001) for predicting survival. The 3-year PFS probability was 86.5% for low-risk patients, 70.6% for intermediate-risk patients, 58.3% for high-risk patients, and 29.8% for very high-risk patients, with a Harrell C statistic of 0.63 (P<.0001). A significant benefit was observed for treatment with FCR compared with BR among patients in the high-risk and very high-risk groups.

References

1. Hillmen P. Role of MRD in the setting of the novel targeted therapies. Presented at: the XVII International Workshop on Chronic Lymphocytic Leukemia; May 12-15, 2017; New York, NY.
2. Howard DR, Munir T, McParland L, et al. Results of the randomized phase IIB ARCTIC trial of low-dose rituximab in previously untreated CLL [published online May 2, 2017]. *Leukemia*. doi:10.1038/leu.2017.96.
3. Munir T, Howard DR, McParland L, et al. Results of the randomized phase IIB ADMIRE trial of FCR with or without mitoxantrone in previously untreated CLL. *Leukemia*. 2017;23(18):4079-4088.
4. Rawstron A, Munir T, Muñoz-Vicente S, et al. Addition of obinutuzumab to ibrutinib enhances depletion of CLL cells in the peripheral blood and bone marrow after 1 month & 6 months of combination therapy: initial results from the Bloodwise TAP IcICLLe extension study. Abstract presented at: the XVII International Workshop on Chronic Lymphocytic Leukemia; May 12-15, 2017; New York, NY. Abstract 242.
5. Muñoz-Vicente S, Bishop R, Hillmen P, et al. The initial report of the Bloodwise TAP CLARITY study combining ibrutinib and venetoclax in relapsed, refractory CLL shows acceptable safety and promising early indications of efficacy. Abstract presented at: the XVII International Workshop on Chronic Lymphocytic Leukemia; May 12-15, 2017; New York, NY. Abstract 249.
6. ISRCTN registry. FLAIR: front-line therapy in CLL: assessment of ibrutinib + rituximab. http://www.isrctn.com/ISRCTN01844152. ISRCTN identifier: 01844152. Accessed June 12, 2017.

Ibrutinib, Fludarabine, Cyclophosphamide, and Obinutuzumab (GA101) for Previously Untreated Patients With Chronic Lymphocytic Leukemia With Mutated *IGHV* and Non-Del(17p)

In young patients with CLL, 6 cycles of FCR yielded CR rates of 40% to 72% and rates of bone marrow MRD negativity of 43% to 58%.[1-7] These outcomes are associated with a 5% risk of therapy-related myelodysplastic syndrome/acute myeloid leukemia.[8] Patients with mutated *IGHV* experience superior PFS vs patients with unmutated *IGHV* after treatment with first-line FCR.[7,9,10] MRD negativity after first-line FCR is also associated with a favorable outcome in patients with mutated *IGHV*, with 5-year PFS rates of approximately 80%.

The phase 3 CLL11 trial demonstrated that first-line obinutuzumab plus chlorambucil induced a higher rate of MRD negativity compared with rituximab plus chlorambucil in patients with CLL.[11] The phase 3 HELIOS trial investigated ibrutinib plus BR vs BR alone in patients with relapsed or refractory CLL/SLL.[12] As assessed by an independent review committee, the PFS at 18 months was 79% for ibrutinib plus BR vs 24% for BR alone (HR, 0.203; 95% CI, 0.150-0.276; *P*<.0001). After a median follow-up of 25.4 months, MRD-negative response rates were 18.0% for ibrutinib plus BR vs 4.8% for BR alone (*P*<.0001).

Dr Nitin Jain presented findings from a trial testing the hypotheses that inducing higher rates of MRD negativity would improve rates of PFS and OS and that reducing the number of chemotherapy cycles from 6 to 3 would reduce the risk of therapy-related myelodysplastic syndrome/acute myeloid leukemia.[13] The investigator-initiated, phase 2 trial enrolled treatment-naive adults with *IGHV*-mutated CLL/SLL. Patients with del(17q) or *TP53* mutations were excluded. The primary endpoint was the rate of CR and CR with incomplete blood recovery (CRi) and the rate of bone marrow MRD negativity after 3 cycles of treatment. All patients received daily ibrutinib (420 mg) plus 3 cycles of fludarabine, cyclophosphamide, and obinutuzumab (FCG). Granulocyte-colony stimulating factor support was allowed. After the primary endpoint assessment, patients who achieved CR/CRi or MRD negativity received 3 more cycles of treatment with ibrutinib and obinutuzumab, followed by 6 cycles of ibrutinib monotherapy. Patients who achieved a partial response (PR) or were MRD positive received 9 cycles of ibrutinib and obinutuzumab. Patients with a negative bone marrow MRD after completion of all 12 treatment cycles stopped ibrutinib monotherapy. Patients who were MRD positive continued ibrutinib monotherapy until disease progression. Responses were assessed by iwCLL 2008 criteria.[14] Blood, bone marrow, and computed tomography scans were performed every 3 months during the first year, then every 6 months. A PR was defined as a lymph node exceeding 1.5 cm. MRD in the bone marrow was assessed by 4-color flow cytometry, with a sensitivity of 10^{-4}.

The first patients were enrolled in April 2016. Data were available for 5 patients who had initiated treatment and 24 who had completed 3 cycles of treatment. Median follow-up was 8.3 months (range, 0.9-13.3 months). One patient was removed from the study after 3 cycles of ibrutinib plus FCG owing to infection with pulmonary *Mycobacterium avium* complex. Another patient was removed from the study after receiving obinutuzumab (100 mg) plus ibrutinib (420 mg) on day 1 of cycle 1 owing to grade 3 infusion-related reaction and grade 4 thrombocytopenia. The 29 patients had a median age of 60 years (range, 60-71 years), and 83% were male. Based on fluorescence in situ hybridization, 69% of patients had del(13q) and 21% had trisomy 12. Cytogenetic analysis was available for 24 patients and showed 58% with diploid karyotype, 25% with (del)13, and 17% with trisomy 12. The most common mutations were *MYD88* (11%) and *SF3B1* (7%). The median level of β2-microglobulin was 2.6 mg/L (range, 1.4-8.1 mg/L).

After 3 treatment cycles, the ORR in 24 patients was 100%, including 42% with a CR/CRi and 58% with a PR (Table 2). All of the 10 patients who achieved a CR or CRi also achieved MRD-negative bone marrow. Of the 14 patients who achieved a PR, bone marrow was MRD-negative in 10 (71%). After 3 cycles, 83% of patients treated with ibrutinib plus FCG were MRD negative vs 26% of patients treated with FCR for 3 cycles (based on historical data). Responses continued to improve over time, with 100% of patients achieving MRD negativity and 77% achieving a CR or CRi at 9 months. Nine patients had ceased treatment after 12 months of therapy and were being monitored for changes in MRD status or relapse. Bone marrow MRD negativity was reported in 50% of the 6 patients who

Table 2. Clinical Response in a Trial Evaluating Ibrutinib Plus Fludarabine, Cyclophosphamide, and Obinutuzumab

	3 Months		Best Response	
	N=24 (%)	Negative for BM MRD (%)	N=24 (%)	Negative for BM MRD (%)
ORR	24/24 (100)	20/24 (83)	24/24 (100)	24/24 (100)
CR/CRi	10/24 (42)	24/24 (100)	18/24 (75)	24/24 (100)
PR	14/24 (58)	10/14 (71)	6/24 (25)	24/24 (100)

BM, bone marrow; CR, complete response; CRi, incomplete complete response; MRD, minimal residual disease; ORR, overall response rate; PR, partial response.

Data from Jain N et al. Abstract 164. The XVII International Workshop on Chronic Lymphocytic Leukemia.[13]

had a β2-microglobulin level of at least 4 mg/L, compared with 94% of the 18 patients with a level of less than 4 mg/L (*P*=.035).

Grade 3/4 AEs included neutropenia (72%), thrombocytopenia (44%), transaminase elevation (13%), atrial fibrillation (3%), arthralgia (3%), and infusion-related reaction (3%). Nine patients (31%) also had a grade 2 infusion-related reaction. Transaminase elevation occurred in 4 patients, but reversed in all by 2 to 4 weeks; these patients resumed therapy without further transaminase elevation. Four patients developed neutropenic fever. Pneumocystis pneumonia, *Mycobacterium avium* complex pulmonary infection, acute cholecystitis, and herpes zoster were observed in 1 patient each. Dose reductions for fludarabine and cyclophosphamide were required in 57% of patients, and ibrutinib dose reductions were required in 18%. Among the 35% of patients with a treatment delay exceeding 2 weeks, the most common reason was thrombocytopenia.

References

1. Böttcher S, Ritgen M, Fischer K, et al. Minimal residual disease quantification is an independent predictor of progression-free and overall survival in chronic lymphocytic leukemia: a multivariate analysis from the randomized GCLLSG CLL8 trial. *J Clin Oncol*. 2012;30(9):980-988.
2. Eichhorst B, Fink AM, Bahlo J, et al; international group of investigators; German CLL Study Group (GCLLSG). First-line chemoimmunotherapy with bendamustine and rituximab versus fludarabine, cyclophosphamide, and rituximab in patients with advanced chronic lymphocytic leukaemia (CLL10): an international, open-label, randomised, phase 3, non-inferiority trial. *Lancet Oncol*. 2016;17(7):928-942.
3. Hallek M, Fischer K, Fingerle-Rowson G, et al; International Group of Investigators; German Chronic Lymphocytic Leukaemia Study Group. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. *Lancet*. 2010;376(9747):1164-1174.
4. Keating MJ, O'Brien S, Albitar M, et al. Early results of a chemoimmunotherapy regimen of fludarabine, cyclophosphamide, and rituximab as initial therapy for chronic lymphocytic leukemia. *J Clin Oncol*. 2005;23(18):4079-4088.
5. Strati P, Keating MJ, O'Brien SM, et al. Eradication of bone marrow minimal residual disease may prompt early treatment discontinuation in CLL. *Blood*. 2014;123(24):3727-3732.
6. Tam CS, O'Brien S, Wierda W, et al. Long-term results of the fludarabine, cyclophosphamide, and rituximab regimen as initial therapy of chronic lymphocytic leukemia. *Blood*. 2008;112(4):975-980.
7. Thompson PA, Wierda WG. Eliminating minimal residual disease as a therapeutic end point: working toward cure for patients with CLL. *Blood*. 2016;127(3):279-286.
8. Benjamini O, Jain P, Trinh L, et al. Second cancers in patients with chronic lymphocytic leukemia who received frontline fludarabine, cyclophosphamide and rituximab therapy: distribution and clinical outcomes. *Leuk Lymphoma*. 2015;56(6):1643-1650.
9. Fischer K, Bahlo J, Fink AM, et al. Long-term remissions after FCR chemoimmunotherapy in previously untreated patients with CLL: updated results of the CLL8 trial. *Blood*. 2016;127(2):208-215.
10. Rossi D, Terzi-di-Bergamo L, De Paoli L, et al. Molecular prediction of durable remission after first-line fludarabine-cyclophosphamide-rituximab in chronic lymphocytic leukemia. *Blood*. 2015;126(16):1921-1924.
11. Goede V, Fischer K, Busch R, et al. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. *N Engl J Med*. 2014;370(12):1101-1110.
12. Chanan-Khan A, Cramer P, Demirkan F, et al;

ABSTRACT SUMMARY Novel Humanised ROR1 Bispecific T-Cell Engager for the Treatment of Chronic Lymphocytic Leukaemia

Bispecific T-cell engagers (BiTEs) are small antibody constructs with 2 different binding sites (Abstract 236). Receptor tyrosine kinase-like orphan receptor 1 (ROR1) is expressed in CLL cells as well as other solid and hematologic tumors, but shows low expression in normal cells. ROR1-BiTE targets an exposed epitope of human ROR1 and CD3, a T-cell antigen. ROR1-BiTE has been shown to induce T-cell mediated cytotoxicity against a panel of hematologic cell lines that express ROR1 and against primary CLL samples. Intraperitoneal injection of the bispecific construct in conjunction with intravenous injection of T cells reduced the volume of established SKW6.4 cells. In mice with established SKW6.4 tumor xenografts, administration of T cells plus ROR1-BiTE prolonged median survival compared with controls (median survival, 50 days vs 18 days; *P*=.034). However, ROR1-BiTe demonstrated poor cytotoxicity in conjunction with autologous patient T cells, and treatment of CLL cells and T cells with ibrutinib yielded poor cytotoxicity by autologous as well as allogeneic T cells. Current studies are investigating whether treatment with ROR1-BiTEs will be feasible in patients who have received treatment with lenalidomide, ibrutinib, and other novel agents.

HELIOS investigators. Ibrutinib combined with bendamustine and rituximab compared with placebo, bendamustine, and rituximab for previously treated chronic lymphocytic leukaemia or small lymphocytic lymphoma (HELIOS): a randomised, double-blind, phase 3 study. *Lancet Oncol*. 2016;17(2):200-211.
13. Jain N, Thompson P, Burger JA, et al. Ibrutinib, fludarabine, cyclophosphamide, and obinutuzumab (GA101) (iFCG) for previously untreated patients with chronic lymphocytic leukemia (CLL) with mutated *IGHV* and non-del(17p). Abstract presented at: the XVII International Workshop on Chronic Lymphocytic Leukemia; May 12-15, 2017; New York, NY. Abstract 164.
14. Hallek M, Cheson BD, Catovsky D, et al; International Workshop on Chronic Lymphocytic Leukemia. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. *Blood*. 2008;111(12):5446-5456.

Characteristics of Patients Treated for CLL in a Real-World Registry: Results From informCLL

The informCLL registry was created to analyze real-world CLL treatment patterns, with an emphasis on novel therapies.[1] The registry is collecting information on baseline demographic and clinical characteristics, treatment sequencing, and outcomes. A prospective, multicenter, observational study of the registry has a planned enrollment of approximately 1000 patients who are starting treatment with novel therapies and 500 patients initiating other approved CLL therapies. Patients from 200 sites in the United States will be enrolled during a 36-month period that began in September 2015. Included patients are at least 18 years old with a clinical diagnosis of CLL/SLL based on iwCLL 2008 diagnostic criteria.[2] Patients initiated treatment within 30 days of registry enrollment and had documentation of any prior CLL/SLL treatment. Response data were available for all patients. Patients receiving CLL treatment as part of an interventional clinical study and those with a life expectancy of less than 6 months were excluded.

Table 3. The Most Common Therapies Initiated at Enrollment in the informCLL Registry

Therapies Prescribed at Registry Enrollment, n (%)	Treatment-Naive (n=132 [%])	Previously Treated With 1 Prior Therapy (n=50 [%])	Previously Treated With ≥2 Prior Therapies (n=59 [%])	Previously Treated With ≥1 Prior Therapies (n=109 [%])
Single-agent ibrutinib	42 (32)	21 (42)	33 (56)	54 (50)
BR	28 (21)	10 (20)	7 (12)	17 (16)
FCR	15 (11)	2 (4)	2 (3)	4 (4)
Single-agent rituximab	9 (7)	7 (14)	7 (12)	14 (13)
Obinutuzumab + chlorambucil	13 (10)	0	1 (2)	3 (3)
Single-agent obinutuzumab	10 (8)	2 (4)	1 (2)	3 (3)
Chlorambucil	1 (1)	2 (4)	0	2 (2)
Idelalisib + rituximab	1 (1)	0	2 (3)	2 (2)
Ibrutinib + venetoclax	0	1 (2)	0	1 (1)

BR, bendamustine/rituximab; FCR, fludarabine, cyclophosphamide, and rituximab.

Adapted from Mato A et al. Abstract 54. The XVII International Workshop on Chronic Lymphocytic Leukemia.[1]

Data from 241 patients were available for an interim analysis. The mean age was 68 years (range, 40-95 years). Most patients were male (66%) and white (92%). The median time from initial diagnosis to treatment at registry enrollment was 41 months. The most common source of health care coverage was Medicare (56%), followed by employer-based coverage (34%), other (19%), and Medicaid (3%). Patients were treatment-naive (n=132) or had received previous treatment (n=109). Among the latter group, the most common prior CLL therapies were BR (23%), rituximab monotherapy (20%), ibrutinib monotherapy (11%), and FCR (10%). The most common therapies initiated at registry enrollment in the treatment-naive group were ibrutinib monotherapy (32%), BR (21%), FCR (11%), and obinutuzumab plus chlorambucil (10%; Table 3). In the previously treated group, the most common therapies were ibrutinib monotherapy (50%), BR (16%), rituximab monotherapy (13%), and FCR (4%).

Among the entire study population, the most common reason for initiating treatment was evidence of progressive marrow failure, followed

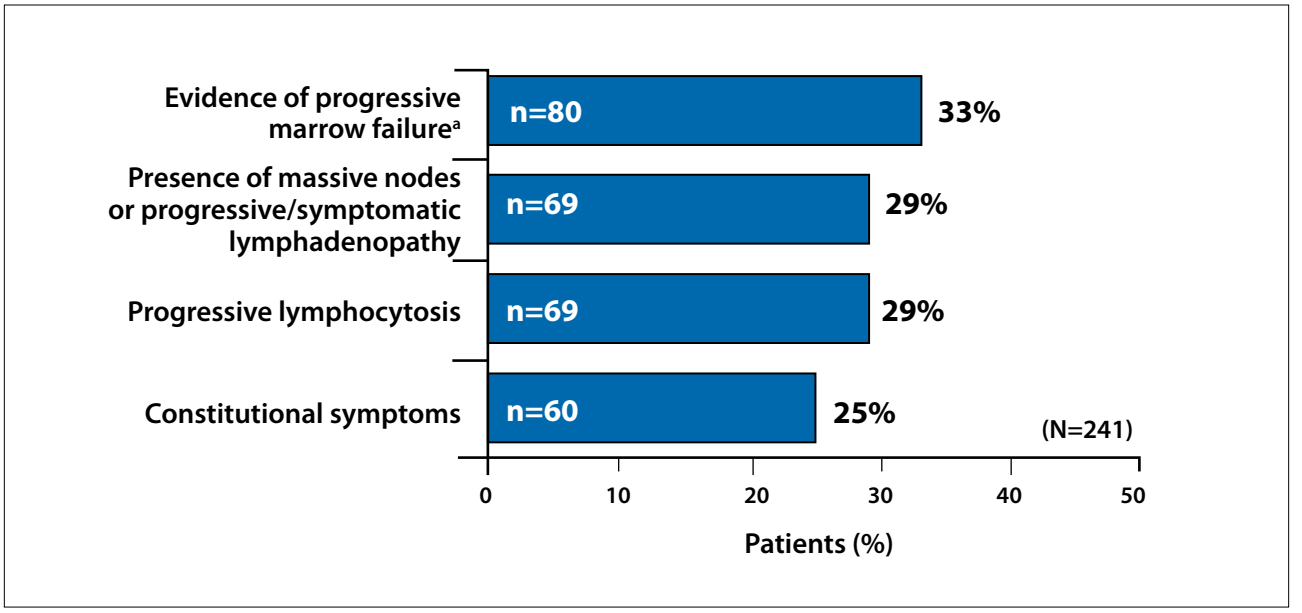

Figure 6. Reasons for initiation of treatment in the informCLL registry. Patients could indicate more than 1 reason for initiating treatment. [a]Caused by splenomegaly or early satiety. Adapted from Mato A et al. Abstract 54. The XVII International Workshop on Chronic Lymphocytic Leukemia.[1]

ABSTRACT SUMMARY Phase II, Multicenter Trial Exploring "Chemo-Sparing" Strategy Associating Obinutuzumab + Ibrutinib Followed by an MRD Driven Strategy, in Previously Untreated Symptomatic Medically Fit Chronic Lymphocytic Leukemia Patients: Preliminary Results

A multicenter, phase 2 study evaluated the efficacy of induction treatment with obinutuzumab plus ibrutinib, followed by a subsequent therapy as determined by patient response (Abstract 140). Treatment-naive patients with active Binet stage A, B, or C CLL and no *TP53* mutation were eligible. Induction treatment consisted of 6 cycles of obinutuzumab plus ibrutinib. Patients who achieved a CR with undetectable MRD received ibrutinib monotherapy for an additional 6 months. Patients with stable or progressive disease were removed from the study. The remaining patients received 4 courses of FCG while continuing daily ibrutinib. Data from 88 patients were evaluated. Among 22 patients available for response at month 9, the ORR was 100% and the CR was 50%. An MRD level between 0.01% and 1% in both the peripheral blood and bone marrow was achieved in 41% of patients. Among 9% of patients, MRD was undetectable in the peripheral blood and bone marrow. Infusion-related reactions occurred mainly during treatment cycle 1 and were generally mild. Eleven serious AEs were observed. Grade 3/4 AEs included neutropenia, thrombocytopenia, and anemia.

by the presence of very large nodes or progressive and/or symptomatic lymphadenopathy, progressive lymphocytosis, and constitutional symptoms (Figure 6). The most common disease-related symptoms at enrollment were fatigue (56%), night sweats (26%), and weight loss (17%). Among the 218 patients with comorbidities at enrollment (91%), the most common were hypertension (59%), type 2 diabetes mellitus without end-organ damage (23%), and pulmonary disorders/chronic obstructive pulmonary disease (12%). At the time of enrollment, 27% of patients had concurrent malignancies, including solid and hematologic tumors.

References

1. Mato A, Sharman J, Pagel J, et al. Characteristics of patients treated for CLL in a real-world registry: results from informCLL. Abstract presented at: the XVII International Workshop on Chronic Lymphocytic Leukemia; May 12-15, 2017; New York, NY. Abstract 54.
2. Hallek M, Cheson BD, Catovsky D, et al; International Workshop on Chronic Lymphocytic Leukemia. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. *Blood*. 2008;111(12):5446-5456.

Highlights From the XVII International Workshop on Chronic Lymphocytic Leukemia: Commentary

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Several presentations at the XVII International Workshop on Chronic Lymphocytic Leukemia provided insight into the management of treatment-naive and relapsed patients. Data from new clinical trials and subanalyses of existing trials were reported.

Dr Nitin Jain presented results from a phase 2 trial of a novel combination of ibrutinib, fludarabine, cyclophosphamide, and the anti-CD20 monoclonal antibody obinutuzumab in previously untreated patients with chronic lymphocytic leukemia (CLL) who required therapy.[1] Importantly, all of these patients had a mutated immunoglobulin heavy chain variable (*IGHV*) gene. As background, 3 recent studies clearly showed that in patients with a mutated *IGHV* gene, there appeared to be a long-term plateau in the progression-free survival (PFS) curve after treatment with fludarabine, cyclophosphamide, and rituximab (FCR).[2-4] The longest follow-up was reported in a study from MD Anderson Cancer Center, where the FCR regimen was developed.[2] This study showed that approximately 60% of patients with the *IGHV* mutation had no evidence of disease 12 to 16 years after treatment. Were these patients cured? I suspect that some were. Even if they were not cured, however, they still had no disease more than a decade after a finite duration of therapy (6 months), which is a very positive outcome. Chemotherapy may provide a cure fraction among patients with a mutated *IGHV* gene.

The idea behind the study by Dr Jain was to enhance the results—make that 60% higher—as well as reduce toxicity, both short-term and long-term.[1] The study modified standard FCR by replacing rituximab with obinutuzumab, a more potent antibody. Ibrutinib was added since it has very high activity as a single agent. Importantly, chemotherapy was limited to 3 cycles, which would reduce the short-tem complications, as well as the small but real risks of developing late myelodysplastic syndrome or acute myeloid leukemia related to treatment with FCR.

Dr Jain presented preliminary data from the trial.[1] All of the patients were older than 18 years, and all had the *IGHV* mutation. Patients with a 17p deletion were excluded from the trial because they are not treated with chemotherapy in the upfront setting.

Patients received ibrutinib, fludarabine, cyclophosphamide, and obinutuzumab for 3 cycles. Treatment was then modified based on the presence of minimal residual disease (MRD) and overall response. Patients with a complete response who were MRD-negative received 3 more months of ibrutinib and obinutuzumab (so chemotherapy was stopped), and then 6 more months of ibrutinib. That brought them to a year of treatment. If they were MRD-negative after 12 cycles, then all therapy was stopped.

When patients remained MRD positive or had only a partial response after receiving the 3 cycles of ibrutinib, fludarabine, cyclophosphamide, and obinutuzumab, treatment consisted of ibrutinib and obinutuzumab for 9 more cycles. Treatment was then discontinued among patients who were MRD-negative. Among MRD-positive patients, treatment with ibrutinib continued until disease progression.

For purposes of comparison, the study used historical data for results after 3 cycles of FCR among patients with the *IGHV* mutation.[5] Historically, most patients were treated with 6 cycles of FCR. After 3 cycles, the bone marrow MRD negativity rate was 26%. The primary endpoint of the study by Dr Jain was to improve on that 3-month response.[1] There were 24 patients who completed 3 cycles of treatment. Some were still receiving maintenance treatment with ibrutinib and obinutuzumab. At 3 months, the bone marrow MRD negativity rate was 83%. This is strikingly better than the historical rate of 26% with FCR alone. The best response so far is MRD negativity in the bone marrow, which was

reported in all 24 patients. Among the 9 patients who were treated for a year, all were MRD-negative and discontinued therapy. No patient developed progressive disease, but the median follow-up was short, at 8.3 months.

The combination of ibrutinib, fludarabine, cyclophosphamide, and obinutuzumab is a very exciting frontline combination for patients with the *IGHV* mutation. The early data are encouraging. The trial continues to accrue patients.

Dr William Wierda presented a poster outlining an ongoing trial evaluating the combination of ibrutinib and venetoclax in treatment-naive patients with CLL.[6] Ibrutinib and venetoclax are the 2 most potent single-agent small molecules available, and they have different mechanisms of action. The preclinical rationale for the use of these agents in combination is based on ex vivo and in vivo data showing that pretreatment with ibrutinib improves the activity of venetoclax and enhances BCL-2 dependence.[7] The study from Dr Wierda is a multicenter, double-blind, placebo-controlled, randomized phase 2 trial. The plan is to enroll 150 treatment-naive patients younger than 70 years who require therapy. The lead-in phase is treatment with ibrutinib at 420 mg once daily for 3 cycles. Then patients are treated with the combination of standard-dose ibrutinib (420 mg once daily) plus standard-dose venetoclax (400 mg once daily) for 12 cycles. Lead-in treatment with ibrutinib is becoming more common in trials combining ibrutinib with venetoclax. This strategy is based on the idea that debulking the patient prior to initiating venetoclax will minimize the risk for tumor lysis. Patients continue treatment with ibrutinib plus venetoclax for at least twelve 4-week cycles, for a year of therapy. Patients are then assigned to treatment based on their MRD status. MRD-negative patients are randomly assigned to treatment with ibrutinib, without venetoclax, or placebo. Neither the patient nor the principle investigator will be aware of which treatment is being used. Patients who are MRD-positive are randomly assigned to receive either ibrutinib alone or ibrutinib plus venetoclax. The primary endpoint for the randomization phase is the 1-year MRD-negative disease-free survival state. The trial began in October, and it is being conducted in the United States, Australia, and Italy. Recruitment and accrual are underway. The study will provide interesting frontline data on a novel small-molecule combination that does not include chemotherapy.

A study by Dr Paolo Ghia evaluated the outcomes of standard-of-care frontline regimens in patients with an unmutated *IGHV* across 3 trials: CLL8, CLL10, and RESONATE-2 (Randomized, Multicenter, Open-Label, Phase 3 Study of the Bruton's Tyrosine Kinase Inhibitor Ibrutinib Versus Chlorambucil in Patients 65 Years or Older With Treatment-Naive Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma [PCYC-1115/1116]).[8-11] The CLL8 trial randomly assigned patients to treatment with fludarabine plus cyclophosphamide or FCR.[9] This trial is the oldest one in the study; it led the US Food and Drug Administration (FDA) to approve FCR for previously untreated patients with CLL. The randomized CLL10 trial built on the results from the CLL8 trial.[10] It compared FCR, as the gold standard, to the popular regimen bendamustine plus rituximab. The randomized RESONATE-2 trial compared ibrutinib vs chlorambucil as frontline therapy in CLL, and led to the FDA approval of ibrutinib in this setting.[11]

There were many patients in these studies. CLL8 had more than 800, and reported the mutational status for more than 600. In the CLL10 trial, there were more than 500 patients, and the mutational status was known for most of them. The RESONATE-2 trial had 269 patients, and most had a known mutational status.

Among patients treated with ibrutinib, the estimated 30-month PFS rates were 81% in patients with the *IGHV* mutation and 87% in those without. Among patients treated with chemotherapy, the rates of 30-month PFS ranged from 83% to 87% in those with the *IGHV* mutation vs 59% to 65% in those without the *IGHV* mutation.

The analysis suggested that ibrutinib may have a particular benefit over chemotherapy among patients without the *IGHV* mutation. Among patients treated with chemoimmunotherapy, response rates are similar regardless of the mutational status, but PFS and overall survival are significantly shorter among those with an unmutated *IGHV* gene. Patients with the unmutated gene have a much poorer prognosis with any chemotherapy-based regimen, including bendamustine plus rituximab, FCR, and chlorambucil-based regimens. In contrast, the analysis by Dr Ghia showed that ibrutinib is not associated with a poorer prognosis among patients with the unmutated gene.[8] In the RESONATE-2 trial, thus far, PFS did not differ according to mutation status.[11] Why would patients without the mutation do better with ibrutinib than chemotherapy? One reason for the poorer outcome with chemotherapy is that patients without the *IGHV* mutation have much stronger signaling through the B-cell receptor. Ligation of the B-cell receptor provides a strong proliferative and survival signal to the cell. Ibrutinib works by inhibiting the B-cell receptor. Ibrutinib appears to be a very effective drug, regardless of the patient's mutational status. It will have even more success over chemotherapy among the high-risk group of patients without the *IGHV* mutation.

An interesting presentation by Dr Thomas Kipps evaluated the outcomes of ibrutinib-treated patients across three randomized phase 3 trials: RESONATE (Ibrutinib Versus Ofatumumab in Patients With Relapsed or

Refractory Chronic Lymphocytic Leukemia; PCYC-1112), RESONATE-2, and HELIOS (A Study of Ibrutinib in Combination With Bendamustine and Rituximab in Patients With Relapsed or Refractory Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma; CLL3001).[11-14] The RESONATE trial compared ibrutinib vs ofatumumab among previously treated patients, and led to FDA approval of ibrutinib in the relapsed setting.[13] The RESONATE-2 trial led to FDA approval of ibrutinib in the frontline setting.[11] The HELIOS trial randomly assigned relapsed patients to bendamustine plus rituximab with or without ibrutinib.[14] An important similarity among these trials is that they all had a comparator arm consisting of a chemotherapy-based regimen.

The data from these 3 trials were pooled and analyzed based on various factors, such as mutational status and the presence of deletion 11q or a complex karyotype.[12] As expected, in the chemotherapy-based comparator arms, a significantly shorter PFS was seen among patients who had an unmutated *IGHV* gene, a complex karyotype, or an 11q deletion. An important finding is that outcome with ibrutinib was not impacted by the presence of the 11q deletion, the complex karyotype, or an unmutated *IGHV*. The analysis shows that the genomic factors that have traditionally led to a poor prognosis with chemotherapy no longer do so with ibrutinib.

Disclosure

Dr O'Brien is a consultant for Amgen, Astellas, Celgene, GlaxoSmithKline, Janssen Oncology, Aptose Biosciences Inc, Vaniam Group LLC, AbbVie, Sunesis, and Alexion. She has received research support from ProNAi, Regeneron, and Acerta. She is a consultant and/or has received research support from Gilead, Pharmacyclics, TG Therapeutics, and Pfizer.

References

1. Jain N, Thompson P, Burger JA, et al. Ibrutinib, fludarabine, cyclophosphamide, and obinutuzumab (GA101) (iFCG) for previously untreated patients with chronic lymphocytic leukemia (CLL) with mutated *IGHV* and non-del(17p). Abstract presented at: the XVII International Workshop on Chronic Lymphocytic Leukemia; May 12-15, 2017; New York, NY. Abstract 164.
2. Thompson PA, Tam CS, O'Brien SM, et al. Fludarabine, cyclophosphamide, and rituximab treatment achieves long-term disease-free survival in *IGHV*-mutated chronic lymphocytic leukemia. *Blood*. 2016;127(3):303-309.
3. Fischer K, Bahlo J, Fink AM, et al. Long-term remissions after FCR chemoimmunotherapy in previously untreated patients with CLL: updated results of the CLL8 trial. *Blood*. 2016;127(2):208-215.
4. Rossi D, Terzi-di-Bergamo L, De Paoli L, et al. Molecular prediction of durable remission after first-line fludarabine-cyclophosphamide-rituximab in chronic lymphocytic leukemia. *Blood*. 2015;126(16):1921-1924.
5. Strati P, Keating MJ, O'Brien SM, et al. Eradication of bone marrow minimal residual disease may prompt early treatment discontinuation in CLL. *Blood*. 2014;123(24):3727-3732.
6. Wierda WG, Siddiqi T, Stevens DA, et al. Phase 2 study of the combination of ibrutinib plus venetoclax in patients with treatment-naïve CLL/SLL. Abstract presented at: the XVII International Workshop on Chronic Lymphocytic Leukemia; May 12-15, 2017; New York, NY. Abstract 188.
7. Deng J, Isik E, Fernandes SM, Brown JR, Letai A, Davids MS. Bruton's tyrosine kinase inhibition increases BCL-2 dependence and enhances sensitivity to venetoclax in chronic lymphocytic leukemia [published online February 4, 2017]. *Leukemia*. doi:10.1038/leu.2017.32.
8. Ghia P, Hillmen P, Moreno C, et al. Outcomes of standard of care regimens in treatment-naïve chronic lymphocytic leukemia (CLL) patients with unmutated immunoglobulin heavy chain variable (*IGHV*) genes. Abstract presented at: the XVII International Workshop on Chronic Lymphocytic Leukemia; May 12-15, 2017; New York, NY. Abstract 188.
9. Stilgenbauer S, Schnaiter A, Paschka P, et al. Gene mutations and treatment outcome in chronic lymphocytic leukemia: results from the CLL8 trial. *Blood*. 2014;123(21):3247-3254.
10. Eichhorst B, Fink AM, Bahlo J, et al; international group of investigators; German CLL Study Group (GCLLSG). First-line chemoimmunotherapy with bendamustine and rituximab versus fludarabine, cyclophosphamide, and rituximab in patients with advanced chronic lymphocytic leukaemia (CLL10): an international, open-label, randomised, phase 3, non-inferiority trial. *Lancet Oncol*. 2016;17(7):928-942.
11. Burger JA, Tedeschi A, Barr PM, et al; RESONATE-2 Investigators. Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. *N Engl J Med*. 2015;373(25):2425-2437.
12. Kipps TJ, Fraser G, Coutre SE, et al. Outcomes of ibrutinib-treated patients with chronic lymphocytic leukemia/small lymphocytic leukemia (CLL/SLL) with high-risk prognostic factors in an integrated analysis of 3 randomized phase 3 studies. Abstract presented at: the XVII International Workshop on Chronic Lymphocytic Leukemia; May 12-15, 2017; New York, NY. Abstract 19.
13. Byrd JC, Brown JR, O'Brien S, et al; RESONATE Investigators. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. *N Engl J Med*. 2014;371(3):213-223.
14. Chanan-Khan A, Cramer P, Demirkan F, et al; HELIOS investigators. Ibrutinib combined with bendamustine and rituximab compared with placebo, bendamustine, and rituximab for previously treated chronic lymphocytic leukaemia or small lymphocytic lymphoma (HELIOS): a randomised, double-blind, phase 3 study. *Lancet Oncol*. 2016;17(2):200-211.

#1 PRESCRIBED THERAPY ACROSS ALL LINES OF CLL SINCE NOVEMBER 2016.*
MORE THAN 25,000 PATIENTS TREATED SINCE APPROVAL[1†]

TAKE CONTROL OF CLL/SLL WITH YOUR FIRST STEP: IMBRUVICA®

Proven results across key efficacy endpoints: PFS and OS[2]

CLL
SLL

IMBRUVICA® (ibrutinib) is a kinase inhibitor indicated for the treatment of patients with:

- Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL)[2]
- CLL/SLL with 17p deletion[2]

*Based on market share data from IMS as of January 2017.
†Based on IMS data February 2014 to date.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hemorrhage - Fatal bleeding events have occurred in patients treated with IMBRUVICA®. Grade 3 or higher bleeding events (intracranial hemorrhage [including subdural hematoma], gastrointestinal bleeding, hematuria, and post-procedural hemorrhage) have occurred in up to 6% of patients. Bleeding events of any grade, including bruising and petechiae, occurred in approximately half of patients treated with IMBRUVICA®.

The mechanism for the bleeding events is not well understood. IMBRUVICA® may increase the risk of hemorrhage in patients receiving antiplatelet or anticoagulant therapies and patients should be monitored for signs of bleeding. Consider the benefit-risk of withholding IMBRUVICA® for at least 3 to 7 days pre- and postsurgery depending upon the type of surgery and the risk of bleeding.

Infections - Fatal and nonfatal infections have occurred with IMBRUVICA® therapy. Grade 3 or greater infections occurred in 14% to 29% of patients. Cases of progressive multifocal leukoencephalopathy (PML) and *Pneumocystis jirovecii* pneumonia (PJP) have occurred in patients treated with IMBRUVICA®. Evaluate patients for fever and infections and treat appropriately.

Cytopenias - Treatment-emergent Grade 3 or 4 cytopenias including neutropenia (range, 13% to 29%), thrombocytopenia (range, 5% to 17%), and anemia (range, 0% to 13%) based on laboratory measurements occurred in patients treated with single agent IMBRUVICA®. Monitor complete blood counts monthly.

Atrial Fibrillation - Atrial fibrillation and atrial flutter (range, 6% to 9%) have occurred in patients treated with IMBRUVICA®, particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of atrial fibrillation. Periodically monitor patients clinically for atrial fibrillation. Patients who develop arrhythmic symptoms (eg, palpitations, lightheadedness) or new-onset dyspnea should have an ECG performed. Atrial fibrillation should be managed appropriately and if it persists, consider the risks and benefits of IMBRUVICA® treatment and follow dose modification guidelines.

Hypertension - Hypertension (range, 6% to 17%) has occurred in patients treated with IMBRUVICA® with a median time to onset of 4.6 months (range, 0.03 to 22 months). Monitor patients for new-onset hypertension or hypertension that is not adequately controlled after starting IMBRUVICA®. Adjust existing antihypertensive medications and/or initiate antihypertensive treatment as appropriate.

Second Primary Malignancies - Other malignancies (range, 3% to 16%) including non-skin carcinomas (range, 1% to 4%) have occurred in patients treated with IMBRUVICA®. The most frequent second primary malignancy was non-melanoma skin cancer (range, 2% to 13%).

Tumor Lysis Syndrome - Tumor lysis syndrome has been infrequently reported with IMBRUVICA® therapy. Assess the baseline risk (eg, high tumor burden) and take appropriate precautions. Monitor patients closely and treat as appropriate.

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RESONATE™-2 FRONTLINE DATA

RESONATE™-2 was a multicenter, randomized 1:1, open-label, Phase 3 trial of IMBRUVICA® vs chlorambucil in frontline CLL/SLL patients ≥65 years (N=269)[2,3]
Patients with 17p deletion were not included in the RESONATE™-2 trial[3]

EXTENDED OVERALL SURVIVAL

IMBRUVICA® significantly extended OS vs chlorambucil[2]

Statistically significant reduction in risk of death[2]

56%

HR=0.44
(95% CI: 0.21, 0.92)

41% of patients crossed over to IMBRUVICA®

Estimated survival rates at 24 months

95% IMBRUVICA®
(95% CI: 89, 97)

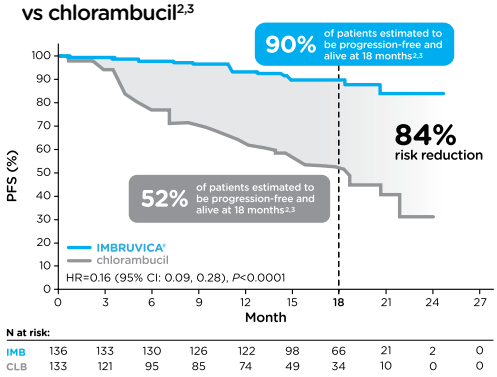
84% chlorambucil
(95% CI: 77, 90)

SECONDARY ENDPOINT: OS

- Median follow-up was 28 months[2]

PROLONGED PROGRESSION-FREE SURVIVAL

IMBRUVICA® significantly extended PFS vs chlorambucil[2,3]



PRIMARY ENDPOINT: PFS

- Median follow-up was 18 months[3]
- IMBRUVICA® median PFS not reached[2]
- Chlorambucil median PFS was 18.9 months (95% CI: 14.1, 22.0)[2]
- PFS was assessed by an IRC per revised iwCLL criteria[3]

Adverse reactions ≥20% across CLL/SLL registration studies[2]

- Neutropenia
- Thrombocytopenia
- Anemia
- Diarrhea
- Musculoskeletal pain
- Nausea
- Rash
- Bruising
- Fatigue
- Pyrexia
- Hemorrhage

Embryo-Fetal Toxicity - Based on findings in animals, IMBRUVICA® can cause fetal harm when administered to a pregnant woman. Advise women to avoid becoming pregnant while taking IMBRUVICA® and for 1 month after cessation of therapy. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. Advise men to avoid fathering a child during the same time period.

ADVERSE REACTIONS

The most commonly occurring adverse reactions in the phase 1b/2 and phase 3 trials in patients with CLL/SLL receiving IMBRUVICA® (≥ 20%) were neutropenia (40%)*, thrombocytopenia (23%)*, anemia (21%)*, diarrhea (42%), musculoskeletal pain (31%), nausea (30%), rash (30%), bruising (29%), fatigue (26%), pyrexia (23%) and hemorrhage (20%).

*Based on adverse reactions and/or laboratory measurements (noted as platelets, neutrophils, or hemoglobin decreased).

Approximately 4%-10% of patients discontinued treatment due to adverse reactions. Most common adverse reactions leading to discontinuation were pneumonia, hemorrhage, atrial fibrillation, rash, and neutropenia (1% each).

Approximately 6% of patients had a dose reduction due to adverse reactions.

DRUG INTERACTIONS

CYP3A Inhibitors - Avoid coadministration with strong and moderate CYP3A inhibitors. If a moderate CYP3A inhibitor must be used, reduce the IMBRUVICA® dose.

CYP3A Inducers - Avoid coadministration with strong CYP3A inducers.

SPECIFIC POPULATIONS

Hepatic Impairment - Avoid use in patients with moderate or severe baseline hepatic impairment. In patients with mild impairment, reduce IMBRUVICA® dose.

Please see the Brief Summary on the following pages.

CI=confidence interval, CLL=chronic lymphocytic leukemia, HR=hazard ratio, IRC=Independent Review Committee, iwCLL=International Workshop on CLL, OS=overall survival, PFS=progression-free survival, SLL=small lymphocytic lymphoma.

References: 1. Data on file. Pharmacyclics LLC. **2.** IMBRUVICA® (ibrutinib) Prescribing Information. Pharmacyclics LLC 2017. **3.** Burger JA, Tedeschi A, Barr PM, et al; for the RESONATE-2 Investigators. Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. *N Engl J Med.* 2015;373(25):2425-2437.

To learn more, visit
IMBRUVICAHCP.com

imbruvica®
(ibrutinib) 140mg capsules

Brief Summary of Prescribing Information for IMBRUVICA® (ibrutinib)

IMBRUVICA® (ibrutinib) capsules, for oral use

See package insert for Full Prescribing Information

INDICATIONS AND USAGE

Mantle Cell Lymphoma: IMBRUVICA is indicated for the treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

Accelerated approval was granted for this indication based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial *[see Clinical Studies (14.1) in Full Prescribing Information].*

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: IMBRUVICA is indicated for the treatment of patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) *[see Clinical Studies (14.2) in Full Prescribing Information].*

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma with 17p deletion: IMBRUVICA is indicated for the treatment of patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) with 17p deletion *[see Clinical Studies (14.2) in Full Prescribing Information].*

Waldenström's Macroglobulinemia: IMBRUVICA is indicated for the treatment of patients with Waldenström's macroglobulinemia (WM) *[see Clinical Studies (14.3) in Full Prescribing Information].*

Marginal Zone Lymphoma: IMBRUVICA is indicated for the treatment of patients with marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy.

Accelerated approval was granted for this indication based on overall response rate *[see Clinical Studies (14.4) in Full Prescribing Information]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

Hemorrhage: Fatal bleeding events have occurred in patients treated with IMBRUVICA. Grade 3 or higher bleeding events (intracranial hemorrhage [including subdural hematoma], gastrointestinal bleeding, hematuria, and post procedural hemorrhage) have occurred in up to 6% of patients. Bleeding events of any grade, including bruising and petechiae, occurred in approximately half of patients treated with IMBRUVICA.

The mechanism for the bleeding events is not well understood.

IMBRUVICA may increase the risk of hemorrhage in patients receiving antiplatelet or anticoagulant therapies and patients should be monitored for signs of bleeding.

Consider the benefit-risk of withholding IMBRUVICA for at least 3 to 7 days pre and post-surgery depending upon the type of surgery and the risk of bleeding *[see Clinical Studies (14) in Full Prescribing Information].*

Infections: Fatal and non-fatal infections have occurred with IMBRUVICA therapy. Grade 3 or greater infections occurred in 14% to 29% of patients *[see Adverse Reactions]*. Cases of progressive multifocal leukoencephalopathy (PML) and *Pneumocystis jirovecii* pneumonia (PJP) have occurred in patients treated with IMBRUVICA. Evaluate patients for fever and infections and treat appropriately.

Cytopenias: Treatment-emergent Grade 3 or 4 cytopenias including neutropenia (range, 13 to 29%), thrombocytopenia (range, 5 to 17%), and anemia (range, 0 to 13%) based on laboratory measurements occurred in patients treated with single agent IMBRUVICA.

Monitor complete blood counts monthly.

Atrial Fibrillation: Atrial fibrillation and atrial flutter (range, 6 to 9%) have occurred in patients treated with IMBRUVICA, particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of atrial fibrillation. Periodically monitor patients clinically for atrial fibrillation. Patients who develop arrhythmic symptoms (e.g., palpitations, lightheadedness) or new onset dyspnea should have an ECG performed. Atrial fibrillation should be managed appropriately, and if it persists, consider the risks and benefits of IMBRUVICA treatment and follow dose modification guidelines *[see Dosage and Administration (2.3) in Full Prescribing Information].*

Hypertension: Hypertension (range, 6 to 17%) has occurred in patients treated with IMBRUVICA with a median time to onset of 4.6 months (range, 0.03 to 22 months). Monitor patients for new onset hypertension or hypertension that is not adequately controlled after starting IMBRUVICA. Adjust existing anti-hypertensive medications and/or initiate anti-hypertensive treatment as appropriate.

Second Primary Malignancies: Other malignancies (range, 3 to 16%) including non-skin carcinomas (range, 1 to 4%) have occurred in patients treated with IMBRUVICA. The most frequent second primary malignancy was non-melanoma skin cancer (range, 2 to 13%).

Tumor Lysis Syndrome: Tumor lysis syndrome has been infrequently reported with IMBRUVICA therapy. Assess the baseline risk (e.g., high tumor burden) and take appropriate precautions. Monitor patients closely and treat as appropriate.

Embryo-Fetal Toxicity: Based on findings in animals, IMBRUVICA can cause fetal harm when administered to a pregnant woman. Administration of ibrutinib to pregnant rats and rabbits during the period of organogenesis caused embryofetal toxicity including malformations at exposures that were 2-20 times higher than those reported in patients with hematologic malignancies. Advise women to avoid becoming pregnant while taking IMBRUVICA and for 1 month after cessation of therapy. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus *[see Use in Specific Populations].*

ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in other sections of the labeling:

- Hemorrhage *[see Warnings and Precautions]*
- Infections *[see Warnings and Precautions]*
- Cytopenias *[see Warnings and Precautions]*
- Atrial Fibrillation *[see Warnings and Precautions]*
- Hypertension *[see Warnings and Precautions]*
- Second Primary Malignancies *[see Warnings and Precautions]*
- Tumor Lysis Syndrome *[see Warnings and Precautions]*

Clinical Trials Experience: Because clinical trials are conducted under widely variable conditions, adverse event rates observed in clinical trials of a drug cannot be directly compared with rates of clinical trials of another drug and may not reflect the rates observed in practice.

Mantle Cell Lymphoma: The data described below reflect exposure to IMBRUVICA in a clinical trial that included 111 patients with previously treated MCL treated with 560 mg daily with a median treatment duration of 8.3 months.

The most commonly occurring adverse reactions (≥ 20%) were thrombocytopenia, diarrhea, neutropenia, anemia, fatigue, musculoskeletal pain, peripheral edema, upper respiratory tract infection, nausea, bruising, dyspnea, constipation, rash, abdominal pain, vomiting and decreased appetite (see Tables 1 and 2).

The most common Grade 3 or 4 non-hematological adverse reactions (≥ 5%) were pneumonia, abdominal pain, atrial fibrillation, diarrhea, fatigue, and skin infections.

Fatal and serious cases of renal failure have occurred with IMBRUVICA therapy. Increases in creatinine 1.5 to 3 times the upper limit of normal occurred in 9% of patients.

Adverse reactions from the MCL trial (N=111) using single agent IMBRUVICA 560 mg daily occurring at a rate of ≥ 10% are presented in Table 1.

Table 1: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with MCL (N=111)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	51	5
	Nausea	31	0
	Constipation	25	0
	Abdominal pain	24	5
	Vomiting	23	0
	Stomatitis	17	1
	Dyspepsia	11	0
Infections and infestations	Upper respiratory tract infection	34	0
	Urinary tract infection	14	3
	Pneumonia	14	7
	Skin infections	14	5
	Sinusitis	13	1
General disorders and administration site conditions	Fatigue	41	5
	Peripheral edema	35	3
	Pyrexia	18	1
	Asthenia	14	3
Skin and subcutaneous tissue disorders	Bruising	30	0
	Rash	25	3
	Petechiae	11	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	37	1
	Muscle spasms	14	0
	Arthralgia	11	0
Respiratory, thoracic and mediastinal disorders	Dyspnea	27	4
	Cough	19	0
	Epistaxis	11	0
Metabolism and nutrition disorders	Decreased appetite	21	2
	Dehydration	12	4
Nervous system disorders	Dizziness	14	0
	Headache	13	0

Table 2: Treatment-Emergent* Decrease of Hemoglobin, Platelets, or Neutrophils in Patients with MCL (N=111)

	Percent of Patients (N=111)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	57	17
Neutrophils Decreased	47	29
Hemoglobin Decreased	41	9

* Based on laboratory measurements and adverse reactions

Ten patients (9%) discontinued treatment due to adverse reactions in the trial (N=111). The most frequent adverse reaction leading to treatment discontinuation was subdural hematoma (1.8%). Adverse reactions leading to dose reduction occurred in 14% of patients.

Patients with MCL who develop lymphocytosis greater than 400,000/mcL have developed intracranial hemorrhage, lethargy, gait instability, and headache. However, some of these cases were in the setting of disease progression.

Forty percent of patients had elevated uric acid levels on study including 13% with values above 10 mg/dL. Adverse reaction of hyperuricemia was reported for 15% of patients.

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: The data described below reflect exposure in one single-arm, open-label clinical trial and three randomized controlled clinical trials in patients with CLL/SLL (n=1278 total and n=668 patients exposed to IMBRUVICA). Study 1 included 51 patients with previously treated CLL/SLL, Study 2 included 391 randomized patients with previously treated CLL or SLL who received single agent IMBRUVICA or ofatumumab, Study 3 included 269 randomized patients 65 years or older with treatment naïve-CLL or SLL who received single agent IMBRUVICA or chlorambucil and Study 4 included 578 randomized patients with previously treated CLL or SLL who received IMBRUVICA in combination with bendamustine and rituximab or placebo in combination with bendamustine and rituximab.

The most commonly occurring adverse reactions in Studies 1, 2, 3 and 4 in patients with CLL/SLL receiving IMBRUVICA (≥ 20%) were neutropenia, thrombocytopenia, anemia, diarrhea, musculoskeletal pain, nausea, rash, bruising, fatigue, pyrexia and hemorrhage. Four to 10 percent of patients receiving IMBRUVICA in Studies 1, 2, 3 and 4 discontinued treatment due to adverse reactions. These included pneumonia, hemorrhage, atrial fibrillation, rash and neutropenia (1% each). Adverse reactions leading to dose reduction occurred in approximately 6% of patients.

Study 1: Adverse reactions and laboratory abnormalities from the CLL/SLL trial (N=51) using single agent IMBRUVICA 420 mg daily in patients with previously treated CLL/SLL occurring at a rate of ≥ 10% with a median duration of treatment of 15.6 months are presented in Tables 3 and 4.

Table 3: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with CLL/SLL (N=51) in Study 1

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	59	4
	Constipation	22	2
	Nausea	20	2
	Stomatitis	20	0
	Vomiting	18	2
	Abdominal pain	14	0
	Dyspepsia	12	0
Infections and infestations	Upper respiratory tract infection	47	2
	Sinusitis	22	6
	Skin infection	16	6
	Pneumonia	12	10
	Urinary tract infection	12	2
General disorders and administration site conditions	Fatigue	33	6
	Pyrexia	24	2
	Peripheral edema	22	0
	Asthenia	14	6
	Chills	12	0
Skin and subcutaneous tissue disorders	Bruising	51	2
	Rash	25	0
	Petechiae	16	0
Respiratory, thoracic and mediastinal disorders	Cough	22	0
	Oropharyngeal pain	14	0
	Dyspnea	12	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	25	6
	Arthralgia	24	0
	Muscle spasms	18	2
Nervous system disorders	Dizziness	20	0
	Headache	18	2

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Table 3: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with CLL/SLL (N=51) in Study 1 (continued)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Metabolism and nutrition disorders	Decreased appetite	16	2
Neoplasms benign, malignant, unspecified	Second malignancies*	12*	0
Vascular disorders	Hypertension	16	8

* One patient death due to histiocytic sarcoma.

Table 4: Treatment-Emergent* Decrease of Hemoglobin, Platelets, or Neutrophils in Patients with CLL/SLL (N=51) in Study 1

	Percent of Patients (N=51)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	69	12
Neutrophils Decreased	53	26
Hemoglobin Decreased	43	0

* Based on laboratory measurements per IWCLL criteria and adverse reactions.

Study 2: Adverse reactions and laboratory abnormalities described below in Tables 5 and 6 reflect exposure to IMBRUVICA with a median duration of 8.6 months and exposure to ofatumumab with a median of 5.3 months in Study 2 in patients with previously treated CLL/SLL.

Table 5: Adverse Reactions Reported in ≥ 10% of Patients and at Least 2% Greater in the IMBRUVICA Treated Arm in Patients with CLL/SLL in Study 2

	IMBRUVICA (N=195)		Ofatumumab (N=191)	
Body System Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders				
Diarrhea	48	4	18	2
Nausea	26	2	18	0
Stomatitis*	17	1	6	1
Constipation	15	0	9	0
Vomiting	14	0	6	1
General disorders and administration site conditions				
Pyrexia	24	2	15	1
Infections and infestations				
Upper respiratory tract infection	16	1	11	2
Pneumonia*	15	10	13	9
Sinusitis*	11	1	6	0
Urinary tract infection	10	4	5	1
Skin and subcutaneous tissue disorders				
Rash*	24	3	13	0
Petechiae	14	0	1	0
Bruising*	12	0	1	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal Pain*	28	2	18	1
Arthralgia	17	1	7	0
Nervous system disorders				
Headache	14	1	6	0
Dizziness	11	0	5	0
Injury, poisoning and procedural complications				
Contusion	11	0	3	0
Eye disorders				
Vision blurred	10	0	3	0

Subjects with multiple events for a given ADR term are counted once only for each ADR term.
The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.
* Includes multiple ADR terms

Table 6: Treatment-Emergent* Decrease of Hemoglobin, Platelets, or Neutrophils in Patients with CLL/SLL in Study 2

	IMBRUVICA (N=195)		Ofatumumab (N=191)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Neutrophils Decreased	51	23	57	26
Platelets Decreased	52	5	45	10
Hemoglobin Decreased	36	0	21	0

* Based on laboratory measurements per IWCLL criteria.

Study 3: Adverse reactions described below in Table 7 reflect exposure to IMBRUVICA with a median duration of 17.4 months. The median exposure to chlorambucil was 7.1 months in Study 3.

Table 7: Adverse Reactions Reported in ≥ 10% of Patients and at Least 2% Greater in the IMBRUVICA Treated Arm in Patients with CLL/SLL in Study 3

Body System Adverse Reaction	IMBRUVICA (N=135)		Chlorambucil (N=132)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders				
Diarrhea	42	4	17	0
Stomatitis*	14	1	4	1
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	36	4	20	0
Arthralgia	16	1	7	1
Muscle spasms	11	0	5	0
Eye Disorders				
Dry eye	17	0	5	0
Lacrimation increased	13	0	6	0
Vision blurred	13	0	8	0
Visual acuity reduced	11	0	2	0
Skin and subcutaneous tissue disorders				
Rash*	21	4	12	2
Bruising*	19	0	7	0
Infections and infestations				
Skin infection*	15	2	3	1
Pneumonia*	14	8	7	4
Urinary tract infections	10	1	8	1
Respiratory, thoracic and mediastinal disorders				
Cough	22	0	15	0
General disorders and administration site conditions				
Peripheral edema	19	1	9	0
Pyrexia	17	0	14	2
Vascular Disorders				
Hypertension*	14	4	1	0
Nervous System Disorders				
Headache	12	1	10	2

Subjects with multiple events for a given ADR term are counted once only for each ADR term.
The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.
* Includes multiple ADR terms

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Study 4: Adverse reactions described below in Table 8 reflect exposure to IMBRUVICA + BR with a median duration of 14.7 months and exposure to placebo + BR with a median of 12.8 months in Study 4 in patients with previously treated CLL/SLL.

Table 8: Adverse Reactions Reported in at Least 10% of Patients and at Least 2% Greater in the IMBRUVICA Arm in Patients with CLL/SLL in Study 4

Body System Adverse Reaction	Ibrutinib + BR (N=287)		Placebo + BR (N=287)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Blood and lymphatic system disorders				
Neutropenia*	66	61	60	55
Thrombocytopenia*	34	16	26	16
Skin and subcutaneous tissue disorders				
Rash*	32	4	25	1
Bruising*	20	<1	8	<1
Gastrointestinal disorders				
Diarrhea	36	2	23	1
Abdominal Pain	12	1	8	<1
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	29	2	20	0
Muscle spasms	12	<1	5	0
General disorders and administration site conditions				
Pyrexia	25	4	22	2
Vascular Disorders				
Hemorrhage*	19	2	9	1
Hypertension*	11	5	5	2
Infections and infestations				
Bronchitis	13	2	10	3
Skin infection*	10	3	6	2
Metabolism and nutrition disorders				
Hyperuricemia	10	2	6	0

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.
* Includes multiple ADR terms
<1 used for frequency above 0 and below 0.5%

Atrial fibrillation of any grade occurred in 7% of patients treated with IMBRUVICA + BR and 2% of patients treated with placebo + BR. The frequency of Grade 3 and 4 atrial fibrillation was 3% in patients treated with IMBRUVICA + BR and 1% in patients treated with placebo + BR.

Waldenström's Macroglobulinemia and Marginal Zone Lymphoma: The data described below reflect exposure to IMBRUVICA in open-label clinical trials that included 63 patients with previously treated WM (Study 5) and 63 patients with previously treated MZL (Study 6).

The most commonly occurring adverse reactions in Studies 5 and 6 (≥ 20%) were thrombocytopenia, diarrhea, neutropenia, fatigue, bruising, hemorrhage, anemia, rash, musculoskeletal pain, and nausea.

Nine percent of patients receiving IMBRUVICA across Studies 5 and 6 discontinued treatment due to adverse reactions. The most common adverse reactions leading to discontinuation were interstitial lung disease, diarrhea and rash. Adverse reactions leading to dose reduction occurred in 10% of patients.

Study 5: Adverse reactions and laboratory abnormalities described below in Tables 9 and 10 reflect exposure to IMBRUVICA with a median duration of 11.7 months in Study 5.

Table 9: Non-Hematologic Adverse Reactions in ≥ 10% in Patients with WM in Study 5 (N=63)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	37	0
	Nausea	21	0
	Stomatitis*	16	0
	Gastroesophageal reflux disease	13	0
Skin and subcutaneous tissue disorders	Rash*	22	0
	Bruising*	16	0
	Pruritus	11	0
General disorders and administrative site conditions	Fatigue	21	0
Musculoskeletal and connective tissue disorders	Muscle spasms	21	0
	Arthropathy	13	0
Infections and infestations	Upper respiratory tract infection	19	0
	Sinusitis	19	0
	Pneumonia*	14	6
	Skin infection*	14	2
Respiratory, thoracic and mediastinal disorders	Epistaxis	19	0
	Cough	13	0
Nervous system disorders	Dizziness	14	0
	Headache	13	0
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	Skin cancer*	11	0

The body system and individual ADR preferred terms are sorted in descending frequency order.
* Includes multiple ADR terms.

Table 10: Treatment-Emergent* Decrease of Hemoglobin, Platelets, or Neutrophils in Patients with WM in Study 5 (N=63)

	Percent of Patients (N=63)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	43	13
Neutrophils Decreased	44	19
Hemoglobin Decreased	13	8

* Based on laboratory measurements.

Study 6: Adverse reactions and laboratory abnormalities described below in Tables 11 and 12 reflect exposure to IMBRUVICA with a median duration of 11.6 months in Study 6.

Table 11: Non-Hematologic Adverse Reactions in ≥ 10% in Patients with MZL in Study 6 (N=63)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	43	5
	Nausea	25	0
	Dyspepsia	19	0
	Stomatitis*	17	2
	Abdominal pain	16	2
	Constipation	14	0
	Abdominal pain Upper	13	0
	Vomiting	11	2
General disorders and administrative site conditions	Fatigue	44	6
	Peripheral edema	24	2
	Pyrexia	17	2
Skin and subcutaneous tissue disorders	Bruising *	41	0
	Rash*	29	5
	Pruritus	14	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain*	40	3
	Arthralgia	24	2
	Muscle spasms	19	3
Infections and infestations	Upper respiratory tract infection	21	0
	Sinusitis*	19	0
	Bronchitis	11	0
	Pneumonia*	11	10

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Table 11: Non-Hematologic Adverse Reactions in ≥ 10% in Patients with MZL in Study 6 (N=63) (continued)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Metabolism and nutrition disorders	Decreased appetite	16	2
	Hyperuricemia	16	0
	Hypoalbuminemia	14	0
	Hypokalemia	13	0
Vascular Disorders	Hemorrhage*	30	0
	Hypertension*	14	5
Respiratory, thoracic and mediastinal disorders	Cough	22	2
	Dyspnea	21	2
Nervous system disorders	Dizziness	19	0
	Headache	13	0
Psychiatric disorders	Anxiety	16	2

The body system and individual ADR preferred terms are sorted in descending frequency order.
* Includes multiple ADR terms.

Table 12: Treatment-Emergent* Decrease of Hemoglobin, Platelets, or Neutrophils in Patients with MZL in Study 6 (N=63)

	Percent of Patients (N=63)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	49	6
Hemoglobin Decreased	43	13
Neutrophils Decreased	22	13

* Based on laboratory measurements.

Additional Important Adverse Reactions: *Diarrhea:* Diarrhea of any grade occurred at a rate of 43% (range, 36% to 59%) of patients treated with IMBRUVICA. Grade 2 diarrhea occurred in 9% (range, 3% to 14%) and Grade 3 in 3% (range, 0 to 5%) of patients treated with IMBRUVICA. The median time to first onset of any grade diarrhea was 10 days (range, 0 to 627), of Grade 2 was 39 days (range, 1 to 719) and of Grade 3 was 74 days (range, 3 to 627). Of the patients who reported diarrhea, 82% had complete resolution, 1% had partial improvement and 17% had no reported improvement at time of analysis. The median time from onset to resolution or improvement of any grade diarrhea was 5 days (range, 1 to 418), and was similar for Grades 2 and 3. Less than 1% of patients discontinued IMBRUVICA due to diarrhea.

Visual Disturbance: Blurred vision and decreased visual acuity of any grade occurred in 10% of patients treated with IMBRUVICA (9% Grade 1, 2% Grade 2). The median time to first onset was 85 days (range, 1 to 414 days). Of the patients with visual disturbance, 61% had complete resolution and 38% had no reported improvement at time of analysis. The median time from onset to resolution or improvement was 29 days (range, 1 to 335 days).

Postmarketing Experience: The following adverse reactions have been identified during post-approval use of IMBRUVICA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hepatobiliary disorders: hepatic failure

Respiratory disorders: interstitial lung disease

Metabolic and nutrition disorders: tumor lysis syndrome *[see Warnings & Precautions]*

Immune system disorders: anaphylactic shock, angioedema, urticaria

Skin and subcutaneous tissue disorders: Stevens-Johnson Syndrome (SJS), onychoclasis

DRUG INTERACTIONS

CYP3A Inhibitors: Ibrutinib is primarily metabolized by cytochrome P450 enzyme 3A (CYP3A). In healthy volunteers, co-administration of ketoconazole, a strong CYP3A inhibitor, increased C_{max} and AUC of ibrutinib by 29- and 24-fold, respectively. The highest ibrutinib dose evaluated in clinical trials was 12.5 mg/kg (actual doses of 840 – 1400 mg) given for 28 days with single dose AUC values of 1445 ± 869 ng • hr/mL which is approximately 50% greater than steady state exposures seen at the highest indicated dose (560 mg).

Avoid concomitant administration of IMBRUVICA with strong or moderate inhibitors of CYP3A. For strong CYP3A inhibitors used short-term (e.g., antifungals and antibiotics for 7 days or less, e.g., ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin) consider interrupting IMBRUVICA therapy during the duration of inhibitor use. Avoid strong CYP3A inhibitors that are needed chronically. If a moderate CYP3A inhibitor must be used, reduce the IMBRUVICA dose. Patients taking concomitant strong or moderate CYP3A4 inhibitors should be monitored more closely for signs of IMBRUVICA toxicity *[see Dosage and Administration (2.4) in Full Prescribing Information].*

Avoid grapefruit and Seville oranges during IMBRUVICA treatment, as these contain moderate inhibitors of CYP3A *[see Dosage and Administration (2.4), and Clinical Pharmacology (12.3) in Full Prescribing Information].*

CYP3A Inducers: Administration of IMBRUVICA with rifampin, a strong CYP3A inducer, decreased ibrutinib C_{max} and AUC by approximately 13- and 10-fold, respectively.

Avoid concomitant use of strong CYP3A inducers (e.g., carbamazepine, rifampin, phenytoin, and St. John's Wort). Consider alternative agents with less CYP3A induction *[see Clinical Pharmacology (12.3) in Full Prescribing Information].*

USE IN SPECIFIC POPULATIONS

Pregnancy: *Risk Summary:* IMBRUVICA, a kinase inhibitor, can cause fetal harm based on findings from animal studies. In animal reproduction studies, administration of ibrutinib to pregnant rats and rabbits during the period of organogenesis at exposures up to 2-20 times the clinical doses of 420-560 mg daily produced embryofetal toxicity including malformations *[see Data].* If IMBRUVICA is used during pregnancy or if the patient becomes pregnant while taking IMBRUVICA, the patient should be apprised of the potential hazard to the fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Animal Data: Ibrutinib was administered orally to pregnant rats during the period of organogenesis at doses of 10, 40 and 80 mg/kg/day. Ibrutinib at a dose of 80 mg/kg/day was associated with visceral malformations (heart and major vessels) and increased resorptions and post-implantation loss. The dose of 80 mg/kg/day in rats is approximately 14 times the exposure (AUC) in patients with MCL and 20 times the exposure in patients with CLL/SLL or WM administered the dose of 560 mg daily and 420 mg daily, respectively. Ibrutinib at doses of 40 mg/kg/day or greater was associated with decreased fetal weights. The dose of 40 mg/kg/day in rats is approximately 6 times the exposure (AUC) in patients with MCL administered the dose of 560 mg daily.

Ibrutinib was also administered orally to pregnant rabbits during the period of organogenesis at doses of 5, 15, and 45 mg/kg/day. Ibrutinib at a dose of 15 mg/kg/day or greater was associated with skeletal variations (fused sternebrae) and ibrutinib at a dose of 45 mg/kg/day was associated with increased resorptions and post-implantation loss. The dose of 15 mg/kg/day in rabbits is approximately 2.0 times the exposure (AUC) in patients with MCL and 2.8 times the exposure in patients with CLL/SLL or WM administered the dose of 560 and 420 mg daily, respectively.

Lactation: *Risk Summary:* There is no information regarding the presence of ibrutinib or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production.

The development and health benefits of breastfeeding should be considered along with the mother's clinical need for IMBRUVICA and any potential adverse effects on the breastfed child from IMBRUVICA or from the underlying maternal condition.

Females and Males of Reproductive Potential: *Pregnancy Testing:* Verify the pregnancy status of females of reproductive potential prior to initiating IMBRUVICA therapy.

Contraception:
Females: Advise females of reproductive potential to avoid pregnancy while taking IMBRUVICA and for up to 1 month after ending treatment. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be informed of the potential hazard to a fetus.

Males: Advise men to avoid fathering a child while receiving IMBRUVICA, and for 1 month following the last dose of IMBRUVICA.

Pediatric Use: The safety and effectiveness of IMBRUVICA in pediatric patients has not been established.

Geriatric Use: Of the 905 patients in clinical studies of IMBRUVICA, 62% were ≥ 65 years of age, while 21% were ≥75 years of age. No overall differences in effectiveness were observed between younger and older patients. Anemia (all grades) and Grade 3 or higher pneumonia occurred more frequently among older patients treated with IMBRUVICA.

Hepatic Impairment: Ibrutinib is metabolized in the liver. In a hepatic impairment study, data showed an increase in ibrutinib exposure. Following single dose administration, the AUC of ibrutinib increased 2.7-, 8.2- and 9.8-fold in subjects with mild (Child-Pugh class A), moderate (Child-Pugh class B), and severe (Child-Pugh class C) hepatic impairment compared to subjects with normal liver function.

The safety of IMBRUVICA has not been evaluated in cancer patients with mild to severe hepatic impairment by Child-Pugh criteria.

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Monitor patients for signs of IMBRUVICA toxicity and follow dose modification guidance as needed. It is not recommended to administer IMBRUVICA to patients with moderate or severe hepatic impairment (Child-Pugh class B and C) *[see Dosage and Administration (2.5) and Clinical Pharmacology (12.3) in Full Prescribing Information].*

Plasmapheresis: Management of hyperviscosity in WM patients may include plasmapheresis before and during treatment with IMBRUVICA. Modifications to IMBRUVICA dosing are not required.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

- *Hemorrhage:* Inform patients of the possibility of bleeding, and to report any signs or symptoms (severe headache, blood in stools or urine, prolonged or uncontrolled bleeding). Inform the patient that IMBRUVICA may need to be interrupted for medical or dental procedures *[see Warnings and Precautions].*
- *Infections:* Inform patients of the possibility of serious infection, and to report any signs or symptoms (fever, chills, weakness, confusion) suggestive of infection *[see Warnings and Precautions].*
- *Atrial fibrillation:* Counsel patients to report any signs of palpitations, lightheadedness, dizziness, fainting, shortness of breath, and chest discomfort *[see Warnings and Precautions].*
- *Hypertension:* Inform patients that high blood pressure has occurred in patients taking IMBRUVICA, which may require treatment with anti-hypertensive therapy *[see Warnings and Precautions].*
- *Second primary malignancies:* Inform patients that other malignancies have occurred in patients who have been treated with IMBRUVICA, including skin cancers and other carcinomas *[see Warnings and Precautions].*
- *Tumor lysis syndrome:* Inform patients of the potential risk of tumor lysis syndrome and to report any signs and symptoms associated with this event to their healthcare provider for evaluation *[see Warnings and Precautions].*
- *Embryo-fetal toxicity:* Advise women of the potential hazard to a fetus and to avoid becoming pregnant during treatment and for 1 month after the last dose of IMBRUVICA *[see Warnings and Precautions].*
- Inform patients to take IMBRUVICA orally once daily according to their physician's instructions and that the capsules should be swallowed whole with a glass of water without being opened, broken, or chewed at approximately the same time each day *[see Dosage and Administration (2.1) in Full Prescribing Information].*
- Advise patients that in the event of a missed daily dose of IMBRUVICA, it should be taken as soon as possible on the same day with a return to the normal schedule the following day. Patients should not take extra capsules to make up the missed dose *[see Dosage and Administration (2.6) in Full Prescribing Information].*
- Advise patients of the common side effects associated with IMBRUVICA *[see Adverse Reactions].* Direct the patient to a complete list of adverse drug reactions in PATIENT INFORMATION.
- Advise patients to inform their health care providers of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products *[see Drug Interactions].*
- Advise patients that they may experience loose stools or diarrhea, and should contact their doctor if their diarrhea persists. Advise patients to maintain adequate hydration *[see Adverse Reactions].*

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Notes


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